CHEST Supplement

DIAGNOSIS AND MANAGEMENT OF LUNG CANCER: ACCP GUIDELINES

Diagnosis and Management of Lung Cancer Executive Summary*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Key words: diagnosis; guidelines; lung cancer; management

Abbreviations: ACCP = American College of Chest Physicians; BAC = bronchioloalveolar carcinoma; CIS = carcinoma *in situ*; DLCO = diffusion capacity of the lung for carbon monoxide; EBUS-NA = endobronchial ultrasound-needle aspiration; EUS-NA = endoscopic ultrasound-needle aspiration; FDG = fluorodeoxyglucose; NSCLC = non-small cell lung cancer; PET = positron emission tomography; PS = performance status; SCLC = small cell lung cancer; SPN = solitary pulmonary nodule; SVC = superior vena cava; TBNA = transbronchial needle aspiration; TTNA = transthoracic needle aspiration

In the 19th century, lung cancer was an unusual tumor; so much so that single case reports of the rare cancer were published in the scientific literature of the day. Things have changed. Other than skin cancer, lung cancer is now the most common cancer and is the most frequent cause of death from cancer in both men and women.

In recognition of the importance of lung cancer in the population and with the rise of evidence-based medicine as a basis for diagnosing the disease and managing those afflicted, in the year 2000 the American College of Chest Physicians (ACCP), through its Health and Science Policy Committee, commissioned the development of evidence-based guidelines on the diagnosis and management of lung cancer. The goal was to assist physicians in achieving the best possible outcomes given the knowledge and capabilities available at the time. The size of the task was daunting, but the goal was laudable and the guidelines were successfully published as a Supplement to *CHEST* in January of 2003.

Fortunately, the pace of discovery in the diagnosis and management of lung cancer has quickened. As a result, the ACCP found it prudent to commission the development of a second edition of the guidelines. This guideline Supplement is the result of that effort and represents the work of nearly 100 voluntary faculty and ACCP staff.

The methodology and grading system used to develop the second edition of the guidelines may be found in a separate chapter. Rigorous adherence to formal guideline methodology was stressed. This attention to process detail and the use of the newly developed ACCP grading system has produced a valid, yet clinically useful document.

In response to suggestions made after the first edition, several new chapters have been added, such as "Diagnostic Surgical Pathology in Lung Cancer," "Bronchioloalveolar Lung Cancer," and "Complementary Therapies and Integrative Oncology in Lung Cancer." A number of chapters have been extensively reworked to encompass recent knowledge; for example, "Screening for Lung Cancer, Management of Patients with Pulmonary Nodules: When is it lung cancer?" (*ie*, the chapter previously termed the "Solitary Pulmonary Nodule"), "Bronchial Intraepithelial

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Neoplasia/Early Central Airways Lung Cancer" (*ie*, the chapter previously termed "The Treatment of Early Stage Non-small Cell Lung Cancer"), and "Palliative Care Consultation," "Quality of Life Measurement," and "Bereavement for End-of-Life Care in Patients with Lung Cancer." All of the chapters have incorporated information and knowledge gleaned from the literature published since 2002.

Recommendations from each of the chapters are listed below under their respective chapter titles. For an in-depth discussion or clarification of each recommendation, readers are encouraged to read the specific chapter in question in its entirety.

Summary of Recommendations

Lung Cancer Chemoprevention

1. For individuals with a > 20–pack-year history of smoking or with a history of lung cancer, the use of beta-carotene supplementation is not recommended for primary, secondary, or tertiary chemoprevention of lung cancer. Grade of recommendation, 1A

2. For individuals at risk for lung cancer and for patients with a history of lung cancer, the use of vitamin E, retinoids, N-acetylcysteine, and aspirin is not recommended for primary, secondary, or tertiary prevention of lung cancer. Grade of recommendation, 1A

3. For individuals at risk for lung cancer or with a history of lung cancer, budenoside, cyclooxygenase-2 inhibitors, 5-lipoxygenase inhibitors, and prostaglandin analogs are not recommended for use for primary, secondary, or tertiary lung cancer chemoprevention outside of the setting of a well-designed clinical trial. Grade of recommendation, 2C

4. In individuals at risk for lung cancer or with a history of lung cancer, the use of oltipraz as a primary, secondary, or tertiary chemopreventive agent of lung cancer is not recommended. Grade of recommendation, 1B

5. For individuals at risk for lung cancer or with a history of lung cancer, the use of selenium, and anethole dithiolethione, for primary, secondary, or tertiary lung cancer chemoprevention is not recommended outside of the setting of a well-designed clinical trial. Grade of recommendation, 1B

6. For individuals at risk for lung cancer or with a history of lung cancer, there are not yet sufficient data to recommend the use of any agent either alone or in combination for primary, secondary, or tertiary lung cancer chemoprevention outside of a clinical trial. Grade of recommendation, 1B

Screening for Lung Cancer

1. We do not recommend that low-dose helical CT be used to screen for lung cancer except in the context of a well-designed clinical trial. Grade of recommendation, 2C

2. We recommend against the use of serial chest radiographs to screen for the presence of lung cancer. Grade of recommendations, 1A

3. We recommend against the use of single or serial sputum cytologic evaluation to screen for the presence of lung cancer. Grade of recommendation, 1A

Diagnostic Surgical Pathology in Lung Cancer

1. When pathologically diagnosing lung cancer, the reporting of histologic type, tumor size and location, tumor grade (if appropriate), lymphovascular invasion, involvement of pleura, surgical margins, and status and location of lymph nodes by station is recommended. Grade of recommendation, 1B

2. In individuals at risk for lung cancer but without symptoms or history of cancer, utilization of single or serial sputum cytologic examinations to screen for the presence of lung cancer is of insufficient clinical benefit and is not recommended. Grade of recommendation, 1A

3. In individuals with pleural-based tumors, when distinguishing between pleural adenocarcinoma and malignant mesothelioma, a structured approach utilizing a limited panel of histochemical and immunohistochemical assays is recommended to increase the diagnostic accuracy. More challenging cases may need additional studies, including ultrastructural analysis. Grade of recommendation, 1B

4. In individuals with parenchymal-based tumors, distinguishing between small cell carcinoma and non-small cell carcinoma of the lung is recommended. For challenging cases, a diagnostic panel of immunohistochemical assays is recommended to increase

diagnostic accuracy. More challenging cases may need additional studies, including ultrastructural analysis. Grade of recommendation, 1B

5. For individuals with glandular producing tumors, distinguishing pure bronchioloalveolar carcinoma (BAC) from adenocarcinoma with or without BAC component is recommended. Grade of recommendation, 1C

6. For individuals with lung tumors whose differential includes primary lung carcinoma vs metastatic carcinoma, a directed panel of immunohistochemical assays is recommended to increase the diagnostic accuracy. Grade of recommendation, 1C

7. For individuals with lung tumors who have had an assessment of pathologic features and staging parameters, the evaluation of pathobiological and molecular markers is appropriate for protocol investigations and is not routinely recommended for clinical management. Grade of recommendation, 1C

8. For individuals with lung tumors who have had an assessment of pathologic features and staging parameters, the determination of occult or micrometastatic disease, utilizing enhanced pathologic or molecular techniques, is not of sufficient clinical utility and is not recommended. Grade of recommendation, 1C

Management of Patients With Pulmonary Nodules: When Is It Lung Cancer?

1. In every patient with a solitary pulmonary nodule (SPN), we recommend that clinicians estimate the pretest probability of malignancy either qualitatively by using their clinical judgment or quantitatively by using a validated model. Grade of recommendation, 1C

2. In every patient with an SPN that is visible on chest radiography, we recommend that previous chest radiographs and other relevant imaging tests be reviewed. Grade of recommendation, 1C

3. In patients who have an SPN that shows clear evidence of growth on imaging tests, we recommend that tissue diagnosis should be obtained unless specifically contraindicated. Grade of recommendation, 1C

4. In a patient with an SPN that is stable on imaging tests for at least 2 years, we suggest that no additional diagnostic evaluation be performed, except for patients with pure ground-glass opacities on CT, for whom a longer duration of annual follow-up should be considered. Grade of recommendation, 2C

5. In a patient with an SPN that is calcified in a clearly benign pattern, we recommend that no additional diagnostic evaluation is necessary. Grade of recommendation, 1C

6. In every patient with an indeterminate SPN that is visible on chest radiography, we recommend that CT of the chest should be performed, preferably with thin sections through the nodule. Grade of recommendation, 1C

7. In every patient with an indeterminate SPN that is visible on chest CT, we recommend that previous imaging tests should be reviewed. Grade of recommendation, 1C

8. In a patient with normal renal function and an indeterminate SPN on chest radiograph or chest CT, we recommend that CT with dynamic contrast enhancement be considered in centers with experience performing this technique. Grade of recommendation, 1B

9. In patients with low-to-moderate pretest probability of malignancy (5 to 60%) and an indeterminate SPN that measures at least 8 to 10 mm in diameter, we recommend that fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging should be performed to characterize the nodule. Grade of recommendation, 1B

10. In patients with an SPN that has a high pretest probability of malignancy (> 60%), or patients with a subcentimeter nodule that measures < 8 to 10 mm in diameter, we suggest that FDG-PET not be performed to characterize the nodule. Grade of recommendation, 2C

11. In every patient with a SPN, we recommend that clinicians discuss the risks and benefits of alternative management strategies and elicit patient preferences. Grade of recommendation, 1C

12. In patients with an indeterminate SPN that measures at least 8 to 10 mm indiameter and who are candidates for curative treatment, observation with serial

CT scans is an acceptable management strategy in the following circumstances:

- **When the clinical probability of malignancy is very low (< 5%)**

- **When clinical probability is low (< 30 to 40%) and the lesion is not hypermetabolic by FDG-PET or does not enhance > 15 Hounsfield units on dynamic contrast CT**
- **When needle biopsy is nondiagnostic and the lesion is not hypermetabolic by FDG-PET**
- **When a fully informed patient prefers this nonaggressive management approach.**

Grade of recommendation, 2C

13. In patients with an indeterminate SPN that measures at least 8 to 10 mm in diameter who undergo observation, we suggest that serial CT scans be repeated at least at 3, 6, 12, and 24 months. Grade of recommendation, 2C

14. In patients with an indeterminate SPN that measures at least 8 to 10 mm in diameter and who are candidates for curative treatment, it is appropriate to perform transthoracic needle biopsy or bronchoscopy in the following circumstances:

- **When clinical pretest probability and findings on imaging tests are discordant; for example, when the pretest probability of malignancy is high and the lesion is not hypermetabolic by FDG-PET**
- **When a benign diagnosis requiring specific medical treatment is suspected**
- **When a fully informed patient desires proof of a malignant diagnosis prior to surgery, especially when the risk of surgical complications is high.**

In general, we suggest that transthoracic needle biopsy be the first choice for patients with peripheral nodules unless the procedure is contraindicated or the nodule is inaccessible. We suggest that bronchoscopybe performed when an air bronchogram is present or in centers with expertise in newer guided techniques. Grade of recommendation, 2C

15. In surgical candidates with an indeterminate SPN that measures at least 8 to 10 mm in diameter, surgical diagnosis is preferred in most circumstances, including:

- **When the clinical probability of malignancy is moderate to high (> 60%)**
- **When the nodule is hypermetabolic by FDG-PET imaging**
- **When a fully informed patient prefers undergoing a definitive diagnostic procedure.**

Grade of recommendation, 1C

16. In patients with an indeterminate SPN in the peripheral third of the lung who chose surgery, we recommend that thoracoscopy be performed to obtain a diagnostic wedge resection. Grade of recommendation, 1C

17. In a patient who chooses surgery with an indeterminate SPN that is not accessible by thoracoscopy, bronchoscopy, or transthoracic needle aspiration (TTNA), we recommend that a diagnostic thoracotomy should be performed. Grade of recommendation, 1C

18. In patients with a SPN who undergo thoracoscopic wedge resection that is found to be cancer by frozen section, we recommend that anatomic resection with systematic mediastinal lymph node sampling or dissection be performed during the same anesthetic. Grade of recommendation, 1C

19. In patients with an SPN who are judged to be marginal candidates for lobectomy, we recommend definitive treatment by wedge resection/segmentectomy (with systematic lymph node sampling or dissection). Grade of recommendation, 1B

20. For the patient with an SPN who is not a surgical candidate and who prefers treatment, we recommend that the diagnosis of lung cancer be confirmed by biopsy, unless contraindicated. Grade of recommendation, 1C

21. For the patient with a malignant SPN who is not a surgical candidate and who prefers treatment, we recommend referral for external beam radiation or to a clinical trial of an experimental treatment such as stereotactic radiosurgery or radiofrequency ablation. Grade of recommendation, 2C

22. For surgical candidates with subcentimeter nodules who have no risk factors for lung cancer, the frequency and duration of follow-up (preferably with low-dose CT) should depend on the size of the nodule. We suggest that:

- **Nodules measuring up to 4 mm in diameter need not be followed up, but the patient must be fully informed of the risks and benefits of this approach**
- **Nodules measuring > 4 to 6 mm should be re-evaluated at 12 months without the need for additional follow-up if unchanged**
- **Nodules measuring > 6 to 8 mm should be followed up sometime between 6 months and 12 months, and then again between**

18 months and 24 months if unchanged. Grade of recommendation, 2C

23. For surgical candidates with subcentimeter nodules who have one or more risk factors for lung cancer, the frequency and duration of follow-up (preferably with low-dose CT) should depend on the size of the nodule. We suggest that:

- **Nodules measuring up to 4 mm in diameter should be re-evaluated at 12 months without the need for additional follow-up if unchanged**
- **Nodules measuring > 4 to 6 mm should be followed up sometime between 6 months and 12 months, and then again between 18 months and 24 months if unchanged**
- **Nodules measuring > 6 to 8 mm should be followed up initially sometime between 3 months and 6 months and then subsequently between 9 months and 12 months, and again at 24 months if unchanged.**

Grade of recommendation, 2C

24. For surgical candidates with subcentimeter nodules that display unequivocal evidence of growth during follow-up, we recommend that definitive tissue diagnosis should be obtained, either by surgical resection, transthoracic needle biopsy, or bronchoscopy. Grade of recommendation, 1C

25. For individuals with subcentimeter nodules who are not candidates for curative treatment, we recommend limited follow-up (in 12 months) or follow-up when symptoms develop. Grade of recommendation, 1C

26. In patients who are candidates for curative treatment with a dominant SPN and one or more additional small nodules, we recommend that each nodule be evaluated individually, as necessary, and curative treatment should not be denied unless there is histopathologic confirmation of metastasis. Grade of recommendation, 1C

27. In surgical candidates with a solitary pulmonary metastasis, we recommend that pulmonary metastasectomy be performed if there is no evidence of extrapulmonary malignancy and there is no better available treatment. Grade of recommendation, 1C

28. In surgical candidates with an SPN that has been diagnosed as small cell lung cancer (SCLC), we recommend surgical resection with adjuvant chemotherapy, provided that noninvasive and invasive staging exclude the presence of regional or distant metastasis. Grade of recommendation, 1C

29. In patients with an SPN in whom SCLC is diagnosed intraoperatively, we recommend anatomic resection (with systematic mediastinal lymph node sampling or dissection) under the same anesthetic if there is no evidence of nodal involvement and if the patient will tolerate resection. Surgery should be followed by adjuvant chemotherapy. Grade of recommendation, 1C

Initial Diagnosis of Lung Cancer

1. In patients suspected of having SCLC based on radiographic and clinical findings, it is recommended that the diagnosis be confirmed by the easiest method (sputum cytology, thoracentesis, fine-needle aspirate, bronchoscopy including transbronchial needle aspiration [TBNA] and endobronchial ultrasound-needle aspiration [EBUS-NA], endoscopic ultrasound-needle aspiration [EUS-NA]), as dictated by the patient's presentation. Grade of recommendation, 1C

2. In patients suspected of having lung cancer who have an accessible pleural effusion, thoracentesis is recommended to diagnose the cause of the pleural effusion. Grade of recommendation, 1C

3. In a patients suspected of having lung cancer who have an accessible pleural effusion, if pleural fluid cytology is negative (after at least two thoracenteses), thoracoscopy is recommended as the next step if establishing the cause of the pleural effusion is believed to be clinically important. Grade of recommendation, 1C

4. In patients suspected of having lung cancer who have a solitary extrathoracic site suspicious for metastasis, it is recommended that tissue confirmation of the metastatic site be obtained if a fine-needle aspirate or biopsy of the site are feasible. Grade of recommendation, 1C

5. In patients suspected of having lung cancer who have lesions in multiple distant sites suspected of metastases but in whom biopsy of a metastatic site would be technically difficult, it is recommended that diagnosis of the primary lung lesion be obtained by the easiest method (sputum cytology, bronchoscopy with TBNA or EBUS-NA, EUS-NA, or TTNA). Grade of recommendation, 1C

6. In patients suspected of having lung cancer who have extensive infiltration of the mediastinum based on radiographic studies,

it is recommended that the diagnosis of lung cancer be established by the easiest and safest method (bronchoscopy with TBNA, EBUS-NA, EUS-NA, TTNA, or mediastinoscopy). Grade of recommendation, 1C

7. In patients suspected of having lung cancer who present with a central lesion with or without radiographic evidence of metastatic disease, in whom a semiinvasive procedure such as bronchoscopy or TTNA might pose a higher risk, sputum cytology is recommended as an acceptable method of establishing the diagnosis. However, the sensitivity of sputum cytology varies by location of the lung cancer. It is recommended that further testing be performed with a nondiagnostic sputum cytology if suspicion of lung cancer remains. Grade of recommendation, 1C

8. In patients suspected of having lung cancer who have a central lesion, bronchoscopy is recommended to confirm the diagnosis. However, it is recommended that further testing be performed if bronchoscopy results are nondiagnostic and suspicion of lung cancer remains. Grade of recommendation, 1C

9. In expert hands, radial probe ultrasound devise can increase the diagnostic yield of flexible bronchoscopy while dealing with peripheral lesions < 20 mm in size. Its use can be considered prior to referring the patient for TTNA. Grade of recommendation, 2B

10. In patients suspected of having lung cancer who have a small (< 2 cm) peripheral lesion, and who require tissue diagnosis before further management can be planned, TTNA is recommended. However, it is recommended that further testing be performed if TTNA results are nondiagnostic and suspicion of lung cancer remains. Grade of recommendation, 1B

11. In a patient suspected of having lung cancer, the diagnosis of non-small cell lung cancer (NSCLC) made on cytology (sputum, TTNA, or bronchoscopic specimens) is highly reliable and can be accepted with a high degree of certainty. Grade of recommendation, 1B

12. The possibility of an erroneous diagnosis of SCLC on a cytology specimen must be kept in mind if the clinical presentation or clinical course is not consistent with that of SCLC. In such a case, it is recommended that further testing (biopsy for histologic evaluation) be performed to establish a definitive cell type. Grade of recommendation, 1B

Initial Evaluation of the Patient With Lung Cancer: Symptoms, Signs, Laboratory Tests and Paraneoplastic Syndromes

1. It is recommended that patients with known or suspected lung cancer receive timely and efficient care. Grade of recommendation, 1B

2. It is recommended that all patients with known or suspected lung cancer have a thorough history, physical examination, and standard laboratory tests as a screen for metastatic disease. Grade of recommendation, 1C

3. It is recommended that patients with lung cancer and a paraneoplastic syndrome not be precluded from potentially curative therapy on the basis of these symptoms alone. Grade of recommendation, 2C

Physiologic Evaluation of the Patient With Suspected Lung Cancer Being Considered for Resection Surgery

1. It is recommended that patients with lung cancer be assessed for curative surgical resection by a multidisciplinary team, which includes a thoracic surgeon specializing in lung cancer, medical oncologist, radiation oncologist, and pulmonologist. Grade of recommendation, 1C

2. It is recommended that patients with lung cancer not be denied lung resection surgery on the grounds of age alone. Grade of recommendation, 1B

3. It is recommended that patients with lung cancer being evaluated for surgery who have major factors for increased perioperative cardiovascular risk undergo a preoperative cardiologic evaluation. Grade of recommendation, 1C

4. In patients being considered for lung cancer resection, spirometry is recommended. If the FEV_1 is > 80% of predicted normal or > 2 L and there is no evidence of either undue dyspnea on exertion or interstitial lung disease, the patient is suitable for resection including pneumonectomy without further physiologic evaluation. If the FEV_1 is > 1.5 L and there is no evidence of either undue dyspnea on exertion or interstitial lung disease, the patient is suit-

able for a lobectomy without further physiologic evaluation. Grade of recommendation, 1C

5. In patients being considered for lung cancer resection, if there is evidence of either undue dyspnea on exertion or interstitial lung disease, even though the FEV_1 might be adequate, measuring diffusion capacity of the lung for carbon monoxide (DLCO) is recommended. Grade of recommendation, 1C

6. In patients being considered for lung cancer resection, if either the FEV_1 or DLCO are < 80% of predicted, it is recommended that postoperative lung function be predicted through additional testing. Grade of recommendation, 1C

7. In patients with lung cancer being considered for surgery, either a percentage of predicted postoperative FEV_1 < 40% or a percentage of predicted postoperative DLCO < 40% indicate an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients undergo exercise testing preoperatively. Grade of recommendation, 1C

8. In patients with lung cancer being considered for surgery, either a product of percentage of predicted postoperative FEV_1 and percentage of predicted postoperative DLCO < 1,650 or a percentage of predicted postoperative FEV_1 < 30% indicate an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

9. In patients with lung cancer being considered for surgery, a maximum oxygen uptake < 10 mL/kg/min indicates an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. These patients should be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

10. Patients with lung cancer being considered for surgery who have a maximum oxygen uptake < 15 mL/kg/min and both a percentage of predicted postoperative FEV_1 and DLCO < 40 are at increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

11. Patients with lung cancer being considered for surgery who walk < 25 shuttles on two shuttle walks or less than one flight of stairs are at increased risk for perioperative death and cardiopulmonary complications with standard lung resection. These patients should be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

12. In patients with lung cancer being considered for surgery, a $Paco_2$ > 45 mm Hg is not an independent risk factor for increased perioperative complications. However, it is recommended that these patients undergo further physiologic testing. Grade of recommendation, 1C

13. In patients with lung cancer being considered for surgery, an arterial oxygen saturation < 90% indicates an increased risk for perioperative complications with standard lung resection. It is recommended that these patients undergo further physiologic testing. Grade of recommendation, 1C

14. In patients with very poor lung function and lung cancer in an area of upper-lobe emphysema, it is recommended that combined lung volume reduction surgery and lung cancer resection be considered if both the FEV_1 and DLCO are > 20% of predicted. Grade of recommendation, 1C

15. It is recommended that all patients with lung cancer be counseled regarding smoking cessation. Grade of recommendation, 1C

Noninvasive Staging of NSCLC

1. For patients with either a known or suspected lung cancer who are eligible for treatment, a CT scan of the chest with contrast including the upper abdomen (liver and adrenal glands) should be performed. Grade of recommendation, 1B

2. In patients with enlarged discrete mediastinal lymph nodes on CT (> 1 cm in short axis) and no evidence of metastatic disease, further evaluation of the mediastinum should be made prior to definitive treatment of the primary tumor. Grade of recommendation, 1B

3. PET to evaluate for mediastinal and extrathoracic staging should be considered in patients with clinical 1A lung cancer being treated with curative intent. Grade of recommendation, 2C

4. Patients with clinical IB-IIIB lung cancer being treated with curative intent should undergo PET (where available) for mediastinal and extrathoracic staging. Grade of recommendation, 1B

5. In patients with an abnormal result on FDG-PET, further evaluation of the mediastinum with sampling of the abnormal lymph node should be performed prior to surgical resection of the primary tumor. Grade of recommendation, 1B

6. For patients with either known or suspected lung cancer who are eligible for treatment, MRI of the chest should not routinely be performed for staging the mediastinum. MRI may be useful in patients with NSCLC when there is concern for involvement of the superior sulcus or brachial plexus involvement. Grade of recommendation, 1B

7. For patients with either known or suspected lung cancer, a thorough clinical evaluation similar to that listed in Table 4 in this chapter should be performed. Grade of recommendation, 1B

8. Patients with abnormal clinical evaluations should undergo imaging for extrathoracic metastases. Site-specific symptoms warrant directed evaluation of that site with the most appropriate study (*eg*, head CT/MRI plus either whole-body PET or bone scan plus abdominal CT). Grade of recommendation, 1B

9. Routine imaging for extrathoracic metastases (*eg*, head CT/MRI plus either whole-body PET or bone scan plus abdominal CT) should be performed in patients with clinical stage IIIA and IIIB disease (even if they have a negative clinical evaluation). Grade of recommendation, 2C

10. Patients with imaging studies consistent with distant metastases should not be excluded from potentially curative treatment without tissue confirmation or overwhelming clinical and radiographic evidence of metastases. Grade of recommendation, 1B

Invasive Mediastinal Staging of Lung Cancer

1. For patients with extensive mediastinal infiltration of tumor (and no distant metastases), radiographic (CT) assessment of the mediastinal stage is usually sufficient without invasive confirmation. Grade of recommendation, 2C

2. For patients with discrete mediastinal lymph node enlargement (and no distant metastases), invasive confirmation of the radiographic stage is recommended (regardless of whether a PET finding is positive or negative in the mediastinal nodes). Grade of recommendation, 1B

3. For patients with discrete mediastinal lymph node enlargement (and no distant metastases), many invasive techniques for confirmation of the N2,3 node status are suggested as reasonable approaches (mediastinoscopy, EUS-NA, TBNA, EBUS-NA, TTNA), given the appropriate experience and skill. Grade of recommendation, 1B

4. For patients with discrete mediastinal lymph node enlargement (and no distant metastases), a nonmalignant result from a needle technique (EUS-NA, TBNA, EBUS-NA, TTNA) should be further confirmed by mediastinoscopy (regardless of whether a PET finding is positive or negative in the mediastinal nodes). Grade of recommendation, 1C

5. For patients with a radiographically normal mediastinum (by CT) and a central tumor or N1 lymph node enlargement (andno distant metastases), invasive confirmation of the radiographic stage is recommended (regardless of whether a PET finding is positive or negative in the mediastinal nodes). Grade of recommendation, 1C

6. For patients with a central tumor or N1 lymph node enlargement (and no distant metastases), invasive staging is recommended. In general, mediastinoscopy is suggested, but EUS-NA or EBUS-NA may be a reasonable alternative if nondiagnostic results are followed by mediastinoscopy. Grade of recommendation, 2C

7. For patients with a peripheral clinical stage I tumor in whom a PET scan shows uptake in mediastinal nodes (and not distant metastases), invasive staging is recom-

mended. In general, mediastinoscopy is suggested, but EUS-NA or EBUS-NA may be a reasonable alternative if nondiagnostic results are followed by mediastinoscopy. Grade of recommendation, 1C

8. For patients with a peripheral clinical stage I tumor, invasive confirmation of the mediastinal nodes is not needed if a PET scan result is negative in the mediastinum. Grade of recommendation, 1C

9. For the patients with a left upper lobe cancer in whom invasive mediastinal staging is indicated as defined by the previous recommendations, it is suggested that invasive mediastinal staging include assessment of the aortopulmonary window nodes (via Chamberlain, thoracoscopy, extended cervical mediastinoscopy, EUS-NA or EBUS-NA) if other mediastinal node stations are found to be uninvolved. Grade of recommendation, 2C

Bronchial Intraepithelial Neoplasia/Early Central Airways Lung Cancer

1. For patients with severe dysplasia, carcinoma *in situ* (CIS), or carcinoma in sputum cytology but with chest imaging studies showing no localizing abnormality, standard white light bronchoscopy is recommended. Autofluorescence bronchoscopy should be used when available. Grade of recommendation, 1B

2. For patients being considered for curative endobronchial therapy to treat CIS in centers where it is available, autofluorescent bronchoscopy may be considered to guide therapy. Grade of recommendation, 2C

3. For patients with known severe dysplasia or CIS in the central airways, standard white light bronchoscopy is recommended at periodic intervals (3 to 6 months) for follow-up. Autofluorescence bronchoscopy should be used when available. Grade of recommendation, 2C

4. For patients with superficial squamous cell carcinoma who are not surgical candidates, photodynamic therapy, electrocautery, cryotherapy, and brachytherapy are recommended as treatment options. Use of Nd:YAG laser therapy is not recommended because of the risk of perforation. Grade of recommendation, 1C

Treatment of NSCLC Stage I and II

1. For patients with clinical stage I and II NSCLC and no medical contraindication to operative intervention, surgical resection is recommended. Grade of recommendation, 1A

2. For patients with clinical stage I and II NSCLC, it is recommended that they be evaluated by a thoracic surgical oncologist with a prominent part of his/her practice focused on lung cancer, even if the patients are being considered for nonsurgical therapies such as percutaneous ablation or stereotactic body radiation therapy. Grade of recommendation, 1B

3. In patients with stage I and II NSCLC who are medically fit for conventional surgical resection, lobectomy or greater resection are recommended rather than sublobar resections (wedge or segmentectomy). Grade of recommendation, 1A

4. In patients with stage I NSCLC who may tolerate operative intervention but not a lobar or greater lung resection due to comorbid disease or decreased pulmonary function, sublobar resection is recommended over nonsurgical interventions. Grade of recommendation, 1B

5. In patients with stage I NSCLC who are considered appropriate candidates for thoracoscopic anatomic lung resection (lobectomy or segmentectomy), the use of video-assisted thoracic surgery by surgeons experienced in these techniques is an acceptable alternative to open thoracotomy. Grade of recommendation, 1B

6. In patients undergoing resection for stage I and II NSCLC, it is recommended that intraoperative systematic mediastinal lymph node sampling or dissection be performed for accurate pathologic staging. Grade of recommendation, 1B

7. For patients with centrally or locally advanced NSCLC in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy. Grade of recommendation, 1B

8. For patients with N1 lymph node metastases (stage II NSCLC) in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy. Grade of recommendation, 1B

9. For patients with completely resected stage IA NSCLC, the use of adjuvant chemotherapy is not recommended for routine use outside the setting of a clinical trial. Grade of recommendation, 1A

10. For patients with completely resected stage IB NSCLC, the use of adjuvant chemotherapy is not recommended for routine use. Grade of recommendation, 1B

11. For patients with completely resected stage II NSCLC and good performance status (PS), the use of platinum-based adjuvant chemotherapy is recommended. Grade of recommendation, 1A

12. For patients with stage I or II NSCLC who are not candidates for surgery ("medically inoperable") or who refuse surgery, curative intent fractionated radiotherapy is recommended. Grade of recommendation, 1B

13. For patients with completely resected stage IA or IB NSCLC, postoperative radiotherapy is associated with a decreased survival and is not recommended. Grade of recommendation, 1B

14. For patients with completely resected stage II NSCLC, postoperative radiotherapy decreases local recurrence but a survival benefit has not been clearly shown, and therefore postoperative radiotherapy is not recommended. Grade of recommendation, 1B

Treatment of NSCLC Stage IIIA: Incidental (Occult) N2 Disease Found at Thoracotomy (Stage IIIA1–2)

Surgical Considerations

1. In patients with NSCLC who have incidental (occult) N2 disease (IIIA2) found at surgical resection and in whom complete resection of the lymph nodes and primary tumor is technically possible, completion of the planned lung resection and mediastinal lymphadenectomy is recommended. Grade of recommendation, 2C

2. In patients with NSCLC undergoing surgical resection, systematic mediastinal lymph node sampling or complete mediastinal lymph node dissection is recommended. Grade of recommendation, 1B

Adjuvant Chemotherapy

3. In patients with resected NSCLC who were found to have incidental (occult) N2 disease (IIIA1–2) and who have good PS, adjuvant platinum-based chemotherapy is recommended. Grade of recommendation, 1A

Adjuvant Radiotherapy

4. In patients with resected NSCLC who were found to have incidental (occult) N2 disease (IIIA1–2), adjuvant postoperative radiotherapy should be considered after adjuvant chemotherapy to reduce local recurrence. Grade of recommendation, 2C

Adjuvant Chemoradiotherapy

5. In patients with resected NSCLC who were found to have incidental (occult) N2 disease (IIIA1–2), combined postoperative concurrent chemotherapy and radiotherapy is not recommended except as part of a clinical trial. Grade of recommendation, 1B

Treatment of NSCLC Stage IIIA: Potentially Resectable N2 Disease (Stage IIIA3)

6. In NSCLC patients with N2 disease identified preoperatively (IIIA3), referral for multidisciplinary evaluation (which includes a thoracic surgeon) is recommended before embarking on definitive treatment. Grade of recommendation, 1C

7. In NSCLC patients with N2 disease identified preoperatively (IIIA3), induction therapy followed by surgery is not recommended except as part of a clinical trial. Grade of recommendation, 1C

8. In NSCLC patients with N2 disease identified preoperatively (IIIA3) who do receive induction chemoradiotherapy as part of a clinical trial, pneumonectomy is not recommended. The subsequent surgical resection in this setting should be limited to a lobectomy. If after induction chemoradiotherapy it appears that a pneumonectomy will be needed, it is recommended that pneumonectomy not be performed and treatment should be continued with full-dose radiotherapy. Grade of recommendation, 1B

9. In NSCLC patients with N2 disease identified preoperatively (IIIA3), primary surgical resection followed by adjuvant therapy is not recommended except as part of a clinical trial. Grade of recommendation, 1C

10. In NSCLC patients with N2 disease identified preoperatively (IIIA3), surgery alone is not recommended. Grade of recommendation, 1A

11. In NSCLC patients with N2 disease identified preoperatively (IIIA3), platinum-based combination chemoradiotherapy is recommended as primary treatment. Grade of recommendation, 1B

Surgical Considerations

12. In NSCLC patients with N2 disease identified preoperatively (IIIA3), surgical debulking procedures are not recommended. Grade of recommendation, 1A

13. In NSCLC patients with N2 disease identified preoperatively (IIIA3) who have incomplete resections, postoperative platinum-based chemoradiotherapy is recommended. Grade of recommendation, 1C

Treatment of NSCLC Stage IIIA: Unresectable, Bulky N2 Disease (Stage IIIA4)

14. In patients with NSCLC who have bulky N2 disease (IIIA4) and good PS, radiotherapy alone is not recommended. Grade of recommendation, 1A

15. In patients with NSCLC who have bulky N2 disease (IIIA4) and good PS, combination platinum-based chemotherapy and radiotherapy are recommended. Grade of recommendation, 1A

16. In patients with NSCLC who have bulky N2 disease (IIIA4), good PS, and minimal weight loss, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy. Grade of recommendation, 1A

Treatment of NSCLC Stage IIIB

1. In selected patients with clinical T4N0-1 NSCLC due to satellite tumor nodule(s) in the same lobe, carinal involvement, or superior vena cava (SVC) invasion, it is recommended that evaluation be performed by a multidisciplinary team that includes a thoracic surgeon with lung cancer expertise to determine if the patient is operable. Surgery is not recommended if there is N2 involvement. Grade of Recommendation, 1C

2. For patients with stage IIIB NSCLC due to N3 disease, treatment with neoadjuvant (induction) chemotherapy or chemoradiotherapy followed by surgery is not recommended. Grade of recommendation, 1C

3. For patients with stage IIIB disease without malignant pleural effusions, PS of 0 or 1, and minimal weight loss (≤ 5%), platinum-based combination chemotherapy is recommended. Grade of recommendation, 1A

4. In patients with stage IIIB NSCLC and PS of 2 or those with substantial weight loss (> 10%), chemoradiotherapy is recommended only after careful consideration. Grade of recommendation, 1C

5. For stage IIIB NSCLC patients with PS of 0 or 1 and minimal weight loss (≤ 5%), concurrent chemoradiotherapy is recommended. Grade of recommendation, 1A

6. The most efficacious chemotherapy drugs to be combined with thoracic radiotherapy and the number of cycles of chemotherapy needed to yield the best results is currently uncertain. No one combination chemotherapy regimen can be recommended. Grade of recommendation, 2C

7. For patients with stage IIIB NSCLC, once-daily thoracic radiotherapy plus chemotherapy is recommended. Grade of recommendation, 1B

8. For stage IIIB patients and either poor PS or disease too extensive to treat with curative intent and symptoms due to chest disease, palliative radiotherapy is recommended. The fractionation pattern should be chosen based on the physician's judgment and patient's needs. Grade of recommendation, 1A

Treatment of NSCLC Stage IV

1. In patients with stage IV NSCLC and a good PS, two-drug combination chemotherapy is recommended. The addition of a third cytotoxic chemotherapeutic agent is not recommended because it provides no survival benefit and may be harmful. Grade of recommendation, 1A

2. Bevacizumab improves survival combined with carboplatin and paclitaxel in a clinically selected subset of the good PS, stage IV NSCLC (nonsquamous histology, lack of brain metastases, and no hemoptysis). In these patients, bevacizumab added to carboplatin and paclitaxel should be considered a therapeutic option. Grade of recommendation, 1A

3. In patients with stage IV NSCLC who are elderly (≥ 70 to 79 years) single-agent chemotherapy is recommended for most patients. Grade of recommendation, 1A

4. However, in patients with stage IV NSCLC who are elderly (≥ 70 to 79 years) and have a good PS and lack significant comorbidities, two-drug combination chemotherapy is recommended as an option. Grade of recommendation, 1B

5. In patients with stage IV NSCLC who are ≥ 80 years old, the benefit of chemotherapy is unclear and should be decided on based on individual circumstances. Grade of recommendation, 2C

6. In patients with stage IV NSCLC and a PS of 2, chemotherapy is recommended based on defined response rates and symptom palliation. Grade of recommendation, 1B

7. In patients with stage IV NSCLC and a PS of 2, no specific recommendation can be given with regard to the optimal chemotherapeutic strategy. A single phase III trial showed a survival benefit to a carboplatin-based doublet compared to a single agent in a prospectively planned subset analysis. Grade of recommendation, 2C

8. It is recommended that patient-reported health-related quality of life be measured using the FACT-L or European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire because it is a significant prognostic factor for survival. Grade of recommendation, 1A

9. It is recommended that patients with stage IV NSCLC receive adequate education about the risks and benefits of chemotherapy to enable active participation in the decision-making process regarding treatment selection. Grade of recommendation, 1C

Special Treatment Issues in Lung Cancer

1. In patients with a Pancoast tumor, it is recommended that a tissue diagnosis be obtained prior to the initiation of therapy. Grade of recommendation, 1C

2. In patients with a Pancoast tumor being considered for curative intent surgical resection, an MRI of the thoracic inlet and brachial plexus to rule out tumor invasion of unresectable vascular structures or the extradural space is recommended. Grade of recommendation, 1C

3. In patients with a Pancoast tumor involving the subclavian vessels or vertebral column, it is suggested that resection be undertaken only at a specialized center. Grade of recommendation, 2C

4. In patients with a Pancoast tumor being considered for curative resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) is recommended. Involvement of mediastinal nodes and/or metastatic disease represent a contraindication to resection. Grade of recommendation, 1C

5. In patients with a potentially resectable, nonmetastatic Pancoast tumor (and good PS), it is recommended that preoperative concurrent chemoradiotherapy be administered prior to resection. Grade of recommendation, 1B

6. In patients undergoing resection of a Pancoast tumor, it is recommended that every effort be made to achieve a complete resection. Grade of recommendation, 1A

7. It is recommended that resection of a Pancoast tumor consist of lobectomy (instead of a nonanatomic wedge resection) as well as the involved chest wall structures. Grade of recommendation, 1C

8. In patients with either a completely or incompletely resected Pancoast tumor, postoperative radiotherapy is not recommended because of lack of demonstrated survival benefit. Grade of recommendation, 2C

9. In patients with an unresectable, but nonmetastatic Pancoast tumor who have good PS, definitive concurrent chemotherapy and radiotherapy is recommended. Grade of recommendation, 1C

10. In patients with Pancoast tumors who are not candidates for curative intent treatment, palliative radiotherapy is recommended. Grade of recommendation, 1B

11. In patients with a clinical T4N0,1M0 NSCLC being considered for curative resection, it is recommend that invasive mediastinal staging, and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) be undertaken. Involvement of mediastinal nodes and/or metastatic disease represent a contraindication to resection. Grade of recommendation, 1C

12. In patients with a T4N0,1M0 NSCLC, it is recommended that resection be undertaken only at a specialized center. Grade of recommendation, 1C

13. In patients with suspected or proven lung cancer and a satellite nodule within the same lobe, it is recommend that no further diagnostic workup of a satellite nodule is undertaken. Grade of recommendation, 1B

14. In patients with a satellite lesion within the same lobe as a suspected or proven primary lung cancer, evaluation of extrathoracic metastases and confirmation of the mediastinal node status should be performed as dictated by the primary lung cancer alone, and not modified due to the presence of the satellite lesion. Grade of recommendation, 1C

15. In patients with NSCLC and a satellite focus of cancer within the same lobe (and no mediastinal or distant metastases), resection via a lobectomy is the recommended treatment. Grade of recommendation, 1B

16. In patients with two synchronous primary NSCLCs being considered for curative surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represent a contraindication to resection. Grade of recommendation, 1C

17. In patients suspected of having two synchronous primary NSCLCs, a thorough search for an extrathoracic primary cancer to rule out the possibility that both of the lung lesions represent metastases is recommended. Grade of recommendation, 1C

18. In patients not suspected of having a second focus of cancer who are found intraoperatively to have a second cancer in a different lobe, resection of each lesion is recommended, provided the patient has adequate pulmonary reserve and there is no N2 nodal involvement. Grade of recommendation, 1C

19. In patients with a metachronous NSCLC being considered for curative surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represent a contraindication to resection. Grade of recommendation, 1C

20. In patients with an isolated brain metastasis from NSCLC being considered for curative resection of a stage I or II lung primary tumor, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represent a contraindication to resection. Grade of recommendation, 1C

21. In patients with no other sites of metastases and a synchronous resectable N0,1 primary NSCLC, resection or radiosurgical ablation of an isolated brain metastasis are recommended (as well as resection of the primary tumor). Grade of recommendation, 1C

22. In patients with no other sites of metastases and a previously completely resected primary NSCLC (metachronous presentation), resection or radiosurgical ablation of an isolated brain metastasis is recommended. Grade of recommendation, 1B

23. In patients who have undergone a curative resection of an isolated brain metastasis, adjuvant whole-brain radiotherapy is suggested, although there is conflicting and insufficient data regarding a benefit with respect to survival or the rate of recurrent brain metastases. Grade of recommendation, 2B

24. In patients who have undergone curative resections of both the isolated brain metastasis and the primary tumor, adjuvant chemotherapy may be considered. Grade of recommendation, 2C

25. In patients with an isolated adrenal metastasis from NSCLC being considered for curative intent surgical resection, invasive mediastinal staging, and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represent a contraindication to resection. Grade of recommendation, 1C

26. In patients with a synchronous resectable N0,1 primary NSCLC, with no other sites of metastases, resection of the primary tumor and an isolated adrenal metastasis is recommended. Grade of recommendation, 1C

27. In patients with no other sites of metastases and a previously completely resected primary NSCLC (metachronous presentation), resection of an isolated adrenal metastasis is the recommended treatment of choice if the disease-free interval is > 6 months and complete resection of the primary NSCLC has been achieved. Grade of recommendation, 1C

28. In patients with a NSCLC invading the chest wall who are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represent a contraindication to resection, and definitive chemoradiotherapy is recommended for these patients. Grade of recommendation, 2C

29. At the time of resection of a tumor invading the chest wall, we recommend that every effort be made to achieve a complete resection. Grade of recommendation, 1B

BAC

1. We recommend the use of the term *BAC* be reserved for those lung cancers that meet the criteria established in the revised World Health Organization classification system for lung tumors. Grade of recommendation, 1B

2. For patients with suspected BAC, we recommend a surgical biopsy be used to establish a histopathologic diagnosis. Grade of recommendation, 1C

3. For patients unable to undergo surgical biopsy, the diagnosis of BAC should be made only with compatible histopathologic pattern on transbronchial or core needle biopsy, and a CT demonstrating a pure ground-glass or pneumonic appearance. Grade of recommendation, 1C

4. For patients whose CT scans show ground-glass attenuation or pneumonic consolidation (suggesting BAC), PET scan results are often false negative, and therefore we recommend that a negative PET scan result be followed by additional diagnostic testing to exclude the presence of cancer. Grade of recommendation, 1C

5. In patients with suspected BAC who are good surgical candidates, a sublobar resection may be appropriate, provided the CT shows a pure ground-glass appearance, intraoperative pathologic consultation confirms pure BAC without evidence of invasion, and surgical margins are free of disease. Grade of recommendation, 1B

6. For patients with good PS and unresectable BAC, we recommend the use of standard chemotherapy. The use of first-line epidermal growth factor receptor-targeted agents should be reserved for patients with poor PS, or those enrolled in clinical trials. Grade of recommendation, 2C

Management of SCLC

1. Routine staging of SCLC includes the following: history and physical examination, CBC counts and comprehensive chemistry panel, CT scan of the chest and abdomen or CT of the chest with cuts going through the entire liver and adrenal glands, CT or MRI of the brain, and bone scan. Grade of recommendation, 1B

2. PET scanning is not recommended in the routine staging of SCLC. Grade of recommendation, 2B

3. Patients with extensive-stage disease should receive four to not more than six cycles of cisplatin- or carboplatin-based combination chemotherapy. Cisplatin could be combined with either etoposide or irinotecan. Grade of recommendation, 1B

4. After chemotherapy, patients achieving a complete response outside the chest and a complete or partial response in the chest could be offered consolidative thoracic radiation therapy in the chest. Grade of recommendation, 2C

5. Outside of a clinical trial, maintenance treatment for patients with extensive-stage or limited- stage disease achieving a partial or complete remission is not recommended. Grade of recommendation, 1B

6. Relapsed or refractory patients with SCLC should be offered further chemotherapy. Grade of recommendation, 1B

7. Elderly patients with good PS (Eastern Cooperative Oncology Group PS of 0 or 1) with intact organ function should be treated with platinum-based chemotherapy. Grade of recommendation, 1A

8. Elderly patients with poor prognostic factors such as poor PS or medically significant concomitant comorbid disease may

still be considered for chemotherapy. Grade of recommendation, 2C

9. Outside of a clinical trial, there is no role for either dose dense/intense initial/induction or maintenance treatment for extensive-stage or limited-stage SCLC. Grade of recommendation, 1A

10. Patients with limited-stage SCLC should be treated with combined concurrent chemoradiotherapy. Patients require referral to a radiation oncologist and a medical oncologist for the consideration of combined modality treatment. Grade of recommendation, 1A

11. If the PS and comorbid illnesses allow, patients with limited-stage disease should be treated with chemotherapy and radiation therapy administered concurrently. Grade of recommendation, 1C

12. In patients eligible to receive early concurrent chemoradiotherapy, patients should be treated with accelerated hyperfractionated radiation therapy concurrently with platinum-based chemotherapy. Grade of recommendation, 1B

13. Patients with limited-stage SCLC achieving a complete remission or resected patients with stage I disease should be offered PCI. Grade of recommendation, 1B

14. Patients with extensive stage SCLC achieving a complete remission should be offered PCI. Grade of recommendation, 1C

15. In patients with SCLC and stage I disease who are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI, abdominal CT plus bone scan) followed by a platinum-based chemotherapy should be offered. Grade of recommendation, 1A

16. In patients with stage I SCLC who have undergone curative intent surgical resection, platinum-based adjuvant chemotherapy is recommended. Grade of recommendation, 2C

17. Patients with mixed SCLC/NSCLC histology should be treated the same as patients with SCLC. All treatment recommendations made for SCLC should apply to this category of patients. Grade of recommendation, 2C

Complementary Therapies and Integrative Oncology in Lung Cancer

1. It is recommended that all patients with lung cancer be specifically asked about the use of complementary and alternative therapies. Grade of recommendation, 1C

2. It is recommended that all patients with lung cancer be given guidance about the advantages and disadvantages of complementary therapies in an open, evidence-based, and patient- centered manner by a qualified professional. Grade of recommendation, 1C

3. In lung cancer patients, mind-body modalities are recommended as part of a multimodality approach to reduce anxiety, mood disturbances, or chronic pain. Grade of recommendation, 1B

4. In lung cancer patients with anxiety or pain, massage therapy delivered by an oncology-trained massage therapist is recommended as part of a multimodality treatment approach. Grade of recommendation, 1C

5. The application of deep or intense pressure is not recommended near cancer lesions or anatomic distortions, such as postoperative changes, as well as in patients with a bleeding tendency. Grade of recommendation, 2C

6. For lung cancer patients, therapies based on putative manipulation of bioenergy fields are not recommended. Grade of recommendation, 1C

7. Acupuncture is recommended as a complementary therapy when pain is poorly controlled or when side effects, such as neuropathy or xerostomia from other modalities, are clinically significant. Grade of recommendation, 1A

8. Acupuncture is recommended as a complementary therapy when nausea and vomiting associated with chemotherapy are poorly controlled. Grade of recommendation, 1B

9. Electrostimulation wristbands are not recommended for managing chemotherapy- induced nausea and vomiting. Grade of recommendation, 1B

10. When the lung cancer patient does not stop smoking despite use of other options, a trial of acupuncture is recommended to assist in smoking cessation. Grade of recommendation, 2C

11. In patients with lung cancer suffering from symptoms such as dyspnea, fatigue, chemotherapy-induced neuropathy, or postthoracotomy pain, a trial of acupuncture is recommended. Grade of recommendation, 2C

12. In patients with a bleeding tendency, it is recommended that acupuncture be performed by qualified practitioners and used cautiously. Grade of recommendation, 1C

13. It is recommended that dietary supplements, in particular herbal products, be evaluated for side effects and potential interaction with other drugs. Those that are likely to interact with other drugs, such as chemotherapeutic agents, should not be used concurrently during chemotherapy or radiation, or prior to surgery. Grade of recommendation, 1B

14. In lung cancer patients who either fail or decline antitumor therapies, it is recommended use of botanical agents occur only in the context of clinical trials. Grade of recommendation, 1C

15. It is recommended that patients be advised to avoid therapies promoted as "alternatives" to mainstream care. Grade of recommendation, 1A

Follow-up and Surveillance of the Lung Cancer Patient Following Curative Intent Therapy

1. In lung cancer patients treated with curative intent therapy, follow-up for complications related to the curative intent therapy should be managed by the appropriate specialist and should probably last at least 3 to 6 months. At that point, the patient should be reevaluated by the multidisciplinary tumor board for entry into an appropriate surveillance program for detecting recurrences and/or metachronous tumors. Grade of recommendation, 2C

2. In lung cancer patients treated with curative intent therapy, and those having adequate performance and pulmonary functions, surveillance with a history, physical examination, and imaging study (either chest radiography or CT) is recommended every 6 months for 2 years and then annually. All patients should be counseled on symptom recognition and be advised to contact their physician if worrisome symptoms were recognized. Grade of recommendation, 1C

3. Ideally, surveillance for recognition of a recurrence of the original lung cancer and/or development of a metachronous tumor should be coordinated through a multidisciplinary team approach. If possible, the physician who diagnosed the primary lung cancer and initiated the curative intent therapy should remain as the health-care provider overseeing the surveillance process. Grade of recommendation, 2C

4. In lung cancer patients following curative intent therapy, use of blood tests, PET scanning, sputum cytology, tumor markers, and fluorescence bronchoscopy is not currently recommended for surveillance. Grade of recommendation, 2C

5. Lung cancer patients who smoke should be strongly encouraged to stop smoking, and offered pharmacotherapeutic and behavioral therapy, including follow-up. Grade of recommendation, 1A

Palliative Care in Lung Cancer

1. All lung cancer patients and their families must be reassured that pain can be relieved safely and effectively. All patients should be questioned regularly about their pain, using the patient's self-report of pain and a simple rating scale as the primary source of assessment. Grade of recommendation, 1A

2. For all patients, individualize medications that are used to control pain. Administer medications regularly, and treat pain appropriately. Document the effectiveness of pain management at regular intervals during treatment. Grade of recommendation, 1A

3. For all patients with mild-to-moderate pain, manage the pain initially with acetaminophen or an nonsteroidal antiinflammatory drug, assuming there are no contraindications to their use. Use opioids when pain is more severe or when it increases. Grade of recommendation, 1B

4. For any patient, if it is anticipated that there will be a continuous need for opioid medication, meperidine is not recommended. It has a short duration of action, and its metabolite normeperidine is toxic and can cause CNS stimulation resulting in dysphoria, agitation, and seizures. Grade of recommendation, 1B

5. For patients whose pain is not controlled by pure analgesic medications, adjunctive medications such as tricyclic antidepressants, anticonvulsants, and neuroleptic agents will often augment the effects of pure analgesic medications. Grade of recommendation, 1C

6. For all patients, administer medications by mouth because of convenience and cost- effectiveness. In patients with lung cancer who cannot take pain medications by mouth, rectal and transdermal administration are recommended. Administration of analgesics by the IM route is not recommended because of pain, inconvenience, and unreliable absorption. Grade of recommendation, 1C

7. For all patients receiving opioids, because constipation is common anticipate it, treat it prophylactically, and constantly monitor it. Grade of recommendation, 1B

8. Encourage all patients to remain active and to care for themselves whenever possible. Avoid prolonged immobilization whenever possible. Grade of recommendation, 1B

9. In patients who have pain associated with muscle tension and spasm, it is recommended that complimentary methods for pain relief such as cutaneous stimulation techniques (heat and cold applications), acupuncture, psychosocial methods of care, and pastoral care be incorporated into the pain management plan, but not as a substitute for analgesics. Grade of recommendation, 1C

10. For patients with advanced lung cancer, provide palliative radiation therapy to control pain. Palliative chemotherapy to decrease pain and other symptoms is recommended, even though the increase in survival may be only modest. Grade of recommendation, 1B

11. In patients with lung cancer who have pain unresponsive to standard methods of pain control, referral to a specialized pain clinic or palliative care consultant is recommended. Grade of recommendation, 1C

12. For all lung cancer patients who complain of dyspnea, it is recommended that they be evaluated for potentially correctable causes, such as localized obstruction of a major airway, a large pleural effusion, pulmonary emboli, or an exacerbation of coexisting COPD or congestive heart falure. If one of these problems is identified, treatment with appropriate methods is recommended. Grade of recommendation, 1C

13. For all lung cancer patients whose dyspnea does not have a treatable cause, opioids are recommended. Also recommended are other pharmacologic approaches such as oxygen, bronchodilators, and corticosteroids. Grade of recommendation, 1C

14. For all lung cancer patients with dyspnea, it is recommended that nonpharmacologic and noninterventional treatments be considered, such as patient and family education, breathing control, activity pacing, relaxation techniques, fans, and psychosocial support. Grade of recommendation, 2C

15. For all lung cancer patients who have troublesome cough, it is recommended that they be evaluated for treatable causes. Grade of recommendation, 1B

16. For all lung cancer patients who have troublesome cough without a treatable cause, it is recommended that opioids be used to suppress the cough. Grade of recommendation, 1B

17. For patients with lung cancer who have pain due to bone metastases, external radiation therapy is recommended for pain relief. A single fraction of 8 Gy is as effective as higher fractionated doses of external radiation therapy for immediate relief of pain. Grade of recommendation, 1A

18. For patients with lung cancer who have pain due to bone metastases, higher fractionated doses of radiation therapy provide a longer duration of pain relief, less frequent need for retreatment, and fewer skeletal-related events than does a single fraction. Grade of recommendation, 1A

19. For patients with lung cancer who have painful bone metastases, bisphosphonates are recommended together with external radiation therapy for pain relief. Grade of recommendation, 1A

20. For patients with lung cancer who have painful bone metastases refractory to analgesics, radiation, and bisphosphonates, radiopharmaceuticals are recommended for pain relief. Grade of recommendation, 1B

21. In patients with lung cancer who have painful bone metastases to long bones and/or weight-bearing bones and a solitary well-defined lytic lesion circumferentially involving > 50% of the cortex and an expected survival > 4 weeks with satisfactory health status,

surgical fixation is recommended to minimize the potential for a fracture. Intramedullary nailing is the preferred approach, especially for the femur or the humerus. Grade of recommendation, 1C

22. In patients with lung cancer who have symptomatic brain metastases, dexamethasone at 16 mg/d is recommended during the course of definitive therapy with a rapid taper and discontinuation within 6 weeks of completion of definitive therapy (either surgery or radiation therapy). Grade of recommendation, 1B

23. Patients with NSCLC and an isolated solitary brain metastasis should be considered for a curative resection of the lung primary tumor, as long as a careful search for other distant metastases or mediastinal lymph nodes has been performed and results are negative. Grade of recommendation, 1C

24. In patients with no other sites of metastases and a synchronous resectable N0,1 primary NSCLC, resection or radiosurgical ablation of an isolated brain metastasis should be undertaken (as well as resection of the primary tumor). Resection of the isolated solitary brain metastases should be followed by whole-brain radiotherapy. Grade of recommendation, 1B

25. For cancer patients with lung cancer who have new onset of back pain, sagittal T1-weighted MRI of the entire spine is recommended for diagnostic purposes. Other diagnostic studies such as plain radiographs, bone scans, or CT myelograms are not recommended. Grade of recommendation, 1C

26. For patients with lung cancer and epidural spinal cord metastases who are not paretic and ambulatory, prompt treatment with high-dose dexamethasone and radiotherapy is recommended. Grade of recommendation, 1B

27. When there is symptomatic radiographically confirmed compression of the spinal cord, neurosurgical consultation must be sought and, if appropriate, surgery should be performed immediately and should then be followed by radiation for patients with metastatic epidural spinal cord compression and generally good PS. Grade of recommendation, 1A

28. For all lung cancer patients with large-volume hemoptysis, bronchoscopy is recommended to identify the source of bleeding, followed by endobronchial management options such as argon plasma coagulators, Nd-YAG laser, and electrocautery. Grade of recommendation, 1C

29. In lung cancer patients with symptomatic malignant pleural effusions, thoracentesis is recommended as the first drainage procedure for symptom relief. Grade of recommendation, 1C

30. In lung cancer patients with symptomatic pleural effusions that recur after thoracentesis, chest tube drainage and pleurodesis are recommended. Grade of recommendation, 1B

31. In patients with SVC obstruction from suspected lung cancer, definitive diagnosis by histologic or cytologic methods is recommended before treatment is started. Grade of recommendation, 1C

32. In patients with symptomatic SVC obstruction due to SCLC, chemotherapy is recommended. Grade of recommendation, 1C

33. In patients with symptomatic SVC obstruction due to NSCLC, stent insertion and/or radiation therapy are recommended. Stents are also recommended for SCLC or NSCLC symptomatic patients with SVC obstruction who do not respond to chemotherapy or radiation therapy. Grade of recommendation, 1C

34. For patients with a malignant tracheoesophageal or bronchoesophageal fistula, stenting of esophagus, airway, or both should be considered for symptomatic relief. Attempts at curative resection or esophageal bypass of the involved airway and/or the esophagus are not recommended. Grade of recommendation, 1C

35. It is recommended that all patients with lung cancer be evaluated for the presence of depression and, if present, treated appropriately. Grade of recommendation, 1C

Palliative Care Consultation, Quality of Life Measurements, and Bereavement for End-of-Life Care in Patients With Lung Cancer

1. For all patients with advanced lung cancer (and their families), it is recommended that palliative care be integrated into their treatment, including those pursuing curative or life-prolonging therapies. Grade of recommendation, 1C

2. For patients with advanced lung cancer, it is recommended that palliative and end-of-life care include involvement of a palliative care consultation team, which should be made available. Grade of recommendation, 1C

3. For patients with advanced lung cancer, it is recommended that standardized evaluations with symptom assessment and abbreviated disease-specific health-related quality-of-life questionnaires should be administered by the responsible member of the health-care team at the appropriate frequency. Grade of recommendation, 1B

4. It is recommended that clinicians of patients who die from lung cancer extend communication with the bereaved family and friends after death. Grade of recommendation, 1C

5. For patients with lung cancer, proactive interventions, such as those listed below, are recommended to improve grief outcomes:

a. Informing the patient and family of foreseeable death within weeks

b. Forewarning family of impending death

c. Enabling effective palliative care, focused on spiritual, existential, physical, and practical concerns.

Grade of recommendation, 1C

6. It is recommended that clinicians of dying patients with lung cancer encourage caregivers to maintain a healthy lifestyle during the period of caregiver burden, as well as during bereavement. Grade of recommendation, 1C

7. It is recommended that clinicians of patients dying from lung cancer honor rituals of death and mourning in a culturally sensitive manner. Grade of recommendation, 1C

Introduction: Diagnosis and Management of Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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To reprise but paraphrase the opening line of the Introduction to the First Edition of the Guidelines: The numbers are still staggering. It is projected that in 2007, cancer of the lung will be diagnosed in 213,380 individuals in the United States (up from 169,400 in 2002; 114,760 men and 98,620 women).[1] More disconcerting is that 160,390 individuals (up from 154,900 in 2002) will succumb to this disease (89,510 men and 70,880 women) during the year.[1] Interestingly, however, the death rate (as opposed to raw numbers) for lung cancer in men has dropped on average by 1.9%/yr from 1991 to 2003. Unfortunately, the death rate in women is up by 0.3% each year from 1995 to 2003. If these current trends continue, the incidence of lung cancer will be identical for men and women during the next decade.

Mortality

Lung cancer continues to be the leading cause of cancer deaths in both men and women in the United States. Deaths from lung cancer in women surpassed those due to breast cancer in 1987 and are expected to account for about 26% of all female cancer deaths in 2006.[1] Thirty-one percent of cancer deaths in men are attributable to lung cancer.[1] Lung cancer causes more deaths than the next four most common cancers combined (colon, $n = 52,180$; breast, $n = 40,910$; pancreas, $n = 33,370$; and prostate, $n = 27,050$).[1]

Once again, the international statistics are no more comforting (and in many cases, more ominous). Approximately 1.2 million people worldwide died of lung cancer in 2002.[2] It is interesting to note that there are more active cigarette smokers in China than there are people in the United States. The full effect of the worldwide tobacco epidemic is yet to come.

Advances Form the Basis for the Second Edition

Despite the ominous statistics, research continues and, fortunately, significant advances have occurred in the 4 years since the First Edition of the Guidelines. This serves as the impetus for the updated recommendations. For example, a number of studies have confirmed a small but significant increase in 5-year survival when adjuvant chemotherapy is administered to selected postsurgical patients.[3] Discussions of the pros and cons of adjuvant chemotherapy are recommended for some categories of fully resected patients with non-small cell lung cancer.

Targeted chemotherapy has been shown to provide a significant mortality benefit in selected clinical situations. Bevacizumab, when added to carboplatin and paclitaxel as first-line chemotherapy, yielded a 2-month increase in median survival (10.2 months vs 12.5 months, $p = 0.0075$).[4] Erlotinib, when administered to patients for whom first-line treatment had failed, provided a 2-month increase in survival (4.7 months vs 6.7 months, $p < 0.0001$).[5] It is hoped that by the time of the Third Edition of these Guidelines, the promise of molecular oncology, pharmacogenomics, and personalized therapy will be more apparent.

New chapters have been included in the Second Edition reflecting the feedback received after the First Edition. Chapters on bronchoalveolar carci-

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noma, integrative oncology, and special topics in pathology are welcome additions to the comprehensive Guidelines. The maturation of several newer diagnostic modalities such as endoscopic ultrasound-guided biopsy and positron emission tomography permit them to be integrated into diagnostic recommendations and algorithms. A broadly expanded chapter on the evaluation of the solitary pulmonary nodule will be of value to the clinician.

Controversial issues, such as lung cancer screening, are addressed and extensively discussed. Observational data have been published suggesting that CT screening can identify lung cancers when they are small and predominantly stage I.[6] It is hoped that the randomized controlled trials currently underway will provide better evidence relating to the important issue of mortality benefit. In the meantime, however, the preferences of a fully informed patient must be weighed heavily. The phrase "fully informed" cannot be overstated. The pros and cons of lung cancer screening are difficult to explain to patients (much less comprehend) yet are crucial to making an informed choice. The Guidelines recommend that that low-dose CT not be used to screen for lung cancer except in the context of a well-designed clinical trial.

The Real Culprit

As mentioned in the First Edition, one must point out that the effort evidenced in this publication would not be necessary but for the real culprit, namely tobacco and tobacco products. Tobacco use is the leading cause of preventable death in this country and accounts for one of every five deaths.[7] Half of regular smokers die prematurely of a tobacco-related disease.[8] Cigarette smoking accounts for approximately 90% of all lung cancer cases in the United States and other countries where cigarette smoking is common.[9] Not to minimize the efforts of clinicians and clinical researchers, it is clear that lung cancer is largely a preventable disease. Elimination of tobacco use is the single most effective method available to address the dismal statistics associated with lung cancer.

Lung Cancer Guidelines Project

In light of the continuing prevalence of lung cancer and the modest yet significant advances in the field, the American College of Chest Physicians (ACCP) through the Health and Science Policy Committee commissioned the development of this Second Edition of the Diagnosis and Management of Lung Cancer: ACCP Evidence-Based Clinical Practice Guidelines. This project was launched in the hope that a systematic review, evaluation, and synthesis of the published literature, along with expert opinion and consensus when necessary, would lead to a series of recommendations that would assist physicians in achieving the best possible outcome for their patients given the knowledge and capabilities available at this time.

The Second Edition of the Guidelines has employed the new ACCP grading system.[10] This grading system classifies recommendations as strong (grade 1) or weak (grade 2) according to the balance among benefits, risks, burdens, and possibly cost, and the degree of confidence in estimates of benefits, risks, and burdens. The system classifies the quality of evidence as high (grade A), moderate (grade B), or low (grade C) according to factors that include the study design, the consistency of the results, and the directness of the evidence. This system was formulated to be simple, transparent, explicit, and consistent with current methodologic approaches to the grading process.

As more fully discussed in the "Methodology" chapter, some of the clinical practice guideline recommendations within this document are appropriate to serve as the basis for performance measures. Criteria for selecting such recommendations are two tiered. First, the evidence and benefits need to be sufficiently strong for the recommendations to have a 1A grade. The second tier of criteria includes the following: (1) practicality for ACCP members and their patients, (2) importance, (3) scientific acceptability, (4) usability, and (5) feasibility. The identified recommendations will be forwarded to the American Medical Association Physicians Consortium for Quality Improvement for consideration for development into performance measures and, eventually, submitted to the National Quality Forum for potential endorsement.

Thank You

The effort expended on this project by many individuals has been truly heroic. The voluntary effort of the Executive Committee, the chapter editors, the writing committees, and the review panels in support of this publication and our patients has been nothing less than impressive. I am very pleased with the final product and hope that it proves to be of benefit to you and your patients.

Special thanks goes to Gene Colice, MD, as Vice-Chair of the Lung Cancer Guidelines Project, and Doug McCrory, MD, as the principal investigator with the Duke University Evidence-based Prac-

tice Center. Both devoted countless hours, nights, and weekends over the past 2 years to ensure the success of the project. Members of the Health and Science Policy Committee, the Thoracic Oncology Network, and the ACCP Board of Regents deserve recognition for their review and editing of the final manuscript. The true driving force, however, behind this effort has been Julia Heitzer, MS, and Sandra Zelman Lewis, PhD, who, as project managers, have brought the project to this point through sheer effort and diplomatic prodding. A thank you is certainly in order.

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Methodology for Lung Cancer Evidence Review and Guideline Development*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **To assemble a geographically diverse panel of experts in the diagnosis and treatment of lung cancer, representative of multiple clinical specialties, with the intention of developing clinically relevant practice guidelines for chest medicine and primary care physicians, including recommendations covering the full spectrum of care of the patient with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).**

Methods: **The Duke University Center for Clinical Health Policy Research was selected to review and summarize the current evidence in the treatment of NSCLC. The BlueCross BlueShield Association Technology Evaluation Center was chosen and funded by the Agency for Healthcare Research and Quality to review and synthesize the current evidence on treatment of SCLC. Other chapters received existing guidelines, systematic reviews, and metaanalyses that were published since the first edition of these guidelines, as collected by the Duke University Evidence-based Practice Center. The writing committees for these chapters conducted searches for the primary articles and additional evidence in their topic area. The expert panel established clinical recommendations founded on the synthesis of this evidence.**

Conclusions: **This section describes the approach used to develop the guidelines, including identifying, evaluating, and synthesizing the evidence, assessing the strength of evidence and grading the individual recommendations, and suggestions for implementation of the guidelines.**

(CHEST 2007; 132:23S–28S)

Key words: clinical practice guidelines; evidence-based medicine; non-small cell lung cancer; small cell lung cancer

Abbreviations: ACCP = American College of Chest Physicians; AHRQ = Agency for Healthcare Research and Quality; EPC = Evidence-based Practice Center; HSP = Health and Science Policy; NSCLC = non-small cell lung cancer; RCT = randomized controlled trial; SCLC = small cell lung cancer

The American College of Chest Physicians (ACCP) through its Health and Science Policy (HSP) Committee develops evidence-based clinical practice guidelines to assist the practicing clinician, patient, and researcher in the diagnosis and management of various cardiopulmonary diseases. In 2003, the ACCP developed the *Diagnosis and Management of Lung Cancer: ACCP Evidence-Based Guidelines*.[1] Since publication of this evidence-based guideline, the field of lung cancer has continued to

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Dr. McCrory was supported by a contract from the ACCP. Drs. Lewis, Colice, Alberts, and Heitzer have no conflicts of interest to disclose.

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expand and evolve. Consequently, the ACCP Board of Regents authorized the HSP Committee to undertake a revision of this guideline. This Second Edition seeks to both update evidence supporting the original guidelines, and to expand the scope of the guidelines to include additional relevant areas.

Panel Composition

The Chair and Co-Chair of the Lung Cancer Guideline Panel were selected by the HSP Committee based on their experience in lung cancer and guideline development. The Chair and Co-Chair selected an Executive Committee to assist in planning the chapter outlines and identifying chapter editors. Nominations for Writing Committee members for the individual chapters were solicited from the chapter editors, ACCP membership, and the ACCP cancer clinical network. The chapter editors and Writing Committee members were approved by the HSP Committee based on established criteria for membership in the guideline development process. The HSP Committee approval process included review by the HSP Subcommittee on Policies and Procedures, which vetted each nominee to ensure that they met the criteria established in the HSP Authorship Policy, and that they did not have conflicts of interest that would preclude their ability to participate or clash with the HSP policy on conflicts of interest.

An international group of > 90 experts, composed of pulmonologists, medical oncologists, radiation oncologists, thoracic surgeons, integrative medicine specialists, oncology nurses, pathologists, health-care researchers, and epidemiologists, was selected through this process to participate as Writing Committee members. In addition, medical and nursing specialty societies and patient advocacy organizations, which have a vested interest in lung cancer, were invited to send representatives to participate in the review of manuscripts and development of recommendations at the final conference. Those accepting the invitation to provide such representation include the American Association for Bronchology; American Cancer Society; American College of Surgeons Oncology Group; American Society of Clinical Oncology; American Society for Therapeutic Radiology and Oncology; American Thoracic Society; Canadian Thoracic Society; International Association for the Study of Lung Cancer; The Lung Cancer Alliance; National Comprehensive Cancer Network; Oncology Nurses Society; and Society of Thoracic Surgeons. Many of these organizations were also represented in the First Edition.

The Executive Panel met for planning purposes on several occasions. The entire Expert Panel convened in July 2006. At this conference, the panel reviewed the content of all chapter recommendations and the rating of the quality of the evidence supporting these recommendations. The method used to grade the strength of the recommendations had been developed by the HSP Committee and was based on the source of the clinical data (*eg*, randomized controlled clinical trial vs case reports) and an estimation of the balance of benefits to harm for the patient population (see grading system, below). This conference was followed by a series of conference calls with chapter editors to ensure that the recommendations closely followed the evidence and did not contradict those of other chapters.

Target Audience

The ACCP promotes interdisciplinary coordination for patient-focused care.[2] The panel of experts provided clinically relevant recommendations synthesized from the results of the evidence review and targeted toward an audience of pulmonologists, oncologists, thoracic surgeons, and primary care physicians who manage patients with lung cancer. In addition, patients with lung cancer and their family members, oncology nurses, hospice workers, chaplains, social workers, and psychologists are expected to gain insight from this set of guidelines.

Scope

The Chair, Co-Chair, and Executive Committee chose to include in the Second Edition of the guidelines most topics from the First Edition. These chapters were not intended to replicate the evidence that was reviewed in the First Edition, but were expanded to include both additional evidence published since that First Edition and subareas of content that were not included in the first version. This edition of the lung cancer guidelines was intended to cover the full spectrum of care domains, from prevention and screening, to diagnosis and staging, treatment, follow-up, and surveillance, palliative, and end-of-life care. The executive committee also determined that selected areas, not included in the First Edition, should be incorporated into the Second Edition of the guidelines, including pathology, bronchoalveolar cell carcinoma, and integrative oncology. Other malignancies that may present in the lung (*eg*, mesothelioma, hamartoma, thymoma, and carcinoid and neuroendocrine tumors) were not included in this edition of the guidelines but might be considered for addition in future guidelines.

In the original guideline, evidence reviews were performed of all guidelines, systematic reviews, and metaanalyses pertinent to lung cancer for all topic areas. In addition, five topic areas were selected for complete systematic reviews of the literature. These five topic areas were screening, prevention, diagnosis, noninvasive staging, and invasive staging. For this edition of the guidelines, the Executive Committee was again provided sufficient resources to fund a general review of guidelines, systematic reviews, and metaanalyses pertinent to all topic areas. Also, adequate funds were available to conduct complete systematic reviews of the literature in five new topic areas: evaluations of solitary pulmonary nodules, stage I and II non-small cell lung cancer (NSCLC), stage IIIA NSCLC, stage IIIB NSCLC, and stage IV NSCLC. The evidence review for the treatment of small cell lung cancer (SCLC) was funded by the Agency for Healthcare Research and Quality (AHRQ). Some support was available to update the original indepth systematic literature reviews. In other individual chapters, literature reviews were performed by the chapter writing committee who conducted literature searches based on selected criteria pertinent to the specific topic areas.

Funding and Conflicts of Interest

Funding for both the evidence review and guideline development was supported by educational grants from AstraZeneca LP, Bristol-Myers Squibb Company, Eli Lilly and Company, Genentech, and sanofi-aventis. Representatives from these companies were neither granted the right of review, nor were they allowed participation in any portion of the guideline development process. This precluded participation in either conference calls or conferences. No panel members or ACCP reviewers were paid any honoraria for their participation in the development and review of these guidelines.

The ACCP approach to the issue of potential or perceived conflicts of interest established clear firewalls to ensure that the guideline development process was not influenced by industry sources. This policy is published on the ACCP Web site at www.chestnet.org. All conflicts of interest within the preceding 5 years were required to be disclosed by all panelists, including those who did not have writing responsibilities, at all face-to-face meetings, the final conference, and prior to submission for publication. The most recent of these conflict of interests are documented in this guideline Supplement. Furthermore, the panel was instructed in this matter, verbally and in writing, prior to the deliberations of the final conference. Any disclosed memberships on speaker's bureaus, consultant fees, grants and other research monies, and any fiduciary responsibilities to industry were provided to the full panel in writing at the beginning of the conference and at submission for publication.

Evidence Review

The ACCP published a request for proposals intended to identify Evidence-based Practice Centers (EPCs) that would be capable of providing both the general and indepth reviews. After review of these proposals, the ACCP chose the Duke University Center for Clinical Health Policy Research, an AHRQ-sanctioned EPC, to perform formal systematic reviews of the current evidence in the five new NSCLC topic areas, as well as to provide a search for the existing guidelines, systematic reviews, and metaanalyses in all of the topics areas. In addition, the AHRQ agreed to fund the BlueCross BlueShield Association Technology Evaluation Center to perform the formal systematic review of literature on SCLC. The Health Outcomes Research Group of the Department of Epidemiology and Biostatistics at Memorial Sloan-Kettering Cancer Center conducted a full-scale review of the literature since the first set of guidelines in the area of screening for lung cancer to assist that particular writing group.

The formal systematic reviews of the five new topic areas were guided by the appropriate chapter editors and their writing committees, in concert with the Executive Committee of the panel. The Executive Committee included Douglas McCrory, MD, MHS, methodologist and primary investigator for the formal systematic reviews. The writing committees for each chapter identified the important treatment issues for which clinical guidance is needed and expressed these as questions. These research questions were used as the bases for the formal systematic literature reviews. The writing committees for the other chapters were provided published guidelines, systematic reviews, and metaanalyses identified as part of the general review of this field by the Duke EPC. Additional computerized searches of literature databases were performed by the writing committees to supplement this material.

The two EPC research teams conducted a variety of systematic computerized bibliographic database searches including the following: (1) a search for systematic reviews, guidelines, and metaanalyses published since the last ACCP lung cancer guideline (MEDLINE, The Cochrane Library, National Guidelines Clearinghouse); (2) targeted searches for reviews in each of five selected treatment sections (solitary pulmonary nodules, stage I and II, stage

IIIA, stage IIIB, stage IV); these searches, run in OVID version of MEDLINE, were performed in July and August 2005 and were limited to publication years since 1995, English language, and human subjects; and (3) searches related to SCLC are described in the evidence chapter on SCLC.

Search terms included the medical subject heading terms *lung neoplasms* (exploded) and *bronchial neoplasms* for the lung cancer concept. Each topic search utilized key words specific to the key questions of interest (complete search strategies are available on request from the authors). The studies identified in this search were provided to the "Treatment" chapter authors and in some cases described in evidence Tables, or more extensive reports. Consistent with the most recent grading scheme for recommendations, individual studies were rated according to study design, and important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) were noted in order to facilitate grading of the body of evidence supporting a recommendation (see below).

Grading of the Evidence and Recommendations

The lung cancer panel was provided guidelines on the grading of evidence and wording of recommendations by the HSP Committee. This guidance was based on work performed by the ACCP Task Force on Grading. This task force reviewed several grading systems that were in place as of March 2005, including the version that had been currently in use by the ACCP for the First Edition of the lung cancer guidelines,[1] with the goal of developing an improved system for future guidelines. The report[3] of this task force explained that the optimum approach would be to meld the best characteristics of several grading systems, creating a more user-friendly and transparent grading system, as described below and in Tables 1–4. This guideline panel was one of the first to use the new scheme.

The ACCP grading system is composed of only two types of recommendations (strong and weak) and two dimensions (the ratio of benefit to harm and the quality of evidence). The benefit-to-harm ratio includes consideration of the clinical improvements in health and quality of life, as well as the burdens, risks, and costs, when applicable, identifiable, and determinable (Table 2). If the advantages of the recommended procedure, service, test, or treatment are greater than the disadvantages or if the disadvantages outweigh the advantages, the benefit-to-harm ratio is said to be imbalanced. Either way, it is clear that there is a direction to the recommendation, positive or negative. When the benefits and harms are more evenly balanced, recommendations are not as strong and patient preferences play a larger role. The same holds true when the balance of benefits and burdens is not clear.

Quality of evidence is the second dimension of the

Table 2—*Balance of Benefits to Risks/Burdens Scale*

Benefits clearly outweigh the risks and burdens	Certainty of imbalance
Risks and burdens clearly outweigh the benefits	Certainty of imbalance
The risks/burdens and benefits are closely balanced	Less certainty
The balance of benefits to risks and burdens is uncertain	Uncertainty

Table 3—*Quality of Evidence Scale*

High	RCTs without important limitations or overwhelming evidence from observational studies*
Moderate	RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies*
Low or very low	Observational studies or case series

*Although the determination of magnitude of the effect based on observational studies is often a matter of judgment, we offer the following suggested rule to assist this decision: a large effect would be a relative risk > 2 (risk ratio < 0.5) [which would justify moving from weak to moderate], and a very large effect is a relative risk > 5 (risk ratio < 0.2) [which would justify moving from weak to strong]. There is some theoretical justification in the statistical literature for these thresholds (the magnitude of effect that is unlikely or very unlikely to be due to residual confounding after adjusted analysis). However, once the decision is made, authors should be explicit in justifying their decisions.

Table 1—*Relationship of Strength of the Supporting Evidence to the Balance of Benefits to Risks and Burdens*

	Balance of Benefits to Risks and Burdens			
Quality of Evidence	Benefits Outweigh Risks/Burdens	Risks/Burdens Outweigh Benefits	Evenly Balanced	Uncertain
High	1A	1A	2A	
Moderate	1B	1B	2B	
Low or very low	1C	1C	2C	2C

Table 4—*Grade of Recommendations Scale*

Grade	Recommendation
1A	Strong
1B	Strong
1C	Strong
2A	Weak
2B	Weak
2C	Weak

grading chart. Quality of evidence is scored in three categories with high-quality evidence obtained from randomized controlled trials (RCTs) without important methodologic limitations based on the study design, the consistency of the results, and the directness of the evidence. In extraordinary circumstances, significant and consistent evidence from observational studies could also be ranked as high quality. RCTs with important methodologic limitations or flaws, inconsistent results, or indirect or imprecise results would be scored as medium quality, as well as exceptionally strong evidence from observational studies. Other observational studies or case-series data would fall into the low quality of evidence category. It is the interface of the quality of the evidence and the balance of benefits to harms or burdens that determines the strength of the recommendation, with a 1A recommendation being the strongest and 2C the weakest, according to the schema in Table 1, which is further clarified in Tables 2–4.

Guideline Writing and Validation Process

Writing committees studied the evidence and summary tables or reviewed the literature for their assigned topics, developing their arguments for the recommendations and suggested grading of those recommendations that were put forth for early drafts. The Executive Committee of the panel, composed of the Chair, Vice-Chair, methodologist, and both project managers, reviewed drafts of each chapter of the manuscript during the writing process. Sections that were determined to be potentially overlapping were shared among the appropriate chapter editors, and conference calls were organized to coordinate the placement of these sections and to confirm that there would be no conflicting information or recommendations.

A conference of the panel was convened in July 2006, prior to which time all panelists, including representatives from the invited organizations, were requested to review the complete manuscript and identify recommendations for which the proposal, wording, or grading were determined to be controversial or could be interpreted as controversial by others, incorrectly evolved from the evidence, disagreement existed with regard to the proposal or the grading, or required full panel discussion and further review for any reason. When the panelists who were present were not in unanimous agreement with the proposed recommendations or the grading of the recommendations, informal group consensus techniques were employed. After the meeting, a series of conference calls were convened to finish the discussions and finalize the recommendations. There were a few chapters for which there was insufficient time for full dialogue during the meeting; in the interest of ensuring that the recommendations followed the evidence, the conference calls were necessary. This process ensured the "buy-in" of the panelists and was deemed to be a worthwhile effort.

Following final chapter revisions and incorporation of these ultimate recommendations and grading, a concluding review was conducted by the guideline panel Executive Committee. The guidelines were then submitted for review and approval to the ACCP HSP Committee, as well as the Thoracic Oncology Network of the college.

The HSP Committee review of the chapters was divided among the members of the committee; in addition, two members were assigned to read all 26 chapters to identify any inconsistencies. HSP members were charged with verifying if the methodology was according to ACCP standards, the literature was well described, the recommendations were based on the evidence, and the grading was accurate. All but four of the chapters were approved on the first review by the HSP Committee. The remaining four chapters were returned to the authors, who responded to comments from the reviewers and the full committee. Written responses and revised chapters were returned to the two designated reviewers of the HSP Committee for final approval, which was received on the second round. Because two of the revised chapters included additional evidence, even though the recommendations did not change, the chapter editors were requested to review and approve the four revised chapters. A conference call was convened to discuss and vote on the acceptance of the recommendations. After approval, the guidelines were forwarded for additional reviews by the Board of Regents. In addition, the journal *CHEST* contracted for outside independent reviews. All reviewers' comments followed the manuscript through every stage of the review process, including submission for publication.

These guidelines have not been field tested, although informal feedback on the First Edition guidelines was used to inform the revised scope and

foci of the Second Edition. Those organizations sending representatives to the final conference were requested to review the final manuscript for endorsement. Endorsements were obtained from the following organizations: American Association for Bronchology, American Association for Thoracic Surgery, American College of Surgeons Oncology Group, American Society for Therapeutic Radiology and Oncology, Asian Pacific Society of Respirology, Oncology Nurses Society, Society of Thoracic Surgeons, and World Association of Bronchology.

Dissemination and Implementation

The publication of the *Diagnosis and Management of Lung Cancer: ACCP Evidence-Based Clinical Practice Guidelines; Second Edition* in *CHEST* is the first of two dissemination vehicles. The circulation of the journal is > 23,000 subscribers and libraries, including six translations and distribution to 107 countries. All subscribers received a copy of this full-text guideline. The ACCP Clinical Resource on Lung Cancer is composed of a printed publication and an accompanying CD-ROM, containing a quick reference guide for physicians and other health-care providers, patient-targeted educational materials, and a set of slides for use in educational or clinical contexts. In addition, the recommendations and grading are personal digital assistant downloadable from the clinical resource. This product is available for purchase from the ACCP. The patient education materials are accessible free of charge on www.chestnet.org.

The implementation and translation of evidence-based clinical practice guidelines facilitates knowledge uptake, critical for practice change, and should ultimately lead to better patient-focused care. The HSP Subcommittee on Implementation has proposed to collaborate with the Governors, Thoracic Oncology Network, and other groups within the ACCP to disseminate and implement the guidelines in their local communities. Residency and specialty training programs are encouraged to use the guidelines in journal clubs and grand rounds. Other organizations that were invited to send representatives to the final conference and review the proposed drafts were also requested to endorse the guidelines and market them to their membership through their own communication channels. As with all ACCP guidelines, these guidelines were submitted to the National Guideline Clearinghouse for posting on their Web site, www.guidelines.gov.

Performance Measures

The ACCP Quality Improvement Committee in partnership with the HSP Committee has been charged with the selection of ACCP clinical practice guideline recommendations for proposed development of performance measures and the fostering of the development, endorsement, and implementation of these performance measures. The panel, with guidance from the Executive Committee, is requested to consider which of the recommendations could be put forth for development into performance measures and which should not. Criteria for selecting those deemed appropriate for this use are two tiered. First, the evidence and benefits need to be sufficiently strong for the recommendations to have 1A grades. The second tier of criteria includes the following: (1) practicality for ACCP members and their patients, (2) importance, (3) scientific acceptability, (4) usability, and (5) feasibility. These recommendations, once identified, are transmitted to the American Medical Association Physicians Consortium for Quality Improvement for consideration for development into performance measures and, eventually, forwarded to the National Quality Forum for potential endorsement.

Conclusion

The goal of this project was to produce updated, evidence-based, clinically relevant guidelines for physicians and other health-care providers managing the care of patients with lung cancer or those who are at risk of lung cancer. The methods employed followed the policies and standards of the ACCP, as described in this chapter and on www.chestnet.org.

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Epidemiology of Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

Anthony J. Alberg, PhD, MPH; Jean G. Ford, MD, MPH; and Jonathan M. Samet, MD

Background: **The objective of this study was to summarize the published literature concerning the epidemiology of lung cancer.**
Methods: **A narrative review of published evidence was conducted, identifying and summarizing key reports that describe the occurrence of lung cancer in populations and factors that affect lung cancer risk.**
Results: **In the United States, lung cancer remains the leading cause of cancer death in both men and women, even though an extensive list of modifiable risk factors has long been identified. The predominant cause of lung cancer is exposure to tobacco smoke, with active smoking causing most cases but passive smoking also contributing to the lung cancer burden.**
Conclusions: **The reductions in smoking prevalence in men that occurred in the late 1960s through the 1980s will continue to drive lung cancer mortality rates downward in men during the first portion of this century, but rates in women have not yet begun to decrease. Fortunately, exposures to major occupational respiratory carcinogens have largely been controlled, but the population is still exposed to environmental causes of lung cancer, including radon, the second leading cause of lung cancer death.** ***(CHEST 2007; 132:29S–55S)***

Key words: air pollution; asbestos; cigarette smoking; epidemiology; lung cancer; nutrition; occupation; passive smoking; radiation; tobacco

Abbreviations: BMI = body mass index; CI = confidence interval; CL = confidence limit; CPS = Cancer Prevention Study; ETS = environmental tobacco smoke; FTC = Federal Trade Commission; IARC = International Agency for Research on Cancer; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; LET = linear energy transfer; RR = relative risk; SSc = systemic sclerosis

The vast majority of lung cancer deaths are attributable to cigarette smoking. Any action that prevents cigarette smoking initiation or promotes cessation among dependent smokers is a step to preventing lung cancer. This includes tobacco control activities to affect policy, such as cigarette taxes and smoke-free workplace legislation, as well as individual-level interventions to prevent the onset or continuation of smoking.

Epidemiologic evidence is the foundation for primary and secondary disease prevention. Epidemiologic approaches are used to track the occurrence of disease, to characterize natural history, and to identify determinants of disease. The benefits of intervention programs, whether based in risk factor inter-

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ventions or screening, are also assessed using epidemiologic approaches. For lung cancer, routine mortality statistics confirmed the clinical impression that the disease became more frequent across the first half of the 20th century. Case-control and cohort studies, the epidemiologic study designs thatare used to evaluate exposure/disease associations, causally linked smoking to lung cancer in investigations reported from the 1950s onward.[1–3] As we have continued to follow lung cancer incidence and mortality rates, we have readily shown that their rise and decline parallel past trends of cigarette smoking.[4] The epidemiologic evidence and the complementary biological understanding of respiratory carcinogenesis have unassailably supported the conclusion that smoking causes lung cancer. Epidemiologic findings are also relevant to patient care, because skilled clinicians weigh alternative diagnoses depending on risk factor profiles of patients.

At the end of the 20th century, lung cancer had become one of the leading causes of preventable death.[5] It was a rare disease at the start of that century, but exposures to new etiologic agents and an increasing life span combined to make lung cancer a scourge of the 20th century. Although tobacco had been widely used throughout the world for centuries, the present pandemic of lung cancer followed the introduction of manufactured cigarettes with addictive properties, which resulted in a new pattern of sustained exposure of the lung to inhaled carcinogens.[6] German scientists in Nazi Germany conducted some of the earliest research on the links between smoking and lung cancer.[7] By the early 1950s, epidemiologic studies in Britain and the United States using the case-control method had shown that cigarettes were strongly associated with the risk for lung cancer[8–10]; this association was corroborated by the pioneering cohort studies of British physicians, US veterans, and volunteers recruited by the American Cancer Society.[11,12] By 1964, the evidence was sufficient to support a conclusion by the US Surgeon General that cigarette smoking caused lung cancer.[11] The Royal College of Physicians had reached the same conclusion 2 years before.[12] Passive smoking, the involuntary inhalation of tobacco smoke by nonsmokers, has also been found to cause lung cancer.[13,14]

Although its predominant cause is now widely known (tobacco smoking), there are other causes as well, some acting in concert with smoking to synergistically increase risk. The suspicion that radon was a cause of lung cancer in underground miners, raised early in the 20th century, led to what was probably the first occupational respiratory carcinogen to be identified[15]; radon in indoor environments is now considered as the second-leading cause of lung cancer in the United States.[16] The list of human occupational causes of lung cancer also includes arsenic, asbestos, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons, radon progeny, and other agents.[17] Outdoor air pollution, which includes combustion-generated carcinogens, is also considered to contribute to the lung cancer burden in urban dwellers. Indoor air contains several respiratory carcinogens, including radon, asbestos, and cigarette smoke. In some developing countries, exposure to fumes from cooking stoves and fires is associated with lung cancer risk. Beginning in the 1970s, associations of diet with lung cancer risk have been vigorously investigated with the anticipation that dietary micronutrients that modify the high lung cancer risk in smokers might be found. The biological basis for prevention of cancer through supplementation of micronutrients is addressed in another article in this supplement.

Even though the epidemiology of lung cancer has been extensively investigated for > 50 years, there are still active areas of research, some quite relevant to prevention. Investigation of lung cancer and diet continues, using both observational and experimental approaches, and concern remains over the risk of indoor and outdoor pollutants, including, for example, radon and diesel emissions. There has also been a need for research to track the risks of smoking over time, because the cigarette has evolved in its design characteristics, and yields of tar and nicotine, as assessed by standard protocol using a machine, have declined since the 1950s. The histologic characteristics of lung cancer in a number of developed countries, including the United States, have also changed in the past few decades such that the frequency of adenocarcinoma has risen and that of squamous cell carcinoma has declined.[4] There is also emerging evidence on genetic determinants of lung cancer risk. A current research approach, termed molecular epidemiology, melds the population and laboratory tools that are used to address susceptibility to environmental carcinogens. Whereas the evidence from the "traditional" epidemiologic approaches conclusively established the carcinogenicity of tobacco smoke, molecular epidemiology should characterize the sequence of molecular and cellular changes as a nonmalignant cell becomes malignant and genetic factors that possibly determine susceptibility to tobacco smoke. Biomarkers of exposure, dosage, susceptibility, and genetic damage may allow epidemiologic investigations to uncover specific pathways of human lung carcinogenesis and provide useful intermediate markers for prevention studies.

Materials and Methods

A narrative review of published evidence on the epidemiology of lung cancer was conducted. Key reports that described the occurrence of lung cancer in populations and factors that affect lung cancer risk were identified. This was accomplished using a combination of approaches that included cataloguing reports from the authors' files and augmented with MEDLINE searches. The MEDLINE searches included a term for "lung cancer" along with additional terms for various exposures that have been studied in relation to lung cancer (*eg*, "cigarette," "smoking," "asbestos," "radiation"). In the updating of recent literature, emphasis was placed on systematic reviews when these were available.

Our objective was to provide a summary of the epidemiologic evidence on lung cancer, with an emphasis on issues that are relevant to prevention. This literature is now extraordinarily large; therefore, we did not attempt to conduct a comprehensive review and systematic synthesis. Such syntheses have been periodically carried out by expert review groups, including the committees assembled to prepare the US Surgeon General's reports on smoking and health and other federal documents and expert committees of other governments and organizations, including the UK Royal College of Physicians and Scientific Committee on Tobacco and the World Health Organization's International Agency for Research on Cancer (IARC). Several relevant reports have been published, including the 2004 IARC monographs on active and involuntary smoking[18] and the 2004 report of the Surgeon General.[19]

The topics covered were agreed on by consensus of the writing committee with initial input from the ACCP Guidelines Panel. As prior versions of this article underwent several rounds of external review, additional topics were added as recommended by the external reviewers, the ACCP Lung Cancer Guidelines Panel, the Thoracic Oncology Network, the Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians. On the basis of the agreement of all parties, we did not attempt to grade the evidence or generate formal guidelines.

Results

Patterns of Occurrence

Survival: The 5-year relative survival rate for lung cancer for the period of 1995 to 2001 was 15.7%, reflecting a steady but slow improvement from 12.5% from 1974 to 1976.[20] The 5-year relative survival rate varies markedly depending on the stage at diagnosis, from 49 to 16 to 2% for local, regional, and distant stage disease, respectively.[20] Stage at diagnosis accounts for the most marked variation in prognosis, but patient characteristics associated with poorer survival also include being older, male, and African American.[20]

Temporal Trends: Because of the high case-fatality rate of lung cancer, incidence and mortality rates are nearly equivalent; consequently, routinely collected vital statistics provide a long record of the occurrence of lung cancer. We are amid an epidemic of lung cancer that dates to the first half of the last century.

Sex: Lung cancer was rare until the disease began a sharp rise around 1930 that culminated by mid-century with lung cancer becoming the leading cause of cancer death among men.[21] The epidemic among women followed that among men, with a sharp rise in rates from the 1960s to the present, propelling lung cancer to become the most frequent cause of female cancer mortality.[21] As the leading cause of cancer death among women, lung cancer is a major women's health issue. As a result of historical cigarette smoking patterns, the epidemic of lung cancer started later in women than men, but in contrast to the situation in men, lung cancer incidence rates in women have not yet begun to decrease consistently.[20] Far more men than women still die from lung cancer each year, but the gender gap in lung cancer mortality is steadily narrowing and will eventually close.[22,23] This trend is due to historical smoking patterns, with smoking prevalence having peaked approximately 2 decades earlier among men than women.[22,23]

Examination of time trends of age-specific lung cancer mortality rates in the United States further highlights the differing epidemic patterns in men compared with women. The sex- and race-specific mortality rates are now almost all decreasing.[22] The rates of lung cancer in the younger age groups have been declining during the past several decades in men and during the past decade in women.[22] As the younger birth cohorts age, their reduced risk for lung cancer foreshadows substantial reductions in the overall occurrence of lung cancer, but the reductions will be greater for men than for women. These patterns all are consistent with population patterns of smoking prevalence over time.[22]

Tobacco smoking accounts for such a large proportion of lung cancer that there have been few data on the occurrence of lung cancer among nonsmokers. Evidence from the American Cancer Society Cancer Prevention Study (CPS) I and II cohorts indicates that there has not been a strong temporal trend in lung cancer death rates among male nonsmokers, but there has been an upward trend among female nonsmokers, mostly confined to elderly women.[23] The data from these cohorts also indicate that among nonsmokers, lung cancer death rates are greater in men than in women and greater in African-American than white women.

Race and Ethnicity: The patterns of occurrence of lung cancer by race and ethnicity make lung cancer a relevant disease for those concerned with the health of minorities. Of particular note is that whereas lung cancer incidence rates are similar among African-American and white women, lung cancer occurrence is approximately 45% higher

among African-American men than among white men.[20] This racial disparity may be partially due to greater susceptibility of African-American smokers to smoking-induced lung carcinogenesis.[24] The higher mortality rates of lung cancer in African-American compared with white individuals reflect not only their higher incidence rate but also the poorer survival from lung cancer among African-American compared with white individuals. The 5-year relative survival rate was 13% lower in African-American compared with white individuals during the period 1995 to 2001.[20] This racial gap persisted within each stage at diagnosis category and for men and women.[20]

Lung cancer mortality rates among Hispanic, Native American, and Asians/Pacific Islander individuals are significantly lower than rates among African-American and non-Hispanic white individuals.[25] Nevertheless, lung cancer poses a considerable public health burden among these groups.

Socioeconomic Status: Lung cancer is more likely to occur in the poor and less educated, a pattern that is observed in many countries worldwide. For example, in Canada, the risk for lung cancer in both sexes was inversely associated with income, education, and social class, even after adjustment for cigarette smoking.[26] In China, those who were classified as low income had a sixfold increased risk of lung cancer compared with those in the high-income category.[27] In the Netherlands, the risk for lung cancer was inversely associated with attained education, an association that was not attributable to occupational exposures.[28] Lower socioeconomic status has also been observed to be associated with later stage at diagnosis.[29]

Socioeconomic status is associated with a constellation of interacting determinants of lung cancer risk, such as smoking, diet, and exposures to inhaled carcinogens in the workplace and general environment. Lower socioeconomic status is associated with an unfavorable profile for all of these factors. Advancing our understanding of the complex linkages between components of socioeconomic status and lung cancer risk is essential to effectively addressing this social class disparity and reducing lung cancer rates in the poorer segments of society.

Geographic Patterns: Lung cancer is the most commonly diagnosed cancer worldwide,[30] but its geographic distribution shows marked regional variation: age-standardized incidence rates range > 60-fold among men and 30-fold among women (Fig 1,

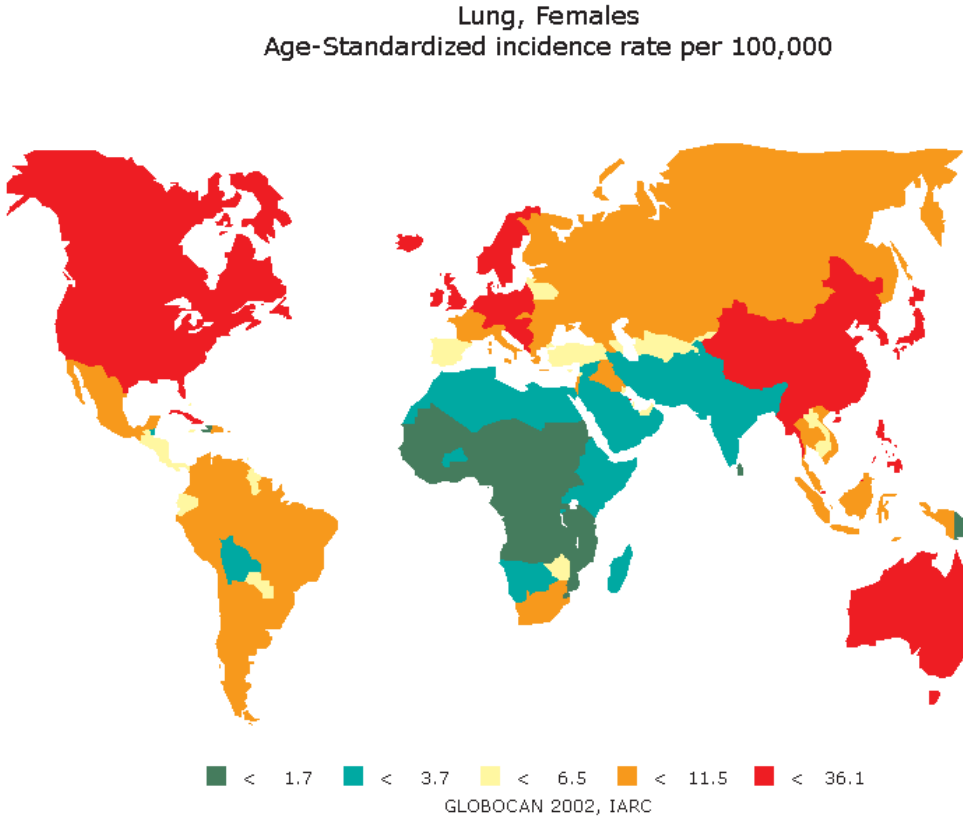

FIGURE 1. Age-adjusted lung cancer incidence rates in women worldwide in 2002. Source: IARC, GLOBOCAN 2002 (www-dep.iarc.fr).

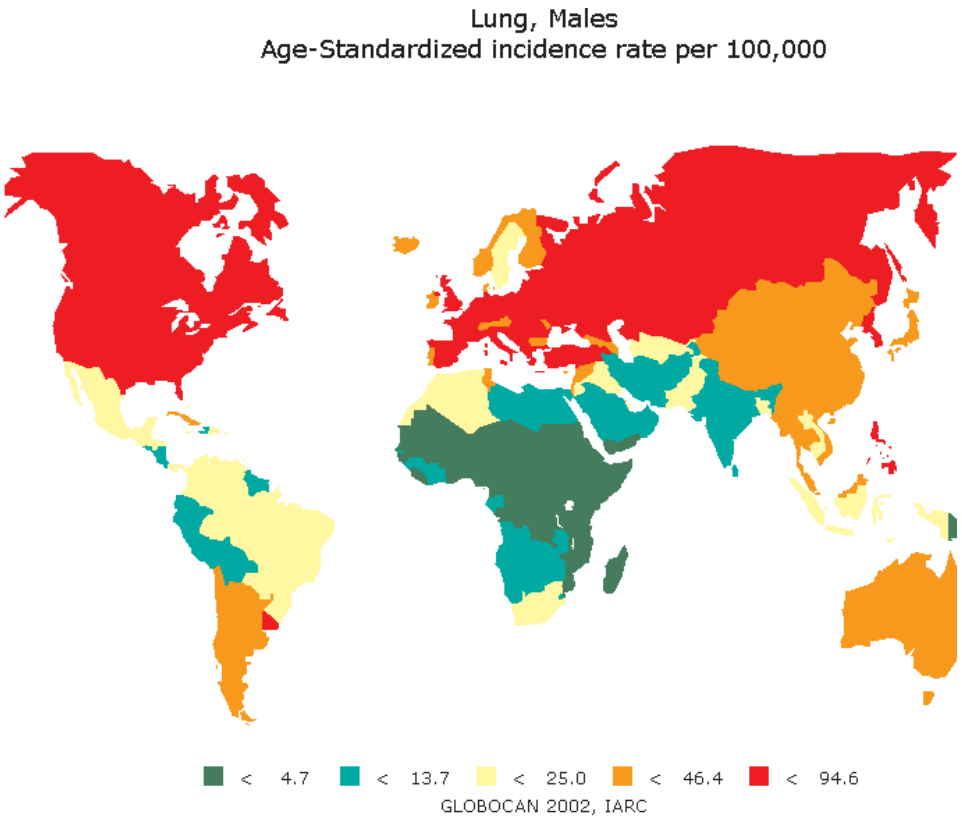

FIGURE 2. Age-adjusted lung cancer incidence rates in men worldwide in 2002. Source: IARC, GLOBOCAN 2002 (www-dep.iarc.fr).

2).[31] Because of differences in cancer registration between countries, caution is needed in interpreting these data. However, this marked variation in rates cannot be explained on the basis of diagnostic practices and data quality alone. Lung cancer tends to be most common in developed countries, particularly in North America and Europe, and less common in developing countries, particularly in Africa and South America.[31] The low rates of lung cancer in Africa are comparable to US rates in 1930, when rates of lung cancer were < 5 per 100,000 for both sexes.[32] In contrast, African-American individuals in the United States, an epicenter, now experience lung cancer incidence rates that are among the highest in the world. As the lung cancer epidemic begins to subside in the developed countries, it is on the rise in the developing world.[30]

Within countries, lung cancer incidence among men invariably exceeds that in women, by well more than 100% in most nations. The international rankings of lung cancer incidence of men and women from the same countries tend to differ only slightly, so the highest rates of lung cancer occur in the same regions of the world for both sexes.

Substantial geographic variation in lung cancer mortality rates has also been observed within countries. For example, during the period 1997 to 2001, the age-adjusted lung cancer mortality rates varied more than threefold between the state with the highest rate (Kentucky, 78 per 100,000) and the state with lowest rate (Utah, 25 per 100,000).[20] Trends in its regional distribution can provide clues about determinants of lung cancer. In the past, rates tended to be highest in urban areas, which led to conjecture that air pollution might be a cause of the lung cancer epidemic.[33] Later on, several hypotheses[34,35] were prompted by patterns observed in a systematic review of US lung cancer mortality rates for the period 1950 to 1969,[36] particularly the rates among men. For example, high rates in coastal areas were postulated to reflect employment in shipyards with attendant asbestos exposure. This hypothesis was then tested in a series of population-based case-control studies that showed that employment in the shipbuilding industry was indeed associated with an excess risk for lung cancer.[37] Another shift then took place in the distribution of lung cancer within the United States, with lung cancer mortality rates among white men becoming highest in the South and lower in the Northeast.[38] This temporal fluidity in the geographic

variation underscores the need for regularly monitoring lung cancer mortality patterns.

Etiology of Lung Cancer

Although the causes of lung cancer are almost exclusively environmental, there is likely substantial individual variation in susceptibility to respiratory carcinogens. The risk for the disease can be conceptualized as reflecting the joint consequences of the interrelationship between the following: (1) exposure to etiologic (or protective) agents, and (2) individual susceptibility to these agents. The "environment" in its broadest sense may influence the risk for disease through direct exposures or indirectly by affecting the likelihood of exposure to exogenous agents. Given the multifactorial etiology of lung cancer, synergistic interactions among risk factors may have substantial consequences for lung cancer risk. These interactions have typically been considered on an agent-by-agent basis, such as the synergistic effect of cigarette smoking on the lung cancer risk from asbestos exposure.[39] Our emerging understanding of cancer genetics indicates the additional relevance of gene/environment interactions.

Given the many risk factors that have been identified for lung cancer, a practical question is the relative contribution of these factors to the overall burden of lung cancer. The "population attributable risk" approach takes into account the magnitude of the relative risk (RR) associated with an exposure along with the likelihood of exposure in the general population. These attributable risk estimates include joint contributions of risk factors that sometimes have synergistic relationships. For example, the attributable risk estimate for cigarette smoking includes the lung cancer risk attributed to the independent effects of cigarette smoking and further includes the risk for lung cancer from smoking as a result of its synergistic interactions with factors such as asbestos and radon. For this reason, the total percentage can be $>100\%$. Lung cancer has a well-characterized set of important risk factors and established synergistic interactions between risk factors, and these reasons contribute to the attributable risks summing to considerably more than 100%. As reviewed next, population attributable risk estimates for lung cancer indicate that in the United States, active smoking is responsible for 90% of lung cancer; occupational exposures to carcinogens for approximately 9 to 15%; radon for 10% of lung cancer,[16] and outdoor air pollution for perhaps 1 to 2%.[40] The contribution of nutritional factors cannot yet be precisely determined; consequently, estimates of the role of dietary factors range widely.[41]

Environmental and Occupational Agents

Smoking: A single etiologic agent (cigarette smoking) is by far the leading cause of lung cancer, accounting for approximately 90% of lung cancer cases in the United States and other countries where cigarette smoking is common.[42] Compared with never-smokers, smokers who have smoked without quitting successfully have an approximate 20-fold increase in lung cancer risk. Few exposures to environmental agents convey such risks for any disease. In general, trends of lung cancer occurrence closely reflect patterns of smoking, but rates of occurrence lag smoking rates by approximately 20 years. Analyses using statistical modeling techniques show a tight association between national mortality rates and smoking.[43] The unequivocal role of cigarette smoking in causing lung cancer is one of the most thoroughly documented causal relationships in biomedical research.[6,44]

The burden of lung cancer that is attributable to smoking has been extensively documented. Using an attributable risk approach, the annual number of deaths caused in the United States by smoking-related lung cancer during the period from 1995 to 1999 was 122,800.[19] Peto et al[42] used a different attributable risk method to quantify the burden of smoking-related deaths from lung cancer in the major developed countries. For 1990, the US total was 127,000, the highest in the world, with country-specific estimates ranging down to 150 for Tajikistan. The total for the developed countries was 457,371.[42] A staggering future burden of lung cancer has been forecast for China, where the numbers are predicted to reach several millions by mid-century.[45,46]

Cigar smoking is also an established cause of lung cancer.[47] The lung cancer risks associated with cigar smoking are substantial but less than the risks observed for cigarette smoking as a result of differences in smoking frequency and depth of inhalation. The same pattern holds true for pipe smoking.[48] With respect to smoking of nontobacco products, the potential role of smoking marijuana on lung cancer risk has been of interest. Despite the plausibility of marijuana as a risk factor for lung cancer, the evidence to date has not documented an association after adjusting for tobacco smoking.[49]

The risk for lung cancer among cigarette smokers increases with the duration of smoking and the number of cigarettes smoked per day.[50] This observation has been made repeatedly in cohort and case-control studies. Risk models have been derived to estimate quantitatively how lung cancer risk varies with number of cigarettes smoked, duration of smoking, and age. Such models are useful for estimating the future burden of lung cancer under various

scenarios of tobacco control. In one widely cited analysis, Doll and Peto[50] proposed a quantitative model for lung cancer risk on the basis of data from the cohort study of British physicians. This model predicted a stronger effect of duration of smoking than of amount smoked per day. Thus, a tripling of the number of cigarettes smoked per day was estimated to triple the risk, whereas a tripling of duration of smoking was estimated to increase the risk 100-fold.[51] These quantitative dimensions of the dosage-response relationship between smoking and lung cancer have implications concerning the now widespread smoking among youths. Those who start at younger ages have a greater likelihood of becoming a heavier smoker and remaining a smoker.[52] The exponential effect of duration of smoking on lung cancer risk markedly increases the lifetime risk for those who become regular smokers in childhood and places them at increased risk at younger ages. Prevention approaches that delay the age of onset of smoking in a population could have substantial impact on the incidence of lung cancer by shortening the duration of smoking. In considering the likelihood of lung cancer in a particular patient, clinicians should give more weight to the duration of smoking and less to actual age.

Cigarette smokers can benefit at any age by quitting smoking. The likelihood of lung cancer developing decreases among those who quit smoking as compared with those who continue to smoke.[52] As the period of abstinence from smoking cigarettes increases, the risk for lung cancer decreases.[53] However, even for periods of abstinence of >40 years, the risk for lung cancer among former smokers remains elevated compared with never-smokers.[53,54] The benefits derived from smoking cessation also depend on the duration of smoking; for a given period of abstinence, the decrease in risk increases as the duration of smoking decreases.[53] In general, studies[55] have shown comparable reductions in risk after cessation regardless of sex, type of tobacco smoked, and histologic type of lung cancer.

The benefits of physician (and other clinician) intervention for smoking cessation are well established.[56] The results of research in this area have been translated into an evidence-based clinical practice guideline for treating tobacco dependence on the basis of the "5 A's": *a*sk whether a patient smokes, *a*ssess willingness to quit, *a*dvise to quit, *a*ssist with quitting, and *a*rrange follow-up.[56]

The composition of cigarettes has evolved considerably since the 1950s. The marketplace has shifted from mainly unfiltered cigarettes to predominantly filtered cigarettes. The filters in use in the United States are predominantly cellulose acetate, whereas charcoal filters are used extensively in Japan and some other countries.[57] In the mid-1960s, ventilation holes were added to the filter, which dilute the smoke with air drawn through them. However, smokers can readily block the holes with their fingers, which are left unblocked by the machines that are used to test cigarettes. There have also been substantial changes in the design of the cigarette and in the tobacco used. Reconstituted tobacco has been used increasingly since the 1960s, there have been changes to the cigarette paper and additives used, and most cigarettes are more ammoniated in the United States.[57]

A concomitant shift toward lowered levels of "tar" and nicotine, as measured by a smoking machine, has occurred.[58] Cigarette tar refers to the condensable residue of cigarette smoke (*ie*, the total particulate matter of cigarette smoke deposited on the filter of the machine, less the moisture and nicotine). Tar is a complex mixture that includes many chemicals that are cancer initiators and/or promoters.[58] Tar and nicotine yields are measured with a smoking machine according to a standardized protocol established by the Federal Trade Commission (FTC) that specifies such details and puff volume, the frequency of puffing, and the length to which the cigarette is to be smoked.[59]

Studies[59] using biomarkers of exposure to and dosage of tobacco smoke components show little relationship of levels of these markers with tar or nicotine yield as measured by the FTC protocol. These studies have been conducted in both the population context and during smoking in the laboratory setting. For example, Coultas et al[60] collected saliva for analysis for cotinine level and end-tidal breath samples for measurement of carbon monoxide level in a population sample of New Mexico Hispanic individuals who were included in a respiratory health survey. After taking account of numbers of cigarettes smoked, biomarker levels were not associated with the yields of tar and nicotine of the current brand smoked. Djordjevic et al[61] evaluated smoking pattern and biomarkers in the laboratory setting, contrasting smokers of medium-yield and low-yield cigarettes. The smokers had greater puff volumes and frequencies than are specified in the FTC protocol and had substantially greater intakes of tar and nicotine than implied by the brand listings. The lack of association of tar and nicotine yields with biomarker levels partially reflects compensatory changes in smoking patterns for those who switch from higher to lower yield products. The compensation includes blocking of the ventilation holes, more frequent and deeper puffs, and an increase in the number of cigarettes smoked.[62]

The gradual reduction in machine-measured tar yield would be expected to have reduced smokers'

exposures to carcinogens if the FTC test protocol were predictive of carcinogen dosages delivered to the lung.[58] However, questions remain as to whether the FTC test method is informative with regard to lung cancer risk or risks for smoking-caused diseases more generally.[62,63] Epidemiologic studies have been conducted to assess whether the seemingly substantial changes in tar and nicotine yield, as measured by the FTC protocol, have resulted in parallel changes in the risk of smoking. Epidemiologic studies have been the key source of information because they can provide direct evidence on the risks of smoking cigarettes, as they are actually smoked during use, including any compensatory behavior.

For lung cancer and for other diseases, three lines of epidemiologic data have been available on changes in products. The first comes from case-control studies that compared the smoking history profiles of people with lung cancer with those of control subjects. The second comes from cohort studies that tracked the risk for lung cancer over time, as the products smoked changed. The third comes from assessment of the temporal changes in age-specific patterns of lung cancer mortality rates in comparison with changes in cigarette characteristics.

The initial evidence came primarily from case-control studies that compared risks in people who had used filter-tipped cigarettes with people who had smoked nonfiltered cigarettes exclusively.[64,65] This evidence suggests that filtered cigarettes and cigarettes with lower tar yields slightly reduce the risk for lung cancer associated with cigarette smoking compared with nonfiltered cigarettes or with higher tar yields.[66–68] This comparison could be made among smokers in the 1960s because there was still a substantial proportion who had not used filtered cigarettes at all. For example, in one of the first studies, Bross and Gibson[64] compared lung cancer risk of smokers of filtered and nonfiltered cigarettes among patients who were seen at Roswell Park Memorial Cancer Institute in Buffalo; individuals were classified as filter cigarette smokers when they had used these products for at least 10 years.

The relevant cohort studies are the American Cancer Society CPS I and CPS II studies and the British Physicians Cohort. In a 1976 publication, Hammond et al[69] compared mortality risks from lung cancer and other diseases by tar yield of products smoked by CPS I participants. The follow-up interval spanned from 1960 to 1972. Smokers were placed into three categories of products smoked: low yield (< 17.6 mg per cigarette), high yield (25.8 to 35.7 mg per cigarette), and medium yield (intermediate). The standardized mortality rate for lung cancer in low- and medium-yield smokers was approximately 80% of the rate in high-yield smokers. A further analysis of tar yield using the same data set confirmed that risk for lung cancer death increased with tar yield.[70]

Further insights have been gained by comparing the risks in the two CPS studies of the American Cancer Society; this comparison addresses whether risks have changed, comparing smokers with disease developing from 1960 to 1972 with a similar group of smokers with disease developing during the initial follow-up of CPS II, from 1980 to 1986.[71,72] If the risk for lung cancer associated with smoking is decreasing over time, then the expectation would be that risks for smokers would be less in CPS II than in CPS I. In fact, the opposite was observed, with increasing lung cancer mortality in male and female smokers in CPS II compared with CPS I.[73]

In an analysis with a similar pattern of findings, Doll et al[74] compared the risks for death from lung cancer and other causes during the first and second 20 years of the 40-year follow-up of the British physician cohort. Lung cancer mortality increased among smokers in the second 20 years (from 1971 to 1991), even though products smoked during this period would have had a substantially lower tar and nicotine yield than those smoked during the first 20 years (from 1951 to 1971). For the first 20 years, the annual lung cancer mortality rate among current smokers was 264 per 100,000, and for the second 20 years, it was 314 per 100,000. In 2004, Doll et al[75] reported the findings at 50 years of follow-up; compared with lifelong nonsmokers, the risk for lung cancer was increased fourfold among former smokers and > 14-fold among current smokers. Among current smokers, the RRs increased from 7.7 to 13.7 to 24.5 among smokers of 1 to 14, 15 to 24, and > 25 cigarettes per day, respectively.

The third line of observational evidence comes from descriptive analyses of age-specific trends of lung cancer mortality.[18,62,76] Successive birth cohorts have had differing patterns of exposure to cigarettes of different characteristics and yields. For example, the cohort of individuals who were born between 1930 and 1940 and started to smoke in the 1950s was one of the first to have the opportunity to smoke primarily filter-tipped cigarettes. Subsequent birth cohorts would have had access to the increasingly lower yield products, whereas earlier cohorts had access initially only to nonfiltered cigarettes. Patterns of temporal change in age-specific rates of lung cancer mortality in younger men have been examined to assess whether there has been a decline greater than expected from changing prevalence, duration, and amount of smoking, thereby indicating a possible effect of cigarette yield.

Data on lung cancer mortality in younger men in the United Kingdom have been interpreted as indi-

cating a possible reduction in lung cancer risk associated with changes in cigarettes.[62,76] A sharp decline in lung cancer mortality has occurred across the past few decades in UK men < 50 years of age. The decline seems greater than anticipated from trends in prevalence and other aspects of smoking: age starting and number of cigarettes smoked. A similarly steep decline has not taken place in the United States. Given the ecologic nature of the data under consideration, uncertainty remains with regard to their interpretation, and alternative explanations have been proposed, including less intense smoking at younger ages in more recent birth cohorts.[62]

This discussion highlights the complexity of isolating the precise effect on lung cancer risk of the continually changing cigarette. The data available to evaluate these effects have limitations, particularly in capturing the experience of successive birth cohorts in either case-control or cohort studies that were appropriately designed. The UK mortality data suggest a greater effect of changes in cigarettes than is found in the case-control and cohort studies. As recommended by the Institute of Medicine,[77] surveillance is needed to track the health consequences of the changing cigarette.

Several expert panels have reviewed the findings. The Institute of Medicine[77] conducted a comprehensive review on various harm reduction strategies for reducing the disease burden caused by smoking, including lower yield cigarettes. There are also new products in various phases of development that are intended to deliver nicotine without direct combustion of tobacco. The Institute of Medicine report concluded that smoking lower-yield products had not been shown to benefit the health of smokers. This topic was addressed in the 2004 report of the US Surgeon General,[19] with the conclusion that "although characteristics of cigarettes have changed during the last 50 years and yields of tar and nicotine have declined substantially, as assessed by the Federal Trade Commission's test protocol, the risk of lung cancer in smokers has not declined."

Results of some case-control and screening studies have suggested a potentially higher risk for smoking-associated lung cancer in women compared with men,[78–80] but methodologic issues cloud the interpretation of these studies, particularly a lack of focus on the most informative comparisons.[81] Furthermore, the evidence from prospective cohort studies fails to support the notion of a sex differential in susceptibility to lung cancer from smoking.[82] The equal rates of lung cancer mortality in younger US men and women corresponding to a time of equal smoking prevalence also provides evidence against an important sex difference in susceptibility to smoking-induced lung cancer.[22] The evidence against this hypothesis outweighs the evidence in favor of the hypothesis on the basis that the results of studies that have compared the RR estimates for men and women for a specific degree of smoking history demonstrate very similar associations.[82]

The development of menthol cigarettes was targeted specifically at African-Americans and women.[83,84] African-Americans are more likely than white individuals (69 vs 29%) to smoke menthol cigarettes,[85] and the menthol smoke delivery levels of common cigarette brands have increased significantly since the 1980's.[86,87] This has led to the hypothesis that menthol cigarettes explain the greater susceptibility to lung cancer from cigarette smoking in black vs white individuals[24] and thus the disparity in lung cancer risk between US black and white individuals, especially among men.

Menthol cigarettes may cause a greater increase in lung cancer risk than nonmenthol cigarettes, either by increasing systemic exposure to toxicants from tobacco smoke or by affecting the metabolism of nicotine and/or tobacco smoke carcinogens. Initially, this hypothesis gained currency because of the potential for increased nicotine uptake through the effects of menthol in the respiratory tract. These include an increase in the smoothness of tobacco smoke, which promotes deeper inhalation; stimulation of cold receptors, which results in airway cooling effects that mask the irritation caused by cigarette smoke, promoting deeper inhalation and altered inhalation frequency; further masking of irritation through anesthetic effects[86,88]; and increased permeability and diffusibility of smoke constituents.[87]

There is limited information on the molecular mechanisms by which mentholation might increase the health risk of smoking. Seventy to 80% of nicotine is metabolized to cotinine, and cytochrome P450 2A6 is responsible for 90% of this conversion.[89] The P450 2A6 gene has multiple functional polymorphisms that vary by race. The observation that menthol competitively inhibits cotinine metabolism by the monkey analog of a human UDP-glucuronyltransferase[90] suggested that inhibition of either CYP2A6 or UDP-glucuronyltransferase by menthol might alter nicotine and cotinine metabolism. African-American and white menthol smokers have similar baseline cotinine levels.[91] Human studies[89,91–93] have suggested that smoking mentholated cigarettes inhibits nicotine metabolism, so smokers experience higher dosages of nicotine for a given level of smoking. Menthol inhibits the microsomal oxidation of nicotine to cotinine,[92] suggesting that smoking mentholated cigarettes may lead to inhibition of nicotine metabolism. In a randomized, crossover study of seven African-American and seven white individuals, Benowitz et al[93] found that the systemic intake of

nicotine was not affected by mentholation, but smoking mentholated cigarettes inhibited the metabolism of nicotine. By slowing the metabolism of nicotine and thereby reducing the need for nicotine from smoking, menthol may reduce the number of cigarettes smoked per day. A menthol effect might explain why African-American individuals smoke fewer cigarettes per day than white individuals. It may also explain, in part, the variation by race and gender in the correlation between cotinine level and cigarettes smoked per day among smokers of menthol cigarettes,[94] possibly reflecting the effect of menthol on nicotine inactivation by P450 2A6.[89]

However, the epidemiologic data suggest that, overall, smokers of mentholated cigarettes do not have an increased risk for lung cancer compared with smokers of nonmentholated cigarettes. This evidence is based primarily on hospital-based case-control studies,[95–98] but also includes a population-based case-control study[99] and a cohort study within a health maintenance organization.[100] Furthermore, menthol cigarettes have not been associated with any specific histologic subtypes of lung cancer.[101]

Evidence that menthol cigarettes might carry greater risks were observed in one case-control study[97] in which black, male, heavy smokers of mentholated cigarettes (> 37.5 pack-years, or ≥ 21 cigarettes per day) had a higher risk than white men with similar smoking histories. In the cohort study,[100] the RR for lung cancer among men but not women was slightly elevated in menthol smokers compared with nonmenthol smokers, with a graded increase in lung cancer risk with increasing duration of menthol cigarette use.

The evidence does not indicate that menthol cigarettes are an important contributor to the high rates of lung cancer in African-American individuals. A more definitive answer to this question will emerge if future studies address several methodologic challenges, including misclassification of menthol cigarette exposure as a result of brand ambiguity; potential for selection bias in hospital-based case-control studies, as a result of lower prevalence of menthol cigarette use among African-American patients at university hospitals used for such studies than in the general population; and lack of information about compensatory mechanisms.[102]

Passive smokers inhale a complex mixture of smoke now widely referred to as secondhand smoke or as environmental tobacco smoke (ETS). Passive smoking was first considered as a possible risk factor for lung cancer in 1981, when two studies that described increased lung cancer risk among never-smoking women who were married to smokers were published. Hirayama[103] reported the findings from a cohort study in Japan that showed that among nonsmoking women, those with a husband who smoked cigarettes were at higher risk for lung cancer than those whose husband was a nonsmoker. A case-control study in Athens reported by Trichopolous et al[104] shortly thereafter replicated this finding. Additional evidence rapidly accrued, such that by 1986 two important summary reports were published. The National Research Council reviewed the epidemiologic evidence and concluded that nonsmoking spouses who were married to cigarette smokers were approximately 30% more likely to have lung cancer develop than nonsmoking spouses married to nonsmokers and that this relationship was biologically plausible.[105] Almost one fourth of lung cancer cases among never-smokers were estimated to be attributed to exposure to passive smoking.[105] The 1986 Surgeon General report also judged passive smoking to be a cause of lung cancer,[13] an inference corroborated by the 1992 review of the evidence and risk assessment by the US Environmental Protection Agency, which classified ETS as a known human (class A) carcinogen.[14] Estimates indicate that passive smoking accounts for approximately 3,000 lung cancer deaths per year in the United States.[14] Since these conclusions were reached, several major studies[106,107] have been conducted to characterize further the association of passive smoking with lung cancer, while taking into account some of the limitations of earlier studies, particularly small sample sizes, exposure misclassification, and omission of some potential confounding factors.

Passive smoking is more weakly associated with lung cancer than is active smoking, as expected given the generally lower dosages of carcinogens that are passively received by the lung of the nonsmoker compared with the dosages received by the active smoker. Because of broad societal implications, the conclusion that this association is causal has generated controversy, some driven by the effort of the tobacco industry to maintain continued questioning of the evidence.[108,109] Questions have been raised about the method of the epidemiologic studies, including confounding and misclassification of exposure to environmental tobacco smoking. Review groups[13,14,106,110] have nonetheless concluded that the association between ETS and lung cancer cannot be attributed to methodologic limitations of epidemiologic data.

Studies have been directed at the specific venues where nonsmokers are exposed to tobacco smoke, including the home, workplaces, and public places. Much of the literature has focused on the increased risk associated with being married to a smoker, an exposure variable that can be readily ascertained. Metaanalyses have been conducted periodically to

summarize the evidence from the epidemiologic studies. A 2002 metaanalysis by Boffetta[111] found a 25% increased risk associated with marriage to a smoker; this excess risk seemed to be due to exposure to passive smoking because it could not be explained by confounding or misclassification. This finding was consistent with the 29% estimated increased risk among women whose husband smoked in the metaanalysis of Taylor et al,[112] who observed that the association was consistent across study designs and in Western and non-Western nations. Workplace exposure to secondhand smoke was associated with a 17% increase in lung cancer risk in the metaanalysis of Boffetta.[111]

The studies of passive smoking provide further evidence documenting the dosage/response relationship between cigarette smoke and lung cancer. The dosages extend to far lower levels than those of active smoking and increased risk is observed, suggesting that there is no threshold for tobacco carcinogenesis.[13]

Lung cancer occurs in multiple histologic types as classified by conventional light microscopy. The four major types include squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell undifferentiated carcinoma; together, these four types of lung cancer account for $>90\%$ of lung cancer cases in the United States.[113] Notable shifts have taken place in the incidence rates of lung cancer by histologic type.[114] After steadily increasing occurrence during the period from 1973 to 1987, adenocarcinoma supplanted squamous cell carcinoma as the most frequent form of lung cancer.[114] Adenocarcinoma increased markedly in all race and sex subgroups.[114]

Despite extensive research, the mechanisms that lead to these different types of lung cancer remain uncertain. Hypotheses have focused on the cells of origin of lung cancers and on pathways of differentiation of malignant cells.[113] An area of active interest is characterizing the likelihood that dysplastic lesions that are detected by fluorescence bronchoscopy will progress to invasive cancer[115] and relating the distribution of these lesions *vis a vis* the distribution of invasive lung cancer tumors on the basis of epidemiologic findings. CT scans are generally being used to identify peripheral lesions (usually adenocarcinoma), whereas fluorescence bronchoscopy is being used for the detection of central airway lesions, predominantly preinvasive squamous cell carcinoma. Smoking has been shown to cause each of the major histologic types, although the dose/response relationship with number of cigarettes smoked varies across the types, being steepest for small cell undifferentiated carcinoma.[115,116] There are a few suggestive links of histologic type with occupational agents: small cell lung cancer has been reported to be in excess in workers who are exposed to chloromethyl ethers and in underground miners who are exposed to radon progeny.[113]

In the initial decades of the smoking-caused epidemic of lung cancer, squamous cell carcinoma was the most frequent type of lung cancer observed in the population, and small cell carcinoma was the next most frequent. In the late 1970s, the first evidence of a shift toward a predominance of adenocarcinoma was noted,[113,117,118] and now adenocarcinoma of the lung is the most common histologic type.[112] The decline in lung cancer rates has been more rapid for squamous cell and small cell carcinomas than for adenocarcinoma, which is just beginning to show a lower incidence rate.[114] In women, the Surveillance, Epidemiology, and End Results[4] data from 1973 to 1996 indicated that the incidence rates of squamous cell, small cell, and large cell carcinomas at least reached a plateau, whereas the rate for adenocarcinoma were still rising.

Although changing patterns of diagnosis and classification of lung cancers could have led to these changes over time, most observers have set aside an artifactual change.[113,117,118] Beginning in the 1970s, new techniques for the diagnosis of lung cancer became available, including the fiberoptic bronchoscope and thin-needle aspiration[119]; improved stains for mucin, the hallmark of adenocarcinoma, were also introduced. Using data from the Connecticut Tumor Registry, Thun et al[119] showed that the rise in adenocarcinoma antedated these diagnostic innovations.

Hypotheses concerning the shift in histopathology have focused on the potential role of changes in the characteristics of cigarettes and consequent changes in the dosages of carcinogens inhaled.[120] Puff volume has likely increased in the past few decades with the possibility that patterns of deposition in the lung have changed, tending toward enhanced deposition of tobacco smoke in the peripheral airways and alveoli.[120] Nitrate levels in tobacco smoke have also increased, which enhances the combustion of tobacco smoke. Although more complete combustion decreases the concentrations of polycyclic aromatic hydrocarbons, the increased production of nitrogen oxides contributes to increased formation of tobacco-specific nitrosamines. An increase in dosage of the potent tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone has been postulated as one factor leading to the increase in adenocarcinoma.[120,121] Nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone induces lung carcinomas, predominantly adenomas and adenocarcinomas, in mice, regardless of route of administration.[121,122]

Few studies can provide data to test these hypoth-

eses because of the need for longitudinal observation of lung cancer risk in relation to the characteristics of the cigarettes smoked over time. Thun et al[119] compared risks for lung cancers of the various histologic types among participants in the American Cancer Society CPS I and CPS II. They found markedly rising risks associated with smoking for adenocarcinoma of the lung in both men and women during the approximate 20 years separating the two studies. Thun et al[119] concluded, "The increase in lung adenocarcinoma since the 1950s is more consistent with changes in smoking behavior and cigarette design than with diagnostic advances." In a study[123] that compared tumor location in lung cancer patients, lower-tar cigarettes were associated with a higher likelihood of peripheral than central tumors.

Diet: Research on diet and lung cancer has now been conducted for nearly 3 decades. The possible role of diet in modifying the risk for lung cancer has been the focus of intensive investigation, driven initially by the rationale that specific micronutrients might have anticarcinogenic activity. The most thoroughly investigated dietary factors are also those that seem to have the greatest implications for prevention: fruits, vegetables, and specific antioxidant micronutrients that are commonly found in fruits and vegetables. Much of the research on diet and lung cancer has been motivated by the hypothesis that diets that are high in antioxidant nutrients may reduce oxidative DNA damage and thereby protect against cancer.[124]

The results of case-control and prospective cohort studies have tended to show that individuals with high dietary intake of fruits or vegetables have a lower risk for lung cancer than those with low fruit or vegetable intake.[125] Evidence from cohort studies[126–130] published since 2000 has tended to reinforce this notion. In the European Prospective Investigation Into Cancer and Nutrition Study,[131] a strong protective association was observed with fruit but not vegetable consumption. A stronger protective association was observed for fruit than vegetable consumption in a pooled analysis of seven cohort studies.[132]

To better understand the basis of this protective association, fruits and vegetables have been grouped into classes and also examined individually in relation to lung cancer risk. For example, tomatoes[133–135] and cruciferous vegetables[129,135] have been associated with a reduced risk for lung cancer in a number of studies, at least for the highest vs lowest categories of consumption. These food-based analyses can help to clarify whether protection against lung cancer is conferred by the complex mixture contained in fruits and vegetables or by the presence of specific biochemical constituents in particular fruits and vegetables.

Fruits and vegetables are the major dietary source of antioxidant micronutrients. Two different strategies are used to evaluate the relationship of micronutrients to lung cancer risk in observational epidemiologic studies: (1) using data summarized from food-frequency questionnaires to estimate micronutrient intake, and (2) drawing blood samples from study participants and assaying the concentrations of micronutrients in circulation. The former approach provides a better average measure of micronutrient exposure, whereas the latter approach has the advantage of measuring micronutrient concentrations closer to the cellular level, where the postulated biological effect occurs. The differences in measurement approaches may lead to different results in certain situations. A metaanalysis[136] of selenium and lung cancer found that selenium intake as measured by questionnaire showed no association (RR, 1.0; 95% confidence limit [CL], 0.8, 1.3), whereas associations in the protective direction were observed for selenium concentrations measured in toenails (RR, 0.5; 95% CL, 0.2, 0.9) or serum (RR, 0.8; 95% CL, 0.6, 1.1).

Studies of both dietary intake[137–140] and prediagnostic blood concentrations[141,142] suggested a protective association between carotenoids and lung cancer. The evidence for vitamin C is scant but suggestive of a protective association, whereas the data on vitamin A has yielded null findings.[143] Reports from cohort studies have tended to reinforce the previous findings of protective associations with intake of a variety of carotenoids[128,135,144] or an antioxidant index.[140] However, a pooled analysis[139] of seven cohort studies did not find strong protective associations with any carotenoids other than β-cryptoxanthin.

More recently, studies have examined phytochemicals such as flavonoids and isothiocyanates in relation to lung cancer risk. Phytochemicals are low-molecular-weight molecules produced by plants. Of the many classes of phytochemicals, those studied in relation to lung cancer include phytoestrogens, flavonoids, and glucosinoids. The tumor-promoting effects of steroid hormones can be blocked by phytoestrogens. Soya beans are a primary source of a specific class of phytoestrogens known as isoflavonoids. Flavonoids exhibit potent antioxidant activity. Flavonoid intake has been at least weakly associated with lung cancer in some of the preliminary studies[145,146] of this topic. Isothiocyanates are metabolites of the class of phytochemicals known as glucosinolates. Isothiocyanates could exert anticancer effects by blocking carcinogens via induction of

phase 2 detoxification enzymes, such as glutathione S-transferase. Cruciferous vegetables contain high concentrations of glucosinolates; therefore, consumption leads to higher endogenous isothiocyanate concentrations. As with cruciferous vegetables,[147] lung cancer risk is consistently lower with higher intakes or urinary levels of isothiocyanates.[148–150] When isothiocyanates have been studied in combination with a common polymorphism in the GSTM1 gene, the decreased risk for lung cancer associated with isothiocyanates has been especially pronounced in people with the GSTM1 null genotype.[148–150] This provides an example of a potential gene/diet interaction that may be relevant to lung carcinogenesis.

Studies of fruits, vegetables, and micronutrients have been the centerpiece of studies of diet and lung cancer, but a wide range of dietary and anthropometric factors have been investigated. For example, the results of a metaanalysis[151] showed that alcohol drinking in the highest consumption categories was associated with increased risk for lung cancer. Anthropometric measures have also been studied, indicating a tendency for people with lower body mass index (BMI) to have increased lung cancer risk relative to heavier people.[152,153] However, effects of both alcohol drinking and low BMI may be difficult to separate from the concomitant effects of smoking. When considering the possible relationships between lung cancer and factors such as alcohol drinking and lower BMI, cigarette smoking cannot be dismissed as a possible explanation.

The overwhelming contribution of cigarette smoking as a cause of lung cancer poses a challenge to detecting the role that other lifestyle factors, such as diet, may play in the cause of lung cancer. Cigarette smoking is now so closely associated with less healthful lifestyles in the United States and some other countries, such as less healthful diets,[154] that it is often difficult to disentangle the dietary factor(s) of interest from the effects of smoking. Cigarette smoke can directly affect circulating concentrations of dietary factors; for example, smokers tend to have lower circulating concentrations of antioxidant micronutrients even after accounting for differences in dietary intake.[154] In addition, associations between dietary factors and lung cancer risk are likely to be far weaker than the association with active smoking, and diet is measured with much greater error in general than is smoking. Even for a dietary factor, such as vegetable consumption, which is fairly consistently associated with a lower risk for lung cancer, the highest exposure category is typically associated with at most a halving in the risk for lung cancer. Therefore, in interpreting the evidence, residual confounding cannot be readily set aside as an explanation for the observed associations between dietary factors and lung cancer.[155]

Chemoprevention Trials: The experimental rationale for trials of beta carotene and retinoids is offered in another article in this *Supplement* ("Lung Cancer Chemoprevention" by Gray et al). Experimental data indicated a potential for prevention with these agents; observational data were supportive of the hypothesis that beta-carotene and retinoids might have chemopreventive activity.[124] However, a protective association between beta-carotene and lung cancer was not found in three randomized, double-blind, placebo-controlled chemoprevention trials[156–158] of beta-carotene reported during the 1990s. In fact, beta-carotene supplementation was associated with an increased risk for lung cancer among the high-risk populations of heavy smokers in the α-Tocopherol β-Carotene Cancer Prevention Study,[156] and smokers and asbestos-exposed workers in the Carotene and Retinol Efficacy Trial.[158]

In summary, observational evidence suggests that smokers who eat more vegetables are at lower risk for lung cancer than those who consume fewer vegetables. The evidence is not as consistent for fruit consumption. The specific constituents of vegetables that confer protection are not known. The results of the chemoprevention trials clearly suggest a more complex role for micronutrients than previously proposed.

Physical Activity: Several studies[159–161] have reported that more physically active individuals have a lower risk for lung cancer than those who are more sedentary, even after adjustment for cigarette smoking. As with the assessment of any lifestyle factor other than smoking with lung cancer risk, potential residual confounding by cigarette smoking needs to be considered as an alternative explanation.

Occupational Exposures: Investigations of occupational groups, often heavily exposed over a long time to workplace agents, have provided substantial understanding of the carcinogenicity of a number of chemicals and physical agents. Among cancers that are associated with occupational exposures, cancer of the lung is the most common.[162] Estimates derived from case-control studies[163–169] of the proportion of lung cancer that is contributed to by occupational exposures, via independent or shared causal pathways, have ranged widely, but most point estimates or ranges have included values from 9 to 15%. Although disagreement persists concerning specific estimates,[170] the message is clear: in industrialized nations, the contribution of occupational exposures

to the lung cancer burden is small compared with that of cigarette smoking, but large compared with contributions of most other exposure classes. Cigarette smoking potentiates the effect of some known occupational lung carcinogens.[40]

Lung cancer has been observed to be associated with many workplace exposures. Workers who are exposed to tar and soot (which contains benzo[a]pyrene), such as coke oven workers,[171,172] in concentrations that exceed those present in urban air[173] are at increased risk for lung cancer. Occupational exposures to a number of metals, including arsenic, chromium, and nickel, are also causes of lung cancer.[174] For many of the worker groups exposed to these agents, there were substantial increments in risk. However, in developed countries, these hazards have largely been controlled.

For some other workplace agents, the evidence has been less clear. The results of numerous case-control and cohort studies are compatible with a weak association between exposure to diesel exhaust and the development of lung cancer.[175] Although inadequate control of cigarette smoking limits the inferences that can be drawn from many of these studies, exposure to diesel exhaust remains a likely explanation for these findings.[175] This association remains a public health concern because the public is exposed to diesel exhaust in urban areas, and in some European countries diesel vehicles are increasingly used.[41]

The question of whether silica dust is a risk factor for lung cancer has been controversial.[176–178] A twofold increase in lung cancer risk was estimated from a metaanalysis[179] of the relationship between silicosis and lung cancer mortality. Effects of smoking were not well controlled in most of the studies.[179] The evidence on silica exposure, absent consideration of the presence of silicosis, is less clear.[180,181] In 1997, the IARC did classify crystalline silica as a human carcinogen[182]; however, some still continue to question its carcinogenicity[181] and the role of silica exposure vs that of fibrosis in people with silicosis.[180]

Asbestos: Asbestos, a well-established occupational carcinogen, refers to several forms of fibrous, naturally occurring silicate minerals.[183] The epidemiologic evidence dates to the 1950s, although clinical case series had previously led to the hypothesis that asbestos causes lung cancer.[184,185] In a retrospective cohort study published in 1955, Doll[186] observed that asbestos textile workers at a factory in the United Kingdom had a 10-fold elevation in lung cancer risk and that the risk was most heavily concentrated during the time frame before regulations were implemented to limit asbestos dust in factories. A sevenfold excess of lung cancer was subsequently observed among insulation workers in the United States.[187,188] The risk for lung cancer has been noted to increase with increased exposure to asbestos[189] and to be associated with the principal commercial forms of asbestos.[190] Whether asbestos acts directly as a carcinogen or through indirect mechanisms, such as causing chronic inflammation that eventually leads to cancer development, remains uncertain.[191,192]

Asbestos and cigarette smoking both are independent causes of lung cancer, but in combination they act synergistically to increase the risk for lung cancer in a manner that is compatible with a multiplicative effect.[193] Cigarette smoking may increase the lung cancer risk associated with asbestos exposure by enhancing retention of asbestos fibers.[194]

Radiation: Epidemiologic studies of populations that were exposed to high doses of radiation showed that lung cancer is one of the cancers associated with exposure to ionizing radiation.[195] However, the risks for low-dose radiation, more relevant to contemporary workers and the general population, have proved difficult to characterize.[195] Assessing the cancer risk that is associated with low-dose radiation among humans is methodologically difficult because the signal-to-noise ratio is highly unfavorable.[196] Nevertheless, large cohort studies,[16,197,198] particularly the study of Japanese atomic bomb survivors, have provided understanding of the risks of low-dose ionizing radiation.

The following two types of radiation, classified by rate of energy transfer to the tissue, are relevant to lung cancer: low linear energy transfer (LET) radiation (*eg*, x-rays, gamma rays) and high-LET radiation (*eg*, neutrons, radon). High-LET radiation produces ionization of relatively higher density in tissues than low-LET radiation, so in equivalent doses, more biological damage is produced by high-LET than low-LET radiation.[199] For both types of radiation, the majority of the epidemiologic evidence comes from cohorts that were exposed at levels substantially greater than those experienced by the general population. Risk assessment methods are then used to estimate risks to the population.

Radon is an inert gas that is produced naturally from radium in the decay series of uranium. Two of the decay products of radon emit α particles that, by virtue of their high energy and mass, can cause damage to the DNA of cells of the respiratory epithelium. Epidemiologic studies[200,201] of underground miners of uranium and other ores have established exposure to radon daughters as a cause of lung cancer. In the miners who were exposed to radon in past centuries, very high lung cancer risks were observed; these fell for more recent workers, but the epidemiologic studies[16] still show clear evi-

dence of existing cancer risk. Cigarette smoking and radon decay products synergistically influence lung cancer risk in a manner that is supraadditive but submultiplicative.[16,201]

Radon is of broader societal interest because it is a ubiquitous indoor air pollutant that enters buildings in soil gas. On average, indoor exposures to radon for the general population are much less than those received by occupational groups such as uranium miners. For example, even the lowest historical radon concentration in a uranium mine is roughly 50 to 100 times higher than in the average home.[201] Exposure to radon in indoor air is also assumed to cause lung cancer, but the magnitude of the risk is uncertain because of the assumptions underlying the extrapolation of findings from uranium miners to the generally lower exposures indoors. These assumptions relate to dose, dose rate, and dosimetry and also reflect the lack of information on risks of exposures of women and children. Strengthening biological evidence supports the assumption that a single hit to a cell by an α particle causes permanent cellular change, an assumption that leads to a nonthreshold dose/response relationship.

The assumptions made by the Environmental Protection Agency and the Biological Effects of Ionizing Radiation IV and VI Committees of the National Research Council led to estimates that approximately 15,000 to 20,000 lung cancer deaths per year in the United States are caused by radon.[202] Case-control studies[203,204] concerning indoor exposure to radon as a risk factor for lung cancer, undertaken to assess risks directly, have produced findings that are generally consistent with downward extrapolation of risk models based on the underground miners. This coherence lends support to using extrapolation of the miner data to estimate the risk of indoor radon.

Epidemiologic data relating low-LET radiation to lung cancer stem from three principal populations: the atomic bomb survivors in Japan,[205] patients with diseases such as ankylosing spondylitis[206] or tuberculosis[207,208] who received multiple radiation treatments, and occupational groups in professions that expose workers to radiation.[209] The single, high-dose exposure of the atomic bomb survivors was associated with significant lung cancer risk.[205] Regardless of their age when the atomic bombs were dropped, the excess of lung cancer did not occur until the survivors reached older ages, when cancer usually occurs,[205] and a consideration of radiation and smoking together suggests an additional relationship.[198]

The risks associated with exposure to lower doses of low-LET radiation have been estimated in two ways. Statistical models have been used to extrapolate from the atomic bomb survivor's data to lower doses. Patients who had tuberculosis and received radiation therapy have also been studied; they were intermittently exposed to radiation. Such intermittent, low-dose exposures may be most pertinent for the general population because this exposure pattern is the most common in technologically advanced societies. Studies of patients with tuberculosis suggest that if any risk for lung cancer is associated with this exposure pattern, then it is small,[207,208] suggesting that the assumptions on which the higher risk estimates that were obtained from the data of atomic bomb survivors may in actual fact not hold.[208]

Low-LET radiation therefore seems to be associated with higher lung cancer risk when exposure occurs at a higher dose rate.[208] These results contrast with those for high-LET radiation, suggesting that the two types of radiation have different dose-rate relationships.[208]

Air Pollution: During a typical day, the average adult inhales approximately 10,000 L of air.[210] Consequently, even the carcinogens that are present in the air at low concentrations are of concern as a risk factor for lung cancer. Extrapolation of the risks associated with occupational exposures to the lower concentration of carcinogens in polluted ambient air leads to the conclusion that a small proportion of lung cancer cases could be due to air pollution.[162,211]

Carcinogens that are generated by combustion of fossil fuels include polycyclic aromatic hydrocarbons and metals such as arsenic, nickel, and chromium.[174] In considering respiratory carcinogenesis, the constituents of "air pollution" will vary by locale and over time depending on the pollution sources.[212] Consequently, epidemiologic investigations of air pollution and lung cancer have been limited by the difficulty of estimating exposure. Nevertheless, descriptive evidence is consistent with a role for air pollution in causing lung cancer. Urbanization and lung cancer mortality are linked.[213–215] This association could arise from differences in the distributions of other lung cancer risk factors, such as smoking and occupational exposures, by degree of urbanization. Adjustment for these factors may considerably attenuate the effect of urban location,[216,217] but an urban effect persists in a number of studies.[40]

Air pollution has been assessed as a risk factor for lung cancer in both case-control and cohort studies. Whereas early evidence from case-control and cohort studies was found wanting, more recently the evidence supports a causal role for air pollution.[218]

Two prospective cohort studies[219,220] that partially addressed weaknesses of earlier studies add evidence that suggests air pollution is weakly associated with the risk for lung cancer. By prospectively studying air pollution levels in relation to risk for lung cancer and

by controlling for possible confounders such as age, smoking, and socioeconomic status at the individual level, these studies surmount some shortcomings noted of much previous research.[221] In a study of six US cities,[219] the adjusted risk for lung cancer mortality in the city with the highest concentration of fine particles was 1.4 times (95% confidence interval [CI], 0.8 to 2.4) higher than in the least polluted city. Using data from the American Cancer Society CPS II, Pope et al[220] observed that compared with the least polluted areas, residence in areas with high sulfate concentrations was associated with an increased risk for lung cancer (adjusted RR, 1.4; 95% CI, 1.1 to 1.7) after adjustment for occupational exposures and the factors mentioned previously. However, unlike in the Six-Cities Study,[222] fine-particulate concentration was not associated with lung cancer risk. In a subsequent update, follow-up was extended to 1998. In that report, the risk for lung cancer was observed to increase 14% for each 10-$\mu g/m^3$ increase in concentration of fine particles.

By contrast, in the American Cancer Society CPS I cohort, air pollution was not associated with lung cancer risk; in that study, men were stratified according to exposures in the workplace, but exposure assessment for air pollution was based on proxy, less specific measures of air pollution.[221] Some case-control studies[223–225] have reported indexes of air pollution to be modestly associated with elevated risks for lung cancer, but others[226] have reported no association.

Another research approach to evaluate the risk of air pollution has been to investigate populations that reside around point sources of pollution, such as factories and smelters. Proximity of residence to the pollution source can be used as a proxy for exposure. Many industries have been studied using this approach. Areas surrounding nonferrous smelters, which emit arsenic, have been of particular interest. An ecologic study reported by Blot and Fraumeni[35] in 1975 suggested that excess lung cancer occurred in US counties with copper, lead, or zinc smelting and refining industries. The results of several subsequent case-control studies[227–229] lend support to this hypothesis by showing that the risk for lung cancer increased the nearer that people lived to nonferrous smelters, after accounting for personal cigarette smoking and employment at the smelter. Other case-control studies[230,231] did not replicate this finding but were also limited by their failure to account for smoking and employment at the smelter.

Doll and Peto,[162] in their 1981 review of the causes of cancer, estimated that perhaps 1 to 2% of lung cancer was related to air pollution. Even in light of more recent findings, this seems to remain a reasonable estimate.[232] The body of evidence linking air pollution to lung cancer is solidifying,[218] but the public health impact of this exposure is small relative to cigarette smoking, at least in developed country settings where research has been conducted. This is to be expected, given that respiratory doses of carcinogens from active smoking are significantly greater than those received from the inhalation of atmospheric contaminants.

An individual's total exposure to air pollution depends on indoor as well as outdoor exposures. Indoor air quality has large potential health implications because people may spend substantial amounts of time indoors. Indoor air pollution may stem from incoming outdoor air or originate indoors from tobacco smoking, building materials, soil gases, household products, and combustion from heating and cooking.[233] A trade-off exists between energy efficiency and indoor air quality because ventilation allows heated/cooled air to escape but improves indoor air quality.[234]

As discussed, in more developed countries, two of the most important indoor pollutants that most strongly increase lung cancer risk in never-smokers are passive smoking[13] and radon.[202] Asbestos exposure may pose a risk to building occupants, but concentrations are generally very low.[183] Of major concern in the developing world is the indoor air contamination resulting from the use of unprocessed solid fuels, notably coal, for cooking and space heating.[235] Mumford et al[236] inferred that smoky coal was likely to be a major determinant of the geographic distribution of lung cancer in Xuan Wei, China, a finding corroborated by an animal model.[237] Evidence supporting a causal association was strengthened by the results of a retrospective cohort study that showed that switching from use of unvented fire pits to stoves with chimneys almost halved the risk for lung cancer.[238]

Host Factors: Genetic susceptibility to lung cancer has long been postulated. Environmental agents, even cigarette smoking, cause lung cancer in only a minority of exposed people, leading to the hypothesis that susceptibility is inherently determined. Epidemiologic studies[244] showing that a family history of lung cancer predicts increased risk further support a genetic basis for lung cancer susceptibility. This long-postulated hypothesis is now being actively addressed using the approach of molecular epidemiology. Full coverage of this topic is beyond the scope of this report; aspects of genetic susceptibility for lung cancer have been reviewed.[239–243]

Familial aggregation of lung cancer has been primarily demonstrated in both case-control and cohort studies.[244] In these studies, a family history of lung cancer tended to be associated with increased

risk for lung cancer; most of the studies controlled for smoking, which is known to aggregate in families. In a large study in Louisiana, segregation analysis suggested that lung cancer inheritance was consistent with a Mendelian codominant autosomal gene determining early onset of disease.[245] Conversely, the largest study of lung cancer in twins reported to date did not provide evidence indicating a genetic basis for susceptibility.[246] Follow-up of 15,924 male twin pairs in the United States did not show greater concordance in monozygotic compared with dizygotic twins, and death rates from lung cancer were similar by zygosity group in surviving twins whose sibling died of lung cancer. The results of a linkage analysis based on 52 extended pedigrees indicated that a locus on chromosome 6q23–25 was associated with a major susceptibility to lung cancer.[247]

In a genetic epidemiology study of lung cancer in nonsmokers in Detroit, Schwartz et al[248] explored familial risk for lung cancer and found an association between risk and a history of lung cancer in a first-degree relative (odds ratio, 1.4; 95% CI, 0.8 to 2.5). The association was much stronger in those aged 40 to 59 years at diagnosis compared with older people. This pattern of risk with age suggests that genetic factors may be more important at younger ages. This general finding was confirmed by a subsequent, complex segregation analysis of the same data.[249]

Research Findings on the Genetic Basis of Lung Cancer: With application of the new and powerful tools of modern molecular and cell biology, research findings are now characterizing the changes in cells that are caused by exposure to tobacco smoke and providing a framework for understanding the genetic and epigenetic basis of lung cancer risk. Figure 3, proposed by Hecht,[121] offers a general schema for the process of carcinogenesis by tobacco smoking. Viewed in the framework set by this type of model, research findings mirror the predictions of the multistage model in many respects and are enhancing understanding of the mechanisms by which smoking causes cancers of the lung and other organs. A rapidly expanding literature addresses dosimetry and metabolism of tobacco carcinogens at the cellular and molecular levels, genetic determinants of susceptibility, and patterns of genetic changes in the tissues of smokers and in the cancers that the tissues develop.[121,241] Much of the research conducted to date has been based in case-control studies that compared the genotypes of lung cancer cases with those of control subjects. Studies have also been conducted using cohort designs with affected and nonaffected people sampled from the cohort and biological samples analyzed for the markers of interest.

The understanding of the epigenetic changes that may be involved in the causal pathway to lung cancer is advancing rapidly. For example, there is increasing evidence that methylation of cytosine in the DNA, leading to hypermethylation of promoter regions, is frequent in most types of cancers, including lung cancer.[250] Promoter regions of many human genes have loci rich in CpG dinucleotides, regions referred as *CpG islands*.[250,251] Hypermethylation of the CpG islands can be detected by polymerase chain reaction methods. Cells with abnormal methylation of genes have been detected in sputum before the diagnosis of lung cancer, suggesting that hypermethylation could be a useful marker for early detection.[252,253]

In a general formulation of determinants of cancer risk, the risk depends on carcinogen exposure and the factors that determine host susceptibility, including genetic predisposition.[254] For tobacco smoking and lung and other cancers, the elements of this paradigm all are topics of inquiry, using the combination of laboratory- and population-based studies indicated in the diagram. Biomarkers are central to the molecular epidemiology approach; the term refers to making measurements of indicators of exposure and dose, susceptibility, and response in biological materials, including tissue samples, blood, urine, and saliva.[255] As research evolves within this paradigm, a more complete biological understanding of the specific events underlying the multistage model, originally proposed on a conceptual basis, can be anticipated.

This framework indicates multiple points where genetically determined host characteristics might be important: carcinogen metabolism and activation,

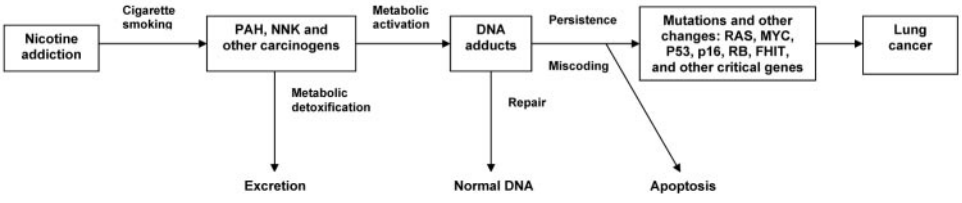

FIGURE 3. Scheme linking nicotine addiction and lung cancer via tobacco smoke carcinogens and their induction of multiple mutations in critical genes. Adapted from Hecht.[121] PAH = polycyclic aromatic hydrocarbon.

and DNA repair capacity, for example. Reviews have been published,[240,256–258] and the evidence has expanded and deepened our understanding of how smoking injures cells and causes cancer and indicates potential approaches to identification of high-risk individuals and molecular screening.

The metabolism of toxic agents, including carcinogens, generally proceeds through two phases.[259] In phase 1, unreactive nonpolar compounds are converted, usually by oxidative reactions, to highly reactive intermediates. These intermediates are then able to form complexes with conjugating molecules in phase 2 conjugation reactions, which are usually less reactive and more easily excreted. However, the intermediate metabolite may react with other cellular components, such as DNA, before conjugation occurs. This binding to DNA may be the first step in the initiation of the carcinogenic process.[259]

Many carcinogenic compounds in tobacco smoke (*eg*, polycyclic aromatic hydrocarbons) undergo metabolic activation by phase 1 enzymes of the cytochrome p450 system to form reactive intermediates that bind to DNA and cause genetic injury. Several of these enzymes have been investigated with regard to lung cancer risk, including CYP1A1. For CYP1A1, the current evidence suggests that two specific polymorphisms, the MspI polymorphism[260] and a polymorphism in exon 7,[261] are associated with increased risks for lung cancer.

Glutathione S-transferase is a phase 2 enzyme that detoxifies reactive metabolites of polycyclic aromatic hydrocarbons. There are at least four genetically distinct classes of the glutathione S-transferases: μ, α, π, and θ. The risk estimates from a metaanalysis[262] indicate that individuals with the GSTM1 null genotype have higher risk for lung cancer than those with the GSTM1 present genotype, but a pooled analysis[262] of data from 21 case-control studies did not indicate that this susceptibility was stronger among cigarette smokers than among nonsmokers. The importance of interactions between genes is highlighted by the joint assessment of the CYP1A1 Ile462Val and GSTM1 null polymorphisms in nonsmokers, which indicated that the combination of the two variant genotypes was associated with a greater than fourfold increased likelihood for lung cancer compared with the combination of the two nonvariant genotypes.[263]

There are other candidates for determinants of susceptibility to lung cancer in smokers, including oncogenes and suppressor genes and DNA repair capacity.[239] One gene of particular interest for lung cancer is p53, a tumor suppressor gene.[254,258] This gene has been described as "at the crossroads" for multiple cellular response pathways that are considered relevant to carcinogenesis.[258] The gene is frequently mutated in lung cancers, > 90% of small cell cancers and > 50% of non-small cell cancers. The spectrum of mutations in smokers seems to be different from that in nonsmokers.[254,258] In fact, Denissenko et al[264] showed binding of an activated metabolite of benzo[a]pyrene to the same p53 codons where mutations are commonly observed in lung cancers in smokers. However, epidemiologic studies[265] of common polymorphisms in the p53 gene have not shown strong associations with lung cancer risk.

Substantial research has been directed at DNA repair and susceptibility to lung cancer and other tumors.[257,266] People with specific rare, recessive traits (*eg*, xeroderma pigmentosa) have long been known to be at increased risk for cancer. DNA repair capacity has now been examined as a specific risk factor for lung cancer, with the underlying hypothesis that lesser capacity would lead to greater lung cancer risk from the multiple DNA-damaging components of tobacco smoke. Although much research remains to be done to clarify the association between variation in DNA repair capacity and lung cancer risk, the evidence suggests that this is a promising lead.[241] There are a variety of phenotypic assays for susceptibility to DNA damage. Individuals with a less proficient DNA repair capacity phenotype as measured by a nonspecific mutagen sensitivity assay have been shown to have an increased risk for lung cancer in some studies.[267,268] Studies of DNA repair genes have been conducted, including studies of *XPA*, *XPD*, radiograph repair complementation groups 1 and 3 (*XRCC1* and *XRCC3*), excision repair cross complementation group 1 (*ERCC1*), and *hoGG1*. One of the most extensively studied DNA repair genes is the nucleotide excision repair gene *ERCC2/XPD* (*eg*, references[269,270]). The evidence to date has not yet revealed a consistent pattern of associations for the Asp312Asn or Lys751Gln polymorphisms of the *ERCC2/XPD* gene.[271] The findings of a review of polymorphisms in three genes in the base excision repair pathway (*OGG1*, *APE1/APEX1*, and *XRCC1*) showed that for the *OGG1* Ser326Cys polymorphism, individuals with the Cys/Cys genotype had an elevated risk for lung cancer (summary odds, 1.24; 95% CL, 1.01, 1.53).[272]

Presence of Acquired Lung Disease: In addition to hereditary factors, increased susceptibility to lung cancer may result from underlying lung disease. Such acquired lung diseases assume two major forms: (1) those that obstruct airflow, such as COPD; and 2) fibrotic disorders that restrict lung capacity, such as pneumoconiosis.[273] Associations between lung cancer and both types of acquired lung disease have been noted, but as mentioned below this topic

is complex and many issues await resolution, even after debate for > 60 years.[274]

A substantial body of evidence suggests that COPD or impaired lung function is associated with the occurrence of lung cancer.[275] Cigarette smoking is the principal cause of both COPD[276] and lung cancer, being so strongly causally associated with both of these illnesses that presuming that statistical adjustment procedures "remove" the effect of cigarette smoking may not be well founded. Therefore, clarifying the relevance of COPD to the development of lung cancer awaits further proof that this association is not accounted for by cigarette smoking. One potential mechanism that is hypothesized to link COPD with lung cancer is α_1-antitrypsin deficiency, and evidence to support this notion includes the observation that the prevalence of α1AD carriers was higher in patients with lung cancer than in the general population and higher in patients who had lung cancer and had never smoked.[249] Alternatively, the presence of COPD may indicate that the affected individual has received a greater dose of tobacco carcinogens than the typical unaffected individual. Regardless of mechanism, the presence of COPD is a clinically useful risk indicator.

Several studies[277–280] found inverse associations between asthma and lung cancer. However, a meta-analysis[281] that rigorously controlled for smoking revealed a positive association between asthma and the risk for lung cancer, especially nonadenocarcinoma lung cancer. Subsequently, asthma was found to be associated with lung cancer mortality in the Second National Health and Nutrition Examination Survey Mortality Study (from 1976 to 1992).[282] Several potential mechanisms have been proposed to explain this association: (1) mucociliary dysfunction leading to accumulation of toxicants, such as lung carcinogens, in the airway; (2) free radical damage to DNA, as a result of imbalance between oxidants and antioxidants; and (3) chronic inflammation, leading to chronic mitogenesis, and increased likelihood of conversion of endogenous DNA damage into mutations.[281] Appropriately designed studies are needed to establish whether and how asthma might increase the risk for lung cancer.

Clarifying the possible relationship between pneumoconioses and lung cancer poses particularly vexing challenges. Even for asbestos exposure, which is clearly established as a potent cause of lung cancer,[190] whether lung cancer results from asbestos *per se* or from asbestosis remains controversial.[191] Asbestos is likely to cause lung cancer via multiple mechanistic pathways.[283,284] For other mineral fibers, the situation is murkier. For example, determining whether silica exposure or silicosis mediates the increased lung cancer risk in silica-exposed individuals has proved difficult.[285,286] The presence of silicosis is associated with an increased risk for lung cancer.[179] Understanding the basis of this association will entail isolating the independent effects of silica exposure and lung fibrosis while taking into account exposure to smoking and other lung carcinogens.[177,192]

Such differences in the pattern of associations between pneumoconioses and lung cancer emphasize that "fibrosis" is not a homogeneous exposure but one that depends on the properties of the specific mineral fiber or other environmental agent. Properties of the agent, such as its size, shape, and durability, and the effects of other exposures such as cigarette smoking are important considerations in assessing the potential harmfulness of an agent.[283]

In addition to pneumoconioses, two other forms of interstitial lung disease (ILD) have been most consistently linked to lung cancer: idiopathic pulmonary fibrosis (IPF) and systemic sclerosis (SSc). The potential relationship between these conditions and lung cancer is controversial, because ILD has alternatively been hypothesized to do the following: (1) cause lung cancer, (2) be caused by lung cancer, and (3) share common pathogenetic mechanisms with lung cancer.[287] Until recently, epidemiologic studies of ILD were hindered by the variable criteria used to diagnose this rare condition. However, recent improvements to an international classification system have facilitated investigation of the potential association between ILD and lung cancer.

The variability in the diagnostic criteria for IPF until 1998 probably contributed to the wide-ranging associations (from increased risk to protection) that have been observed between IPF and lung cancer.[287] The results of autopsy studies have shown high rates of lung cancer in patients with IPF.[287] However, IPF, specifically, usual interstitial fibrosis, is a histopathologic marker of inflammatory response to a variety of toxic exposures that are common in lung cancer, including connective tissue disease, chemotherapy, radiotherapy, and surgery. In the absence of clinical data, autopsy findings are prone to overestimate the role of IPF as a risk factor for lung cancer. However, estimates based on registry data may have limited validity as a result of possible misclassification of smoking status and the lack of histologic confirmation. Misclassification of IPF in such studies likely attenuates the association between IPF and lung cancer.[192] Similarly, in studies that rely on death certificates, underreporting may lead to the lower reported lung cancer prevalence among individuals who had a diagnosis of IPF, compared with the general public.

ILD may also occur in the context of SSc, a rheumatologic disorder with a myriad of local and/or

systemic manifestations. ILD, which occurs in most cases of SSc, is the major cause of morbidity and mortality as a result of SSc. Lung cancer is the most frequently reported malignancy in SSc, usually occurring in patients with SSc and concurrent ILD.

Compared with the general population, lung cancer occurs more frequently among those with SSc, especially those with ILD, even after adjustment for cigarette smoking.[287] A mechanism proposed to explain this association is genetic damage induced by inflammation and fibrosis and the subsequent repeated cellular injury and repair.[287] Another hypothesis for the increased lung cancer risk seen in patients with SSc relates to enhanced lung cancer susceptibility resulting from the frequent use of immunosuppressive drugs.[287] Alternatively, the potential role of repeated chest imaging resulting in overdiagnosis bias cannot be ruled out as an explanation for the observed associations between SSc and lung cancer.[287]

Conclusions

The path to preventing lung cancer is charted by the identification of numerous exposures that are causally associated with lung cancer. If steps can be taken to reduce or eliminate the exposure to these agents, then this would be expected to reduce the risk for lung cancer. Preventive strategies can be pursued in the public policy arena or in public health interventions directed at individual behavior. Cigarette smoking provides a useful example to illustrate the multiple levels that can form the basis of preventive strategies. In the legislative/regulatory arena, examples of tobacco control strategies include legislation that limits cigarette advertising, that reduces children's access to cigarettes, and that prohibits smoking in the workplace. Litigation against cigarette manufacturers has also proved to be a productive component of tobacco control strategies, as exemplified by the settlement between states and the tobacco industry. Behavioral interventions to prevent children and adolescents from starting to smoke cigarettes and behavioral/pharmacologic interventions to promote smoking cessation are individual-level approaches that, if successful, could be expected to reduce the occurrence of lung cancer.

In developing lung cancer prevention strategies, certain patient groups warrant particular attention. Steps need to be taken toward the goal of reducing the very high lung cancer incidence rates in African-American men.[288] Lung cancer is a major women's health issue. As a result of historical cigarette smoking patterns, the epidemic of lung cancer started later in women than in men; but in contrast to the situation in men, lung cancer incidence rates in women have not yet begun to decrease consistently.[25] Although lung cancer remains a critical public health problem, the decrease in the overall lung cancer burden that is occurring in the United States, as in much of the developed world, reflects the successes of preventive strategies. A critical global priority is to prevent the uptake of cigarette smoking in developing countries where smoking prevalence is still low in order to prevent the increase in morbidity and mortality from lung cancer that is certain to follow an increase in smoking prevalence.

A consideration of the epidemiology of lung cancer consistently reinforces one major theme: the pandemic of lung cancer is a consequence of the tragic and widespread addiction to cigarettes throughout the world. Curtailing the pandemic of lung cancer will require preventing youths from starting to smoke cigarettes and effectively promoting smoking cessation among addicted smokers. There are other causes that also need control, but fortunately there have been successes in reducing exposures to occupational carcinogens in countries of the developed world.

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Lung Cancer Chemoprevention*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **Lung cancer is the most common cause of cancer death in the United States. Cigarette smoking is the main risk factor. Former smokers are at a substantially increased risk for lung cancer compared with lifetime never-smokers. Chemoprevention is the use of specific agents to reverse, suppress, or prevent the process of carcinogenesis. This article reviews the major agents that have been studied for chemoprevention.**

Methods: **Articles of primary, secondary, and tertiary prevention trials were reviewed and summarized to obtain recommendations.**

Results: **None of the phase III trials with the agents beta carotene, retinol, 13-cis-retinoic acid, α-tocopherol, N-acetylcysteine, or acetylsalicylic acid has demonstrated beneficial, reproducible results. For facilitating the evaluation of promising agents and for lessening the need for a large sample size, extensive time commitment, and expense, focus is now turning toward the assessment of surrogate end point biomarkers for lung carcinogenesis. With the understanding of important cellular signaling pathways, various inhibitors that may prevent or reverse lung carcinogenesis are being developed.**

Conclusions: **By integrating biological knowledge, more trials can be performed in a reasonable time frame. The future of lung cancer chemoprevention should entail the evaluation of single agents or combinations that target various pathways while working toward identification and validation of intermediate end points.** ***(CHEST 2007; 132:56S–68S)***

Key words: acetyl salicylic acid; apoptosis; biomarkers; chemoprevention; cyclooxygenase-2 inhibitors; lung cancer; proliferation; protein kinase C; selenium; signal transduction pathways; tyrosine kinase inhibitors; vitamin A; vitamin E

Abbreviations: ADT = anethole dithiolethione; ATBC = α Tocopherol β-Carotene; CARET = Beta-Carotene and Retinol Efficacy Trial; CI = confidence interval; COX = cyclooxygenase; HOPE = Heart Outcomes Prevention Evaluation; HR = hazard ratio; LOX = lipoxygenase; MCM2 = minichromosome maintenance factor 2; PG = prostaglandin; PGI = prostacyclin; PKC = protein kinase C; RR = relative risk; SEB = surrogate end point biomarker

The number of newly diagnosed cases of lung cancer in the United States in 2007 is estimated to be 213,380. Lung cancer causes more death (160,390) than colorectal cancer (52,180), breast cancer (40,910), and prostate cancer (27,050) combined.[1] The annual worldwide incidence of lung cancer is > 3,000,000 and continues to rise. The single most important risk factor is smoking. Approximately 20% of the US adult population continues to smoke. In those who smoke, the risk for lung cancer

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is on average 10-fold higher than in lifetime never-smokers (defined as a person who has smoked < 100 cigarettes in their lifetime). There were 45.4 million former smokers in the United States in 2003.[2] Although smoking prevention and cessation remain essential in the overall strategy for lung cancer prevention, former smokers continue to have an elevated risk for lung cancer for years after quitting.[3] In fact, more than one half of lung cancers occur in those who have stopped smoking.

At the time of diagnosis, the majority of patients have stage IIIB to IV disease, which carries a 5-year survival of < 5%. Efforts to improve this dismal outcome have more recently been directed at chemoprevention to reduce the incidence and mortality of lung cancer.

The rationale for chemoprevention is based on two main concepts, multistep carcinogenesis and "field cancerization," which can be used to explain the process of lung carcinogenesis as it occurs over time and throughout the entire bronchoalveolar epithelium. Multistep carcinogenesis is based on the theory that the progression of normal bronchoepithelial cells to a malignant lesion entails a multistep process involving numerous morphologic and molecular modifications. A series of alterations that lead to malignant transformation with unregulated clonal expansion and cellular proliferation occur over time. The morphologic correlate of multistep carcinogenesis is the progression of bronchial epithelium from hyperplasia to metaplasia to increasing grades of dysplasia and carcinoma *in situ* onward to invasive carcinoma. Specific genetic abnormalities that correlate with the morphologic steps that are involved in the evolution to malignancy have been described.

Physiologically, proliferation of bronchoepithelial cells is required to replace cells lost at the lumen and to repair epithelial damage caused by environmental influences. To control proliferation in response to tissue damage, a complex system of intercellular communication that includes epithelial cells, stroma, and inflammatory cells has evolved.[4] The vehicles of communication are growth factors, cytokines, peptides, and lipid metabolites and their respective cellular receptors. Their functions include induction and suppression of not only proliferation but also migration, contact inhibition, angiogenesis, apoptosis, and antitumor immunity. Reactive oxygen species that are generated during inflammation can result in DNA damage and may thus trigger or accelerate carcinogenesis.

In 1953, it was first established that many areas of the aerodigestive tract are simultaneously at risk for cancer formation as a result of exposure to carcinogens.[5] This concept is known as field cancerization and serves to explain the synchronous presence of various premalignant and malignant lesions at different locations in the aerodigestive tract of the same person. The high rate of second primary cancers in individuals who underwent curative treatment for an aerodigestive malignancy provides further evidence for field cancerization.

Tobacco exposure is among the most preventable causes of morbidity and mortality in the United States. It includes smokeless tobacco and pipe and cigar use. The most important of these is cigarette smoke. It has been estimated that the majority of lung cancer is associated with cigarette smoking.[6,7] Given the harm associated with tobacco use, it is important not only to promote the cessation of tobacco use but also to prevent the initiation.

For reducing the incidence of smoking, tobacco prevention is also an imperative public health focus. The key is to provide early information about the harms of tobacco exposure to middle and high school students. Policies and programs exist and continue to be developed to educate youth on the harms of tobacco use given its potential for dependency and associated morbidity and mortality.

Advocacy efforts have been increasingly successful at limiting tobacco use and public exposures to environmental tobacco smoke. Some of these methods include strict regulation of tobacco advertisements, increases in tobacco taxes, and comprehensive smoking bans for indoor and public outdoor areas.

Another major public health focus in the United States is tobacco cessation. Numerous cessation programs are available for those who would like to quit. These range from behavioral therapy to pharmacologic interventions. As an essential aspect of all primary care practices, all patients should be asked about smoking status, and counseling and advice should be provided when needed. This has been associated with an increase in smoking cessation.[8] By providing mutual support, behavior modifications, and coping skills, group therapy has been found to be an effective method.[9] The use of pharmacologic interventions such as all forms of nicotine replacement (including nicotine spray, gum, and patches), bupropion, and varenicline (partial agonists of nicotinic acetylcholine receptors) have been effective in increasing smoking cessation rates.[10–16] Other techniques, such as acupuncture and hypnosis, to date, have not been effective.[17]

Smoking cessation results in a decrease in precancerous lesions from 27 to 7%.[18] For those who have quit smoking for 10 years (15 years), the risk for lung cancer may be 30 to 50% (80 to 90%) less than that of current smokers.[3,18]

Many options are available to help with smoking cessation. Physicians are strongly encouraged to

discuss these options with their patients to develop individualized cessation plans. Still, half of lung cancers occur in those who have stopped smoking. To help reduce the incidence of lung cancer, recent efforts have been directed to chemoprevention. Chemoprevention is defined as the use of specific agents to reverse, suppress, or prevent the process of carcinogenesis.[19] The first and most powerful step in lung cancer chemoprevention is avoidance of continued carcinogen exposure, for instance, through smoking cessation. However, people who have smoked in the past and have successfully quit have a substantially higher risk for lung cancer development than people who are lifetime never-smokers.[19] Chemoprevention as a means of reducing cancer incidence has been successful for breast cancer and prostate cancer.[20,21] For lung cancer, chemoprevention is an area that needs further exploration for proper recommendations to be formed. This article discusses the methods used to obtain articles and grade recommendations. It is organized into sections: (1) high-risk populations, (2) various chemopreventive interventions investigated to date, (3) arachidonic acid pathway studies, (4) studies using other pathways, and (5) future studies.

Materials and Methods

In 2005 to 2006, a panel of experts corresponded to update the previous recommendations on the use of lung cancer chemoprevention agents. The panel consisted of investigators who were experienced in the formulation, design, and execution of chemoprevention clinical trials. Deliberations were resolved to establish guidelines for practitioners to use for patients at high risk for lung cancer.

For obtaining various lung cancer chemoprevention guidelines, a systematic review of the literature was performed (see "Methods and Grading" chapter). These guidelines were focused on primary, secondary, and tertiary lung cancer chemoprevention studies that were mostly funded by the National Cancer Institute. Additional information was obtained by performing a literature search of the PubMed and Medline databases and review of the Thoracic Oncology NetWork reference lists. For establishing study quality, recommendations were organized by the panel of experts on the writing committee and then graded by the standardized American College of Chest Physicians methods (see "Methodology for Lung Cancer Evidence Review and Guidelines Development" chapter). Before final approval, this chapter was reviewed by all panel members, which included a multidisciplinary team that consisted of thoracic surgeons, medical oncologists, radiation oncologists, and pulmonologists, followed by review by the Thoracic Oncology NetWork, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians. Following are key considerations in designing chemoprevention trials for lung cancer.

Identification of Candidate Agents

The selection of chemoprevention agents involves a careful process. First, sufficient *in vitro* and animal model data should exist to support the use of a specific agent. The use of specific agents should not be based solely on epidemiologic data. Recent advances in tumor biology have resulted in the development of agents that target specific cellular pathways that are thought to be crucial for tumor development and progression. Therapies can now be directed at various steps that are involved in carcinogenesis. Agents that target DNA repair may prevent or reverse the initial development of mutations that frequently are found in bronchial atypia. Rather than prevent the initiation process, other agents may inhibit promotion or progression. As more evidence and data are obtained regarding the molecular pathways that are involved in these processes, these agents may serve as realistic targets for future drug development and therapeutic interventions.

Other issues must be considered when selecting agents for chemoprevention trials. A favorable safety profile must be associated with the chosen drug because it may be used for prolonged periods of time in a putatively healthy, albeit high-risk, population to prevent disease. Agents should be easy to administer such that compliance will be high. In addition, the agent should be readily available and affordable.

Populations at Risk for Lung Cancer

Chemoprevention trials can be divided into three types: primary prevention, secondary prevention, and tertiary prevention. In primary prevention trials, participants have no evidence of lung cancer. Such trials are targeted at high-risk individuals, for instance, those with a significant smoking history. Secondary prevention studies involve the use of participants who have evidence of premalignacy, such as sputum atypia or dysplasia on bronchial sampling. Individuals who have a history of being cured from their primary lung cancer are the focus of tertiary prevention trials (second primary tumor prevention). The practical rationale for selecting high-risk individuals is to reduce the sample size and duration of therapy. However, it is important to recognize that individuals who are at high risk, such as active smokers with ongoing smoke exposure, may have a different biology of disease than former smokers. As a result, the outcome of a trial may be adverse in one group (smokers) yet beneficial in another (former smokers). In the end, the ultimate goal of lung cancer chemoprevention is to reduce disease incidence and mortality. Within each trial category, guidelines are needed for enrollment criteria.

Smoking and Risk for Lung Cancer

Chemoprevention trials typically focus on high-risk populations. The main criteria for selection of patients to lung cancer chemoprevention trials are based on smoking history. In addition, airway obstruction and environmental factors, such as asbestos exposure, family history, and obstructive disease, have well-established hazard ratios (HRs) for lung cancer risk and have been used as factors for identifying special cohorts (see "Epidemiology of Lung Cancer" chapter).[22] Case-control studies[23–25] linking smoking to lung cancer became available in the 1950s. These were confirmed by prospective cohort studies[26–29] that supported the conclusion that smoking causes lung cancer. Many studies[30] have demonstrated that a longer smoking duration, younger age of initiation, and a higher number of packs per day increase the risk for lung cancer. The 12-year follow-up data of the American Cancer Society's Cancer Prevention Studies followed $>$ 1 million individuals and included smokers, nonsmokers, and former smokers. An individual with a history of smoking $\geq$ 40 cigarettes a day for 35 to 39 years has a mortality risk from lung cancer of 19.45 compared with an individual who has

a history of 1 to 9 cigarettes daily for 20 to 24 years, whose lung cancer-related mortality risk is 1.26.[31] When evaluating numerous trials, individuals with a ≥ 30–pack-year smoking history have higher rates of lung cancer.[30] There seems to be a continuum between risk and 10, 20, and 30 pack-years of smoking; still, no one level has been accepted as a definitive threshold for what is considered high risk. What is known is that the risk for lung cancer for nonsmokers is significantly less than the risk for smokers.

Dysplasia and Risk for Lung Cancer

The progression from a benign to a malignant lesion in the bronchial epithelium involves a multistep process. Changes occur in concert at both the molecular and the cellular levels, enhancing the ability of a cell to proliferate, evade cell death, and invade the basement membrane. Before becoming invasive, morphologic descriptions include hyperplasia, metaplasia, dysplasia, and carcinoma *in situ*. In general, hyperplasia and metaplasia are not necessarily premalignant, because these lesions can spontaneously regress and can be found after trauma or along with chronic inflammation. Dysplasia and carcinoma *in situ* are considered the principal premalignant lesions, although these, too, can spontaneously regress, albeit at a lower frequency than hyperplasia and metaplasia.[32] Specific genetic alterations are associated with the steps involved. Wistuba et al[33] demonstrated an increase in molecular abnormalities, including loss of heterozygosity, when lesions progressed from normal to carcinoma *in situ*. Molecular characteristics of dysplastic lesions that seem to be associated with progression to carcinoma *in situ* are high telomerase activity, increased Ki-67 labeling index, and p53 positivity.[34] These may correlate with an increased risk for subsequent carcinoma, although this has not been clearly demonstrated.

Saccomanno et al[35] demonstrated that sputum atypia could be seen 4 to 5 years before the development of lung cancer. A population with sputum atypia is at increased risk for lung cancer development.[36,37]

On the basis of these observations, the National Cancer Institute sponsored three lung cancer screening trials in the 1970s using chest radiograph and sputum cytology as screening tools. One of these trials, conducted at Johns Hopkins University ("the JHU cohort"), addressed the utility of sputum cytology as a screening tool. The study showed that 10% of participants with moderate atypia on sputum cytology and no overt evidence for lung cancer developed lung cancer up to 9 years later. Of those with severe atypia, lung cancer developed in > 40% during the same time period.[38]

Second Primary Lung Cancer

The development of second primary tumors is common in patients with previously treated lung cancer. After resection of a lung cancer, there is a 1 to 2% risk for a second lung cancer per patient per year.[39] Those who do have a second lung cancer have a median survival of 1 to 2 years and a 5-year survival of approximately 20%.[39] As such, chemoprevention in this population is an important area of research.

Results

Vitamins as Chemoprevention Agents With Lung Cancer as an End Point

Beta Carotene Use in Former and Current Smokers and Those With Asbestos Exposure: A diet rich in fruits and vegetables (at least three servings per day) is associated with a lower cancer incidence as based on epidemiologic data. The α Tocopherol β-Carotene (ATBC) study[40] randomly assigned 29,133 people to receive beta carotene, α tocopherol, both, or placebo. Study participants averaged 57.2 years of age, 20.4 cigarettes per day, and 35.9 years of smoking. They were followed up for 5 to 8 years. The incidence of lung cancer in the study group was 18% higher than in the placebo group ($p < 0.01$). When this trial was completed, a second trial to evaluate beta carotene was under way. The Beta-Carotene and Retinol Efficacy Trial (CARET) evaluated high-risk current and former smokers with a > 20–pack-year history of smoking (n = 14,254) or with asbestos exposure and a 15-pack-year smoking history (n = 4,060). Forty percent of the > 20–pack-year smoking history group were women. The participants were randomly assigned to receive either a combination of beta carotene and vitamin A or placebo. An early analysis was performed because of the finding of the ATBC trial. The relative risk (RR) for lung cancer in the active treatment group was 1.28 (95% confidence interval [CI], 1.04 to 1.57; $p = 0.02$). In a subgroup analysis, the RR for lung cancer in current smokers was 1.40 (95% CI, 1.07 to 1.87), whereas the RR in participants who were no longer smoking at the time of randomization was 0.80 (95% CI, 0.48 to 1.31). As a result of these findings, the CARET was terminated 21 months early. Both of these trials demonstrated a higher incidence of lung cancer in those who had received the beta carotene.

In the United States, the Physicians Health Study evaluated 22,071 physicians who ranged in age from 40 to 84 years[41]; 11% were current smokers, and 39% were former smokers. The participants were randomly assigned to beta carotene or placebo. There was no difference in lung cancer rates in those who received the beta carotene (82 lung cancers in the beta carotene group vs 88 in the placebo group).

The Women's Health Study explored the use of 50 mg of beta carotene every other day vs placebo in 39,876 women who were ≥ 45 years old. Thirteen percent of the women were smokers. The study was terminated early, and the median treatment duration was 2.1 years. There was no significant difference in the development of any site-specific cancer including lung cancer (30 cases vs 21 cases, respectively).[42]

Recommendation

1. For individuals with a smoking history > 20 pack-years or a history of lung cancer, the use of beta carotene supplementation is not recom-

mended for primary, secondary, or tertiary chemoprevention of lung cancer. Grade of recommendation, 1A

Vitamin E Use in Men With a Smoking History: Epidemiologic data support that vitamin E (α tocopherol) has antitumor properties such that individuals with high levels of vitamin E are less likely to have cancer. The ATBC study[40] was published in the New England Journal of Medicine in 1994. It involved 14 study sites, mainly based in Finland. More than 29,000 high-risk participants were randomly assigned to α tocopherol, beta carotene, both, or placebo. The participants were men who ranged in age from 50 to 60 years and had smoked at least five cigarettes per day. The primary end point was diagnosis of lung cancer, and the secondary end point was diagnosis of any cancer. Participants were followed up for 5 to 8 years. There was a nonsignificant reduction in the incidence of lung cancer by 2%.

The Heart Outcomes Prevention Evaluation (HOPE) trial was an international, randomized, double blind, placebo-controlled trial that evaluated participants who were ≥ 55 years of age and had vascular disease or diabetes from 1993 to 1999. The trial was extended to 2003 and was known as the *HOPE TOO* trial. A total of 9,541 participants enrolled in the HOPE trial, and 7,030 continued on the HOPE TOO trial. The participants were treated with 400 IU/d vitamin E or placebo. The trial included 174 centers, and follow-up was for a median duration of 7 years. Lung cancer incidence did not differ between the vitamin E and placebo treatment arms either in the primary analysis of the HOPE trial (69 cases [1.4%] vs 92 cases [2%]; $p = 0.04$) or in the HOPE TOO trial (58 cases [1.6%] vs 74 cases [2.1%]; $p = 0.16$).[43] Participants in the vitamin E arm were found to have a higher rate of heart failure ($p = 0.03$).

The Women's Health Study explored the use of 600 IU of vitamin E every other day vs placebo in 39,876 women who were ≥ 45 years of age and were followed up for 10.1 years. There was no significant difference in lung cancer incidence between the treatment and placebo arms (RR, 1.09; 95% CI, 0.83 to 1.44).[44]

Vitamin A in Current or Former Smokers: Epidemiologic data supported the idea that fruits and vegetables that are high in vitamin A lower the incidence lung cancer. In 1996, the results of the CARET were published.[45] This study evaluated 18,314 high-risk patients with either > 20 years of smoking or > 15 years of smoking and a history of asbestos exposure. Participants were randomly assigned to vitamin A and beta carotene or placebo. Participants were either current smokers or smokers who had quit in the previous 6 years. This study found a RR of 1.28 ($p = 0.02$) for lung cancer in the treatment arm compared with placebo.

13-Cis-Retinoic Acid in Patients With Stage I Lung Cancer: Preclinical and early clinical studies have suggested that retinoids have chemopreventive effects. A large randomized trial[46] of 1,166 participants who had stage I lung cancer that was treated with curative intent were randomly assigned to received placebo or isotretinoin. HRs were 1.08 (95% CI, 0.78 to 1.49) for time to second primary tumor, 0.99 (95% CI, 0.76 to 1.29) for recurrence, and 1.07 (95% CI, 0.84 to 1.35) for mortality. Isotretinoin did not decrease the incidence of second primary tumors. In a subgroup analysis, current smokers who were treated with isotretinoin had increased mortality compared with former smokers and nonsmokers (HR, 1.56; 95% CI, 1.09 to 2.24; $p = 0.01$).

N-Acetylcysteine: Preclinical data have demonstrated that N-acetylcysteine has antitumor properties. A large clinical study[47] evaluated this agent in 1,023 patients who had non-small cell lung cancer (pT1-T3, N0-1, or T3, N0) that was treated with curative intent. Patients were randomly assigned to N-acetylcysteine, retinyl palmitate (vitamin A), both, or no intervention. The primary end points were recurrence, death, or second lung cancer. No significant differences were noted between the groups.

Other Agents for Chemoprevention

Acetylsalicylic Acid: There is literature supporting a protective role of aspirin and nonsteroidal antiinflammatory drugs on development of cancer. Three major trials have been conducted, which evaluated the use of acetylsalicylic acid in lung cancer prevention. The UK Physicians' Health Study was a 6-year, randomized trial that evaluated 5,139 healthy male doctors who were receiving 500 mg/d aspirin.[48] Eleven percent were current smokers, and 39% were former smokers. The lung cancer death rate in the aspirin group was 7.4/10,000 person-years vs 11.6/10,000 person-years in the placebo group. This difference was not statistically significant. In 1989, the results of the United States Physicians Health study[49] was published. This study evaluated 22,071 physicians and did not demonstrate a decreased rate of lung cancer in participants who had taken aspirin.

More recently, the results of the Women's Health Study[50] were published; this was a randomized trial of 39,876 US women who were treated with either 100 mg of aspirin or placebo every other day.

Approximately 13% were current smokers, and 35.8% were former smokers. There was an average of 10.1 years of follow-up. Lung cancer was a secondary end point. Lung cancer developed in a total of 205 participants. The RR for lung cancer in the aspirin group was 0.78, which did not reach statistical significance.

Recommendation

2. For individuals who are at risk for lung cancer and patients with a history of lung cancer, the use of vitamin E, retinoids, N-acetylcysteine, and aspirin is not recommended for primary, secondary, or tertiary prevention of lung cancer. Grade of recommendation, 1A

Surrogate End Point Biomarkers Under Development

Double-blind, randomized, phase III trials are considered the "gold standard" for proof of superiority of a novel therapy over current standard of care. Lung cancer incidence should be the primary end point. Because of the large number of required participants and long intervention/follow-up time, such trials pose a formidable challenge to conduct successfully from a logistical as well as a financial perspective.

To allow for testing of an increased number of promising agents over a short period of time, the use of surrogate end point biomarkers (SEBs) is being explored as an alternative to cancer incidence. However, because such trials do not use a definitive clinical end point (*eg*, cancer incidence), promising results obtained require confirmation in a phase III design.

The identification of SEBs that are reliably associated with cancer incidence is of paramount importance. Examples of SEBs currently used include premalignancy by morphologic criteria and proliferative markers by immunohistochemistry, specifically Ki-67 and minichromosome maintenance factor 2 (MCM2). Other potential SEBs are molecules targeted by the specific agents under investigation.

Biomarkers that are under study include dysplasia, Ki-67, MCM2, and others. However, no surrogate marker has been validated; therefore, use of such markers is limited to phase II efficacy trials that require subsequent confirmation in a phase III trial using cancer incidence and/or mortality as the end point.

Dysplasia has long been used as a SEB for lung cancer in many chemoprevention trials. Carcinogenesis involves a progression from a precancerous lesion to invasive disease. Not all dysplasia will progress to cancer. There are data to suggest that 58% of dysplastic lesions will regress spontaneously.[51] A statistically significant change must occur in the bronchoepithelium for chemopreventive agents to have a noticeable impact. On histopathologic review, a complete or near-complete regression of dysplasia in the treatment vs control arm should be demonstrated.

Given the importance of dysregulated proliferation to the carcinogenesis process, several proliferation indexes have been studied as potential SEBs. Ki-67 is an epitope of a nuclear protein recognized by the MIB-1 monoclonal antibody. The protein is frequently expressed throughout the cell cycle of proliferating cells and has not been detected in nonproliferating cells. During interphase, Ki-67 is located primarily in nucleolar and perinucleolar regions in association with condensed chromatin.[52] The function of the Ki-67 protein is still unknown,[53] although it seems to be required for cell progression through the cell cycle.[54,55] MCM2 is a new proliferation marker and one of six members of the MCM protein family. These serve as components of "licensing factor," which is essential for initiation of DNA replication and for limiting replication to one round per cell cycle.[56,57] The MCM proteins are also associated with replication forks and are likely to stimulate the unwinding of the parental DNA strands at these forks.[58]

Other markers under investigation include molecular end points such as epidermal growth factor receptor, human epidermal growth factor 2 receptor, p53, Bcl2/Bax, and telomerase, among others. Proteomics and GeneChip arrays are platforms under investigation for SEB development. However, marker validation remains a major challenge to ensure reproducibility and clinical relevance for any of the SEBs in lung cancer chemoprevention trials.

For instance, it has been reported that plasma levels of folate are lower in smokers with bronchial metaplasia than in those with normal mucosa.[59] In 1988, a randomized, controlled, prospective intervention trial in smokers with bronchial metaplasia was published.[60] Seventy-three men with at least a 20–pack-year history of smoking were stratified according to smoking level and randomly assigned to placebo or folate, 10 mg, and hydroxocobalamin, 500 μg. Therapy was administered for 4 months, and patients were followed up by direct cytologic comparison. The supplemental group did show significantly greater reduction in atypia ($p = 0.02$). However, results from this study are limited by the rate of spontaneous variation in the sputum samples, the small sample size, and the short duration of therapy.

Arachidonic Pathway and Lung Cancer Chemoprevention

Arachidonic acid is metabolized to prostaglandins (PGs) and prostacyclin (PGI) by the cyclooxygenase (COX) pathway, whereas leukotrienes are formed via the lipoxygenase (LOX) pathway. Their end products are thought to be involved in carcinogenesis.

Two isoforms of COX exist: COX-1 and COX-2. COX-1 exists in most cells and is constitutively active. In contrast, COX-2 is induced by inflammatory and mitogenic stimuli that lead to increased PG formation in inflamed and neoplastic tissues.[61,62] Despite having similar structures, COX-2 can be selectively inhibited.

Evidence exists to support arachidonic pathway modulation for inhibition of carcinogenesis. Corticosteroids are known modulators of the ecosanoid-signaling pathway. Synthesized glucocorticoids have been demonstrated to block the development of cancer in A/J mice with induced pulmonary adenomas. COX-2 expression has been demonstrated in premalignant and malignant bronchial cells.[63] Higher levels are associated with a poor prognosis in those with non-small cell lung cancer.[64,65] It has been demonstrated in mouse models that by inhibiting COX-2 with celecoxib, the rate of growth of lung cancer and number and size of metastasis could be decreased.[66] The expression of COX-2 has been shown to enhance tumorigenesis by regulation of angiogenesis via CXCL 5 and 8[67–69] and epidermal growth factor receptor,[70,71] invasion via CD44[72–74] and matrix metalloproteinases,[72,74–77] apoptosis via survivin[78,79] and insulin-like growth factor,[80–82] and antitumor immunity via interleukin-10 and -12.[83–88] However, not all preclinical carcinogenesis models have shown chemopreventive efficacy.[89]

5-LOX is an enzyme involved in the conversion of arachidonic acid to leukotrienes. Leukotrienes are proinflammatory and enhance cell adhesion.[90] Leukotrienes seem to affect the development and progression of lung cancer. This is based on data demonstrating that 5-LOX is expressed in lung cancers,[91] 5-LOX inhibitors reduced the multiplicity and incidence of lung tumors in mice,[92] and 5-LOX metabolites may play a role in angiogenesis.[93]

Lung Cancer Chemoprevention Trials With Arachidonic Acid Pathway Modulators

Several studies have been completed and are ongoing to evaluate the use of arachidonic acid pathway modulators for lung cancer chemoprevention. The following is an overview of these trials.

Budesonide: Lam et al[94] evaluated the use of inhaled budesonide, a corticosteroid that is used for the treatment of asthma, in 112 smokers with bronchial dysplasia and found no effect on bronchial dysplastic lesion or on the prevention of new lesions. A modest decrease in p53 and Bcl2 protein expression in bronchial samples was noted as well as a slightly higher rate of resolution of lung nodules on CT.

Celecoxib for Primary Chemoprevention of Lung Cancer in High-Risk Smokers: Several clinical trials to address the use of celecoxib for lung cancer prevention are underway. The results of a pilot, phase IIa trial[90,95,96] in high-risk smokers performed at University of California, Los Angeles suggested that celecoxib may reduce PGE2 production, inhibit immunosuppression, and modulate SEBs. A follow-up, larger phase IIb trial focusing on heavy former smokers is evaluating the effect of celecoxib on cellular and molecular events associated with lung carcinogenesis. Another phase IIb trial of celecoxib in current and former smokers is being conducted at MD Anderson Cancer Center.

Other Arachidonic Pathway Metabolites: A clinical trial of the 5-LOX inhibitor zileuton is under way at the Karmanos Cancer Institute to address the effect of zileuton on bronchial dysplasia (primary end point) and multiple molecular markers (secondary end points) in at-risk smokers or patients with curatively treated aerodigestive cancers. Another metabolite of arachidonic acid is PGI. It has been demonstrated that up-regulation of PGI resulted in decreased tumorigenicity in mice that were exposed to carcinogens.[30] The University of Colorado is enrolling participants in a phase II, randomized clinical trial to evaluate the effectiveness of iloprost, a PGI analog. End points include the comparison of phenotypic modulation of bronchial epithelium between the two groups, as well as evaluation of multiple molecular markers.

Recommendation

3. For individuals who are at risk for lung cancer or have a history of lung cancer, budesonide, COX-2 inhibitors, 5-LOX inhibitors, and PGI analogs are not recommended for use for primary, secondary, or tertiary lung cancer chemoprevention outside the setting of a well-designed clinical trial. Grade of recommendation, 2C

Impact of Information Regarding Cardiovascular Risk Associated With COX-2 Inhibitors: In late 2004, unfavorable news was released regarding an in-

creased cardiovascular risk with the use of COX-2 inhibitors rofecoxib and celecoxib. The Vioxx GI Outcomes Research Study[97] evaluated 8,076 patients who had rheumatoid arthritis and received rofecoxib vs naproxen; the RR for a cardiac event associated with rofecoxib was 2.38 ($p = 0.002$). The Celecoxib Long-term Arthritis Safety Study[98] involved 8,059 patients with both osteoarthritis and rheumatoid arthritis and compared celecoxib with nonsteroidal antiinflammatory drugs; in this trial, no significant difference in cardiovascular events was demonstrated between the two groups.

In 2001, Merck started the Adenomatous Polyp Prevention on Vioxx trial,[99] which was stopped early because of the finding of an increased risk for adverse thrombotic cardiovascular events after 18 months of therapy over placebo during an interim analysis. One study[100] in chemoprevention of colorectal cancer also reported an increased cardiovascular risk with prolonged use of celecoxib. The finding led to the suspension of the aforementioned clinical trials in lung chemoprevention in late December 2004. In February 2005, after careful consideration, the Food and Drug Administration concluded that the benefits of celecoxib outweigh the potential risks in properly selected and informed patients. Advisors to the Food and Drug Administration also recommended that COX-2 inhibitors continue to be studied in the treatment and prevention of cancer. With the addition of new monitoring guidelines as well as exclusion criteria to safeguard the well-being of study participants, it is believed that the potential benefits from the studies outweigh the risks.

Future Directions for Chemoprevention

Selenium: Epidemiologic data have demonstrated an association between high selenium exposure and a reduction in lung cancer risk.[101] The mechanism of action is thought to be related to oxidative stress pathways, modification of gene expression through DNA methylation, and suppression of COX-2 and 5-LOX expression.[102–104]

The Nutritional Prevention of Cancer trial[105] was designed to evaluate the role of selenium in reducing the incidence of nonmelanomatous skin cancer. The trial did not demonstrate a decrease in skin cancer but did show a 26% decrease in lung cancer risk. A phase IIA chemoprevention trial using selenium was completed at the Moffitt Cancer Center to evaluate toxicity and modulation of biomarkers in current and former smokers. Although selenium was very well tolerated, analysis of samples from the 14 individuals who completed the trial showed no alterations in the biomarkers that were assessed (p53 by immunohistochemistry in sputum, proliferating cell nuclear antigen and p16 by immunohistochemistry in bronchial biopsies, and apoptosis by terminal deoxynucleotidyl transferase-mediated digoxigenin-deoxyuridine nick-end labeling in bronchial biopsies.

Easter Cooperative Oncology Group protocol E5597 is a phase III, double-blind, placebo-controlled study of selenium (200 μg of L-selenomethionine) in the prevention of second primary lung cancers in patients who have had a complete resection of a pathologically staged T1/2N0M0 non-small cell lung cancer. The primary end point of the trial is the incidence of second lung cancers. Intermediate biomarkers are also studied as potential surrogates for lung cancer. This is a national, multiinstitutional, cooperative group trial with an accrual goal of 1,960 patients. The study is powered to detect a 40% relative decrease in the 2.0% annual incidence rate of second lung cancers in this cohort of patients and is still in the accrual stage.

Organosulfurs: The organosulfur compounds oltipraz and anethole dithiolethione (ADT) belong to the dithiolethione class. They have antitumor activity as a result of their antioxidant, chemopreventive, chemotherapeutic, and radiopreventive properties.[106] Furthermore, oltipraz was thought to inhibit macromolecule adducts of carcinogens by inducing phase II detoxifying enzymes.[107] For further investigation of this in relation to tobacco, a phase I chemoprevention trial using oltipraz was initiated. Participants received 0, 200, or 400 mg/wk oltipraz for 12 weeks and were followed up with bronchoscopies at 1 and 12 weeks. No significant difference was found between the two groups, but the oltipraz group did have substantial toxicity. In an earlier trial,[107,108] oltipraz was combined with N-acetylcysteine. This trial was stopped early as a result of hepatotoxicity.

ADT is available in Europe and Canada for the treatment of xerostomia as a result of radiation. In 2002, data from a randomized phase II study[109] that evaluated ADT vs placebo for secondary chemoprevention of lung cancer was published. Although there was no statistical difference in histologic regression of bronchial dysplasia, there was a statistical difference in the progression rate: 8% vs 17%.[109]

Recommendations

4. For individuals at risk for lung cancer or have a history of lung cancer, the use of oltipraz as a primary, secondary, or tertiary chemopreventive agent of lung cancer is not recommended. Grade of recommendation, 1B

5. For individuals at risk for lung cancer or

have a history of lung cancer, the use of selenium and ADT for primary, secondary, or tertiary lung cancer chemoprevention is not recommended outside the setting of a well-designed clinical trial. Grade of recommendation, 1B

Looking Forward, New Targets

Many other targeted therapeutic agents have potential as chemopreventive agents. Table 1 lists potential targets for lung cancer chemoprevention.

Protein kinase C (PKC) is involved in cellular proliferation, apoptosis, and mobility.[110] Enzastaurin, a PKC-β inhibitor, is being studied in patients with glioblastoma, lung cancer, and non-Hodgkin lymphoma. The role of PKC in carcinogenesis is complex. Since there are 12 known isoforms with distinct and at times opposing effects. The β isoform is activated by growth factors. Enzastaurin competes with the adenosine triphosphate-binding site of PKC-β. More specific, in lung cancer cells, enzastaurin demonstrates inhibitory activity on intracellular signaling proteins.[111,112] Because of its molecular mechanism of action and low adverse effect profile, this drug is a possible candidate for chemoprevention in high-risk individuals. As demonstrated by the COX-2 inhibitor experience, extensive data on safety and efficacy are needed before novel agents can be applied to the realm of chemoprevention.

Ras is an oncogene that is important for cancer cell survival. Farnesyltransferase inhibitors block ras farnesylation. They have been tested extensively in A/J mice and transgenic mice and are strong chemopreventive agents.[113–115] This prompted further investigation in patients with lung cancer. The adverse effects experienced by participants in these trials included myelosuppression, nausea, diarrhea, abdominal pain, and fatigue. The clinical toxicity limits this drug as a candidate for chemoprevention despite the impressive preclinical data.

Table 1—*Potential Target Molecules for Lung Cancer Chemoprevention Trials*

COX-2
PGI-2
Histonedeacetylase
Insulin-like growth factor binding protein 3
Mammalian target of rapamycin
Epidermal growth factor receptor
PKC
Signal transduction and activator of transcription-3
5-, 12-LOX
VEGF
Farnesyltransferase
Protein kinase B

RECOMMENDATION

6. For individuals at risk for lung cancer or have a history of lung cancer, there are not yet sufficient data to recommend the use of any agent either alone or in combination for primary, secondary, or tertiary lung cancer chemoprevention outside a clinical trial. Grade of recommendation, 1B

CONCLUSION

Chemoprevention is a developing area of research. The main goal of lung cancer chemoprevention is to find an effective agent with a favorable toxicity profile for patients who are at high risk for primary or secondary lung cancer. A number of compounds have been tested, but results of trials to date have been either negative or, in the case of those evaluating beta carotene and retinoids in active smokers, deleterious. Table 2 summarizes the large phase III trials that have been conducted. In addition, several smaller, phase II chemoprevention trials have been performed that used morphologic parameters, such as metaplasia and dysplasia in bronchoepithelial biopsy specimens or cellular atypia in cytologic sputum specimens, as intermediate end points. Agents that have been investigated include various retinoids,[116–120] folate and vitamin B12,[60] and budesonide,[94] but none has demonstrated improvement.

Some of the phase III trials, although largely disappointing, nonetheless provided useful lessons that continue to shape the design of ongoing chemoprevention trials, including the importance of taking into consideration environmental as well as host factors when conducting chemoprevention trials in lung cancer. These large trials have underscored that small increases in adverse effects cannot be appreciated without large and lengthy clinical trials; however, small increases may have a large public health impact given the number of people at risk. Finally, these trials have reinforced the lesson that nutritional supplements, just like other pharmacologic interventions, can have significant adverse effects; therefore, these agents must also be tested in rigorous clinical trials.

With the understanding of important cellular signaling pathways, various inhibitors that may prevent or reverse lung carcinogenesis are being developed. Many trials are under way to evaluate agents such as selenium and COX-2 inhibitors. For helping to lessen the need for a large sample size, extensive time commitment, and expense, focus has turned toward assessment of SEBs for lung

Table 2—*Results of Large-Scale Chemoprevention Trials in Lung Cancer*

Intervention	Study	Year	End Point	No. of Participants	Results
Aspirin	UK Physicians Health Study[48]	1988	Lung cancer	5,139	Negative
Aspirin	US Physicians Health Study[49]	1989	Lung cancer	22,071	Negative
Beta carotene	US Physicians Health Study[41]	1996	Lung cancer	22,071	Negative
Vitamin E	ATBC[40]	1994	Lung cancer	29,133	Negative
Beta carotene	ATBC[40]	1994	Lung cancer	29,133	Harmful
Beta carotene and retinyl palmitate	CARET[45]	1996	Lung cancer	18,314	Harmful
Retinyl palmitate	Euroscan[47]	2000	Second primary lung cancer	2,592	Negative
N-Acetylcysteine	Euroscan[47]	2000	Second primary lung cancer	2,592	Negative
13-Cis-retinoic acid	NCI Intergroup Trial[46]	2001	Second primary lung cancer	1,166	Negative
Aspirin	US Women's Health Study[50]	2005	Lung cancer	39,876	Negative

carcinogenesis. By integrating biological knowledge, more pilot trials can be performed in a shorter time frame. For individuals who are at high risk for lung cancer or have a history of lung cancer, it is strongly recommended to encourage them to participate in lung cancer chemoprevention trials.

The future of lung cancer chemoprevention should entail the evaluation of single or drug combinations that will target multiple pathways while working toward identification and validation of intermediate end points. Despite this promising future, no one agent is recommended for use in the chemoprevention of lung cancer.

Summary of Recommendations

1. For individuals with a smoking history >20 pack-years or with a history of lung cancer, the use of beta carotene supplementation is not recommended for primary, secondary, or tertiary chemoprevention of lung cancer. Grade of recommendation, 1A

2. For individuals at risk for lung cancer and for patients with a history of lung cancer, the use of vitamin E, retinoids, N-acetylcysteine, and aspirin is not recommended for primary, secondary, or tertiary prevention of lung cancer. Grade of recommendation, 1A

3. For individuals at risk for lung cancer or have a history of lung cancer, budesonide, COX-2 inhibitors, 5-LOX inhibitors, and PGI analogs are not recommended for primary, secondary, or tertiary lung cancer chemoprevention outside the setting of a well-designed clinical trial. Grade of recommendation, 2C

4. For individuals at risk for lung cancer or have a history of lung cancer, the use of oltipraz as a primary, secondary, or tertiary chemopreventive agent of lung cancer is not recommended. Grade of recommendation, 1B

5. For individuals at risk for lung cancer or have a history of lung cancer, the use of selenium and ADT for primary, secondary, or tertiary lung cancer chemoprevention is not recommended outside the setting of a well-designed clinical trial. Grade of recommendation, 1B

6. For individuals at risk for lung cancer or have a history of lung cancer, there are not yet sufficient data to recommend the use of any agent either alone or in combination for primary, secondary, or tertiary lung cancer chemoprevention outside a clinical trial. Grade of recommendation, 1B

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Screening for Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **Lung cancer typically exhibits symptoms only after the disease has spread, making cure unlikely. Because early-stage disease can be successfully treated, a screening technique that can detect lung cancer before it has spread might be useful in decreasing lung cancer mortality.**
Objectives: **In this article, we review the evidence for and against screening for lung cancer with low-dose CT and offer recommendations regarding its usefulness for asymptomatic patients with no history of cancer.**
Results: **Studies of lung cancer screening with chest radiograph and sputum cytology have failed to demonstrate that screening lowers lung cancer mortality rates. Published studies of newer screening technologies such as low-dose CT and "biomarker" screening report primarily on lung cancer detection rates and do not present sufficient data to determine whether the newer technologies will benefit or harm. Although researchers are conducting randomized trials of low-dose CT, results will not be available for several years. In the meantime, cost-effectiveness analyses and studies of nodule growth are considering practical questions but producing inconsistent findings.**
Conclusions: **For high-risk populations, no screening modality has been shown to alter mortality outcomes. We recommend that individuals undergo screening only when it is administered as a component of a well-designed clinical trial with appropriate human subjects' protections.**
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Key words: biomolecular markers; chest radiograph; low-dose CT; lung cancer screening; sputum cytology

Abbreviations: CXR = chest radiograph; ELCAP = Early Lung Cancer Action Project; LDCT = low-dose CT; QALY = quality-adjusted life year; SEER = Surveillance, Epidemiology, and End Results

Renowned for poor outcomes, lung cancer is expected to claim the lives of 160,390 Americans in 2007. [1] When diagnosed during early stages, lung cancer can be treated with surgical resection; however, symptomatic patients almost always present with advanced-stage disease. In principle, screening might intercept some fraction of eventually fatal cases of lung cancer earlier in the disease course. If intercepted early, when the cancer is localized and resectable, and then successfully removed, the outcomes of the patient might be altered. Randomized, controlled trials in the 1970s and 1980s did not validate this principle. These controlled studies showed that screening did detect more early-stage cancers, leading to increased rates of surgery, but there was no evidence that the cancers that were found through screening were actually cancers that would have progressed to cause advanced disease. Instead, the intervention and control arms in these studies had the same frequency of advanced cancer diagnoses and deaths from lung cancer, despite the

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intervention (screened) subjects' receiving a diagnosis more often of early lung cancer. Going forward, the hope is that a more sensitive screening modality, that can identify smaller lung cancers, will succeed where chest radiograph (CXR) has failed, preventing both advanced cases of lung cancer and deaths from lung cancer by intercepting the disease earlier.

Exhaustive reviews of lung cancer screening techniques have been published elsewhere, including one published by the American College of Chest Physicians in 2003.[2] All of these reports are in near complete consensus that screening for lung cancer with either CXR or sputum cytology is not appropriate.[2]

Materials and Methods

To update previous recommendations on lung cancer screening, we identified by a systematic review of the literature (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), the primary analysis of individuals who were screened for lung cancer between 2002 and May 2005, as well as studies that provided insights into the theoretical basis of screening or the clinical behavior of lung cancers found through screening. Supplemental material appropriate to this topic was obtained by literature search of a computerized database (Medline) and review of the Thoracic Oncology NetWork reference lists of relevant articles. Recommendations were developed by the writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), and reviewed by all members of the lung cancer panel before approval by the Thoracic Oncology Network, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians. This article is intended as an update of the existing lung cancer screening guidelines and focuses only on recent developments and recent new studies of screening technologies. The initial article contained a comprehensive literature review on the topic.

Results

Low-dose CT (LDCT) scanning remains the most promising of lung cancer screening techniques, but the results of ongoing randomized trials are not expected for at least another 2 to 3 years. In the meantime, researchers have pursued other approaches to evaluating the impact of CT screening on lung cancer outcomes and also focused on other issues that might affect how screening is used, such as investigating the hazard that smaller, early-stage, LDCT-detected nodules pose; the cost-effectiveness of LDCT as a screening modality; and the survival of subgroups of subjects who have been screened. Alternatives to imaging technologies such as biomolecular marker screening and proteomics are early in their development.

Because very limited data regarding the impact of any of the new screening modalities on patient outcomes have become available since the publication of our last set of guidelines, our conclusions regarding the efficacy of various approaches to lung cancer screening have not changed meaningfully. They continue to be broadly consistent with those published by other organizations (Table 1),[39,40] and our conclusions are consistent with a recent health technology assessment of lung cancer screening with LDCT, conducted for the National Health Service R&D Health Technology Assessment Programme.[3] Many organizations are not yet offering recommendations regarding CT screening in advance of results from the National Lung Screening Trial, a randomized, controlled trial of LDCT. The guidelines that we offer are meant to help physicians and patients discuss the potential risks and benefits of lung cancer screening and to ensure that patients who agree to be screened appreciate that screening for lung cancer with any modality should be considered experimental, and that they are entitled to protections that are afforded all human subjects who agree to participate in research.

Screening With LDCT

Using relatively low radiation exposure to create a low-resolution image of the entire thorax, LDCT screening is capable of detecting very small, early-stage cancers so that their shape and growth can be observed noninvasively. Previous research has demonstrated that compared with CXR, LDCT detects approximately three times as many small lung nodules; of those that are subsequently diagnosed as cancer, the overwhelming majority are stage I.[4] For the additional early detection to benefit patients substantially, these early lung cancers that are found through LDCT must be reasonably likely to progress to advanced lung cancer, such that they represent a reasonable proportion of cancers that would otherwise manifest as advanced disease and lead to death. Because only data from observational studies of LDCT screening are available and do not include a control group, it is hard to determine whether increased detection of early-stage lung cancers by LDCT screening will lead to a decreased frequency of either advanced lung disease or death as a result of lung cancer.

Previous screening studies that evaluated CXR raised some general concerns about screening with any type of imaging. These studies[2,5,6] showed that although screening does increase the rate of detection of early-stage lung cancers, it fails to reduce the number of late-stage lung cancers or the risk for dying from lung cancer. One possible explanation for this is that screening detects a large number of small, slowly growing, less aggressive lung cancers that are unlikely to progress to a point that they cause clinical

Table 1—*Guidelines on Screening for Lung Cancer*

Recommending Body	Topic	Recommendation
National Cancer Institute (http://www.cancer.gov/cancertopics/pdq/screening/lung/healthprofessional)	CXR and sputum cytology	On the basis of fair evidence, screening does not reduce mortality from lung cancer. On the basis of solid evidence, screening would lead to false-positive results and unnecessary invasive diagnostic procedures and treatments.
National Cancer Institute (http://www.cancer.gov/cancertopics/pdq/screening/lung/healthprofessional)	LDCT	The evidence is inadequate to determine whether screening reduces mortality from lung cancer. On the basis of solid evidence, screening would lead to false-positive results and unnecessary invasive diagnostic procedures and treatments.
American Cancer Society[39]	CXR and sputum cytology	Lung cancer screening is not a routine practice for the general public or even for people who are at increased risk, such as smokers
US Preventive Services Task Force (http://www.ahrq.gov/clinic/uspstf/uspslung.htm)	CXR, sputum cytology, and LDCT	The evidence is insufficient to recommend for or against screening asymptomatic individuals for lung cancer with LDCT, CXR, sputum cytology, or a combination of these tests.
Canadian Coordination Office for Health Technology Assessment (http://www.cadth.ca/media/pdf/213_ct_cetap_e.pdf)	LDCT	Currently, the evidence does not exist to suggest that detecting early-stage lung cancer reduces mortality. At present, screening for lung cancer with multislice/helical CT would be premature.
Society of Thoracic Radiology[40]	LDCT	Mass screening for lung cancer is not currently advocated. Suitable subjects who wish to participate should be encouraged to do so in controlled trials so that the value of CT screening can be ascertained as soon as possible.

disease while missing cancers that advance rapidly and cause the majority of deaths from lung cancer. The phenomenon of detecting more slowly growing cancers through screening is well accepted and is referred to as *length-biased sampling*. However, the amount of overlap between screening-detected cancers and lung cancers that will ultimately cause death remains uncertain. That LDCT is a more sensitive technology than CXR does not necessarily equate to LDCT finding more aggressive cancers; it could equate to detecting more small, indolent cancers that would have never grown to a size detectable by conventional CXR. If true, then this might mean that rather than benefiting patients more than CXR, LDCT screening could instead lead to more unnecessary and nonbeneficial procedures than CXR.

Natural History of Clinically Apparent and CT-Detected Lung Cancers: Findings on Doubling Rates

Some research has explored use of the volume-doubling rate to predict the threat posed by smaller, screening-detected lung nodules, based on the hypothesis that nodules that are rapidly growing (*ie*, rapidly "doubling in size") are more likely to cause significant disease. In other words, doubling times are examined on the basis of the assumption that the rate of doubling over a brief time period is at least crudely reflective of a tumor's past behavior and can be used as a proxy for the future behavior of the tumor; therefore, rapidly doubling cancers are more likely to continue to double in size rapidly. Even though the simplifying assumption that cancers double at a constant rate undoubtedly is inaccurate, the general model of doubling times can help to delineate differences in behavior between CT-detected lung cancers and the lung cancer that is common in clinical practice. To that end, the model is theoretically useful for evaluating nodules that are detected by CT screening and also for assessing whether CT-detected nodules have a clinical behavior that is as aggressive as lung cancer that is sporadically detected, usually in advanced stages. This issue is also discussed in the chapter addressing solitary pulmonary nodules.

Because the total number of doublings that typically precede cardinal clinical events have been identified and previous estimates of doubling times have been published, it is possible to assess directly whether reported doubling times of CT-detected nodules fits the doubling times that would be most consistent with the natural history of lung cancer, something that can be accomplished by evaluating epidemiologic data.

For instance, previous studies[7,8] estimated that 20 doublings are interposed between the initial cell division and a tumor's having a diameter of 1 mm; 22 doublings before a tumor theoretically is visible, and

28 doublings before a tumor clearly is visible by CT screening; 35 doublings before it reaches a size at which it is usually clinically apparent; and 40 to 41 doublings to reach a diameter of 100 mm, at which point it is usually lethal. These key time points are illustrated in Figure 1.

Given these time points, we evaluated various hypothetical rates of doubling and the extent to which they mimicked the timing of lung cancer events as documented in the epidemiologic literature on lung cancer. We then compared the most probable doubling rates that fit the epidemiologic literature with the reported doubling rates of CT-detected lung cancer to determine whether CT-detected lung cancers grew more slowly than sporadically detected lung cancers, which today account for nearly all of the deaths from lung cancer.

Figure 1 illustrates the results of the analysis. If the doubling time is 40 days, for instance, and it takes 22 doublings for a tumor to be visible on CT, then the time from first cell division to visibility is 880 days (40 × 22), or 2.4 years (Fig 1). At this rate, the same tumor will take 3.8 years to reach 35 doublings, which is the size at which it would typically be detected in a clinical setting, and 4.6 years (41 doublings) to reach the size at which it likely causes death. We can also see that the average "lead time" (the time between typical CT and clinical detection) would comprise 7 doublings (35 doublings minus 28 doublings) and so in this case would equate to 280 days (a little more than 9 months). The typical time from clinical detection to death (*ie*, the "mean survival") would comprise 6 doublings (41 doublings minus 35 doublings), or 240 days (8 months). The same calculations for slower volume doubling rates, which would be more consistent with longer times between key events, are also shown in Figure 1.

We evaluated three pieces of epidemiologic information on the natural history of sporadically detected lung cancer and determined the range of doubling times that fit the data the best:

1. The Surveillance, Epidemiology, and End Results (SEER) data show that the "mean" survival time for patients with clinically detected lung cancer is < 1 year, even when treated with modern therapies. This survival time is consistent with shorter doubling rates of 40 to 65 days, which equates to a survival time of 0.8 to 1.3 years. By contrast, doubling times of 180 days would equate to a mean survival after diagnosis of 2.4 years, as seen in Figure 1.
2. The SEER data show that the median survival of patients who receive a diagnosis of stage I non-small cell lung cancer and are not treated with surgery is on the order of 14 months.[9] This result is most consistent with a doubling rate near 70 days. By contrast, a doubling time of 180 days would equate to a mean survival of 5.3 years.
3. Research regarding the impact of smoking cessation on lung cancer risk has been shown that risk begins to decline within just a few years of smoking reduction or cessation.[10–12] This finding is most consistent with a doubling time of 40 to 65 days. At a doubling rate in this range, the time from the first cell division to the time of usual clinical presentation would be approximately 3.8 to 6.2 years. By contrast, doubling rates of 180 or 400 days would equate to a 17.7-

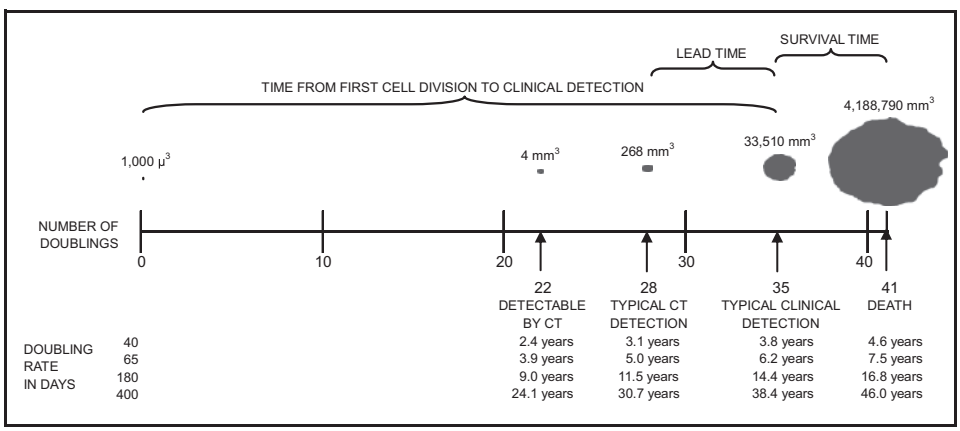

FIGURE 1. Timeline of lung cancer progression by number of tumor doublings and volume doubling rate. The volume doubling rate (measured in days) was calculated using the formula $DR = (t \bullet \ln 2)/\ln (d_2/d_1)$,[37] where t equals time in days, d_1 is the diameter at first scan, and d_2 the diameter at second scan. The size of initial lung cancer cell for all calculations was 1,000 μm.[7] Although the size of a lung cancer cell may vary significantly,[38] this will affect only the time from first cell division to first possible detection, not the time between detection and other clinical events.

or 38.4-year gap between smoking cessation and a fall in risk for lung cancer.

On the basis of epidemiologic benchmarks and the assumption that the model of doubling time is somewhat robust across the natural history of lung cancer, the evidence suggests that doubling times of approximately 40 to 70 days are most consistent with the natural history of lung cancers that are responsible for most lung cancer deaths. In this light, it is useful to examine reported doubling times in screening studies to help determine to what extent cancers that are detected by screening double at rates that are slower than the rates that are consistent with the natural history of the disease. For instance, Hasegawa et al[13] reported that among 61 lung cancers identified by CT screening, the doubling times ranged from 149 to 813 days—all rates much slower than the 40- to 70-day doubling times that best fit the epidemiologic data. Yankelevitz et al[14] documented that even CXR screening detects more slowly doubling lung cancers: only a minority of stage I lung cancers that were detected by CXR screening in the landmark New York and Mayo lung screening studies had doubling times < 100 days. By contrast, 35 and 11% of these cancers, respectively, had doubling times > 300 days. In other words, if doubling times are indicative of clinical behavior, then most lung cancers that are detected through screening are quite a bit more indolent than lung cancers that account for most clinical disease.

Cost-effectiveness of LDCT

Researchers have been eager to determine the cost-effectiveness of lung cancer screening, a task made difficult by the absence of efficacy data (Table 2).[15,17,18,41] Two studies have examined the cost of a single, "prevalence" screening compared with no screening on the basis of the apparent shift in stage distribution reported in the Early Lung Cancer Action Project (ELCAP) cohort (85% stage I in screening arm vs 21% stage I in the no-screening arm).[15,16] Both estimated the incremental cost-effectiveness for screening a population with high lung cancer prevalence rates (2.7%, also derived from the ELCAP study) and low lung cancer prevalence rates ($\leq 1\%$) and used similar costs for CT scans. Wisnivesky et al[16] estimated that a one-time LDCT scan will cost roughly $2,500 per life-year gained under the assumption of high prevalence and $19,000 per life-year gained under the assumption of low prevalence, assuming a 1.5-year lead-time bias. One-way sensitivity analyses showed that increasing the rate of overdiagnosis to 30% increased cost-effectiveness estimates to roughly $10,000 per life-year; with 50% of cases overdiagnosed, the incremental cost-effectiveness was closer to $80,000.

Also assessing a prevalence screen, the baseline model of Marshall et al[15] assumed 100% detection rate for true cancers and a 21% benign nodule (false-positive) detection rate. With a 5-year cost horizon, these assumptions yielded cost-effectiveness estimates of $5940 per life-year gained for a high prevalence cohort and $23,100 for a low prevalence cohort. In two-way sensitivity analyses, a 1-year lead-time bias increased estimates to $15,274 and $58,183 per life-year gained under assumptions of high and low prevalence, respectively. Maintaining the adjustment for lead time while varying the rate of benign nodule detection generated cost-effectiveness ratios between $11,500 and $20,400.

At least three additional studies have explored the cost-effectiveness of annual LDCT screening, two of which presented their results in quality-adjusted life years (QALYs). A separate study by Marshall et al,[17] using the same assumptions about effectiveness described previously, estimated that for an annual screening for 5 years, the incremental cost-effectiveness per QALY was $19,533. Sensitivity analyses considered a 1-year decrease in survival to account for potential confounding by lead-time and overdiagnosis biases, yielding a cost-effectiveness ratio of $50,473 per QALY. Taking a slightly different approach, Mahadevia et al[18] stratified individuals by smoking status: continuing, quitting, and former (those who had quit > 5 years earlier). Expected diagnoses and mortality rates were obtained from SEER, and the model was sensitive to the degree of stage shift, adherence to screening, degree of length or overdiagnosis bias, cost of CT, and anxiety about indeterminate nodules. For current smokers, effectiveness was modeled as a 50% stage shift with a resulting 13% decrease in lung cancer mortality during the first 20 years. The incremental cost-effectiveness per QALY gained was $116,300 for current smokers. For quitting and former smokers, the corresponding projections were $558,600 and $2,322,700 per QALY, respectively. In sensitivity analyses, only improbably favorable conditions generated costs within the range of the estimates provided by other studies: $42,500 for current, $75,300 for quitting, and $94,400 for former smokers. It should be noted, however, that this study examined costs over a longer time horizon and considered numerous variables in its baseline model that the other cost-effectiveness studies elected to omit.

Although these analyses are highly speculative, from a public health decision-making perspective, they provide a useful preliminary indication of the practicability of screening for lung cancer. Generally, the models that assume some impact from lead-time bias and the detection of indolent (*ie*, overdiagnosed) lung cancers generate cost-effectiveness ratios that

Table 2—*Estimates of Cost-effectiveness per Life-Year Gained of Lung Cancer Screening With LDCT*

Source	Cohort	Prevalence	Screening Regimen	Effectiveness	Time Horizon	Cost of Screening LDCT (Diagnostic CT), $	Cost-effectiveness per LYG, $†
Mahadevia et al,* 2003[18]	100,000 current, quitting, and former smokers; 60 yr old; >20 pack-year smoking history; 55% male	Varied with smoking status: 0.43 incidence for current smokers	Annual screening for 20 yr	50% stage shift	1–40 yr of follow-up for occurrence of clinical events	300 (429)	Current, 116,300; quitting, 558,600; former, 2,322,700
Marshall et al,* 2001[15]	100,000 smokers; 60–74 yr old; median 45 pack-year smoking history; 45% male	High risk, 2.7%	Annual screening for 5 yr	85% stage I (21% in control arm)	5 yr	150 (280)	50,473
Chirikos et al, 2002[41]	Cohort characteristics modeled in treatment costs and life expectancy	High risk, 2.7%; low risk, < 2.7%	Annual screening for 5 yr	50% localized disease (20% in the control arm)	15 yr	291 (340–416)	46,513
Marshall et al, 2001[17]	100,000 smokers; 60–74 yr old; median 45 pack-year smoking history; 45% male	High risk, 2.7%; low risk, 0.7%	One-time screening	85% stage I (21% in control arm)	5 yr	150 (not reported)	15,274
Wisnivesky et al, 2003[16]	1,000 participants; ≥ 60 yr old; ≥ 10 pack-year smoking history	High risk, 2.7%; low risk, 1.0%	One-time screening	85% stage I (21% in control arm)	1 yr after diagnosis, including terminal care costs	165 (300)	$2,500

*Estimates of cost-effectiveness are quality adjusted.
†All estimates include lead time of 1 to 1.5 years with the exception of the results from the Chirikos study, which do not adjust for lead time. LYG = life-year gained.

are fairly unattractive. Analyses that assume that all screening-detected cancers behave like typical clinical lung cancer and that each early-detected cancer displaces a case of advanced lung cancer tend to make screening more appealing. Perhaps a more useful function of these studies is their illustration of the significant impact that defining risk has on the potential cost-effectiveness of screening. Clearly screening only the people who are at very high risk for developing lung cancer will improve the efficiency of the test and its incremental cost-effectiveness; however, identifying the population at greatest risk remains a difficult task. One study[19] found that individual risk among smokers varied greatly on the basis of a person's smoking exposure, packs smoked per day, age, gender, and asbestos exposure. However, a large reservoir of cancers may appear in individuals who are at relatively lower risk, of whom there are many, such as groups of former smokers.[20] That the incremental cost-effectiveness for LDCT screening can theoretically differ by as much as $2,000,000 according to present smoking status alone shows how critical a rigorous definition of "high risk" would be going forward, assuming that some approach is demonstrated to be beneficial.

LDCT Ongoing and Future Studies

At least two randomized trials of LDCT are under way. The National Lung Screening Trial has randomly assigned 50,000 high-risk smokers, between 55 and 74 years of age, to annual screening with LDCT or CXR at 36 sites in the United States (http://www.cancer.gov/nlst/screeningcenters). The study is designed to have a 90% power to detect a mortality reduction of 20% by 2009. The NELSON trial,[21] a collaboration between the Netherlands and Belgium, has randomly assigned 16,000 smokers to LDCT screening intervention at years 1, 2, and 4 or usual care and advice on smoking cessation. Designed to measure cost-effectiveness and powered to detect a 25% mortality reduction $>$ 10 years, the study is set to close in 2016.

Available Estimates of the Impact of LDCT Screening on Lung Cancer Mortality and Survival

Although there are not yet comparative data on the rate of lung cancer mortality among patients who are screened with LDCT compared with what might have happened had individuals not been screened, some preliminary analyses are pessimistic. In a study of 1,520 smokers and former smokers who received 5 years of annual LDCT scans at the Mayo Clinic, Swensen et al[22] found that lung cancer incidence and mortality rates were comparable to those in the Mayo Lung Project, after adjusting subsets by age and sex. The Mayo Lung Project was a study of CXR screening that demonstrated no reduction in lung cancer mortality among screened subjects. Patz et al[23] modeled the mortality rates for these same patients enrolled in the study at the Mayo Clinic as well as subjects enrolled in one of the ELCAP trials, by estimating the stage-specific number of lung cancer deaths over the person-years at risk in each subset. The findings were then compared with those of the original Mayo Lung Project, in which the lung cancer mortality rates were 4.4 deaths per 1,000 person-years in the intervention arm and 3.9 deaths per 1,000 person-years in the usual care arm. This approach produced estimates of similar or higher mortality rates in the LDCT-screened groups: 4.1 deaths per 1,000 person-years in the Mayo Clinic CT trial and 5.5 deaths per 1,000 person-years in the ELCAP trial.

The international ELCAP reported on the lung cancer-specific survival of 412 subjects who had screening-detected clinical stage I lung cancer, who represented 1.3% of 31,567 subjects who had been screened by the group for lung cancer.[24] The investigators reported that this subgroup, which was followed up for a median of 3.3 years, experienced lung cancer-specific survival that was superior to the overall survival of similar patients seen in epidemiologic cohorts. Sobue et al[25] also reported that as part of the Anti-Lung Cancer Association Project, 5-year survival for individuals with screening-detected lung cancer was much higher (65 to 76%) than current 5-year survival rates for sporadically detected lung cancers.

These studies that exclusively examine survival of individuals with screening-detected lung cancer have two weaknesses that limit the inferences that can be drawn. For example, in the international ELCAP analysis, there is no information on the outcomes of the 98.7% of subjects who did not have screening-detected stage I lung cancer, so the reader cannot determine whether a large or small number of lung cancer deaths occurred among the subjects. Second, the comparators in these studies are intrinsically biased, because screening improves survival through lead-time and length-time biases, even in the absence of an impact on natural history; therefore, these studies provide limited information regarding the potential benefit or harm of LDCT screening.

Conclusions

LDCT

At present, the risks of LDCT are readily observable, but the impact on mortality remains unknown. Even if LDCT is ultimately shown to effect a mortality reduction, the legitimate concern about overdiagnosing cancers, the uncertainty about how to assess nodule growth

rates, the influence of patient risk level on effectiveness and cost-effectiveness, and the high rates of benign nodule detection and subsequent treatment prompted by such detection all suggest that the cumulative consequences of screening may not be favorable. However, the high rate of small nodule detection is a reason for optimism. Given the conflicting data and the potential benefit to the public health of an early detection modality that is capable of reducing the frequency of advanced lung cancer and death from lung cancer, it is appropriate to pursue research studies that are designed to clarify the issues that remain unanswered at this time. Several randomized trials are evaluating the risks and benefits of LDCT screening in the United States and Europe, particularly focused on patients who are at high risk for lung cancer. There may very well be further such studies begun; if so, then it would be appropriate for physicians to help interested patients identify and enroll in such studies. Any such trial should have a reasonable possibility of generating new knowledge about the harms and benefits of screening and should have appropriate human subjects protections in place, including informed consent procedures. By contrast, the evidence to date does not support offering LDCT screening for individuals, irrespective of their risk for lung cancer, in the absence of an experimental protocol that has been approved by and is being overseen by an institutional review board. This recommendation applies only to individuals with no history of lung cancer. Disease surveillance for individuals with a history of lung cancer is addressed in a separate chapter.

Screening With Biomolecular Markers

Several promising biomolecular marker tests, including sputum analysis and screening the breath for volatile organic compounds and DNA alterations, have gained momentum as lung cancer screening techniques. Evaluated primarily in the context of a supplement to CXR in the randomized, controlled trials in the 1970s and 1980s, sputum cytology was not shown to confer any mortality benefit. Because the trials were often underpowered and seldom concentrated on sputum cytology, its discrete efficacy was unclear.[26] Newer research is focusing on similarly noninvasive technologies that test for biomarkers that are unique to lung cancer.[27,28] Although no single marker is likely to indicate malignant nodules, one strategy that tests for volatile organic compounds has shown that the presence of as few as nine compounds may suggest extant lung cancer.[29,30] More recently, Carpagnano et al[31] showed that micro satellite (DNA) alterations that are specific to lung cancer can also be detected in exhaled breath condensate, which may lead to a more sensitive screening tool. In addition, sensor array analysis using an electric nose has shown promising sensitivity (71.4%) and specificity (91.9%) for lung cancer detection and may ultimately be less expensive than laboratory-based screening tests.[32]

Another evolving screening strategy uses proteomics, identifying patterns of genetic changes in blood and tissue that might signify lung cancer.[33] Researchers[34] have explored expanding this technique to analyze multiple tumor-associated antibodies at once, which may improve the accuracy of screening tests. A proteomic profile of tissue may also be used to screen for both invasive lung tumors and preinvasive lesions and may help to characterize the entire process of lung tumor development on a molecular level.[35] Potentially useful for both screening and monitoring, pattern diagnostic technologies might eventually lead to advancements in therapeutic targeting and customized treatments for patients.[36]

Biomolecular Markers

Biomolecular marker screening techniques for the early detection of lung cancer are still under investigation. Biomarker screening limits patient exposure to potentially damaging constituents such as radiation and tends to be brief and easy for the patient. It remains unclear whether the tests under development will be associated with excesses of false-positive and false-negative results. Screening with biomarkers requires further clinical validation as well as subsequent cost-effectiveness evaluation before any formal recommendation may be made.

Summary of Recommendations

1. We do not recommend that low-dose CT be used to screen for lung cancer except in the context of a well-designed clinical trial. Grade of recommendation, 2C

2. We recommend against the use of serial chest X-rays to screen for the presence of lung cancer. Grade of recommendation, 1A

3. We recommend against the use of single or serial sputum cytologic evaluation to screen for the presence of lung cancer. Grade of recommendation, 1A

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Diagnostic Surgical Pathology in Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

Arnold M. Schwartz, MD, PhD, FCCP; and Donald E. Henson, MD

Objective: **The objective of this study was to provide evidence-based background and recommendations for the development of American College of Chest Physicians guidelines for the diagnosis and management of lung cancer.**

Methods: **A systematic search of the medical and scientific literature using MEDLINE, MDCONSULT, UpToDate, Cochrane Library, NCCN guidelines, and NCI/NIH search engines was performed for the years 1990 to 2006 to identify evidence-based and consensus guidelines. The search was limited to literature on humans and articles in the English language.**

Results: **The pathologic assessment of lung cancers is based on a set of well-accepted findings, including histologic type, tumor size and location, involvement of visceral pleura, and extension to regional and distant lymph nodes and organs. Bronchial-based incipient neoplasia needs to be recognized both grossly and microscopically because these lesions may be multifocal and represent multistep carcinogenesis and may be amenable to therapy. Cytologic assessment of the individual with no symptoms is, as yet, of insufficient clinical benefit for screening of lung cancer. In challenging situations of pathologic differential diagnosis, additional studies may provide information that enables the separation of distinct tumor types. Pathobiological and molecular biological studies may yield prognostic and predictive information for clinical management and should be considered as part of protocol studies. Enhanced pathologic and molecular techniques may identify the presence of micrometastatic disease within lymph nodes; however, the clinical utility of these approaches is still unresolved. Intraoperative consultations have high diagnostic accuracy and may aid ongoing treatment and management decisions.**

Conclusions: **Pathologic assessment is a crucial component for the diagnosis, management, and prognosis of lung cancer. Selective diagnostic techniques and decision analysis will increase diagnostic accuracy. Cytologic screening, molecular characterization of tumors, and micrometastatic analysis are potential but not yet proved modalities for the evaluation of lung cancers.**

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Key words: adenocarcinoma; immunohistochemistry; mesothelioma; non-small cell carcinoma; pathology; small cell carcinoma; squamous cell carcinoma

Abbreviations: AAH = atypical adenomatous hyperplasia; BAC = bronchioloalveolar carcinoma; CEA = carcinoembryonic antigen; CIS = carcinoma *in situ*; CK = cytokeratin; SCCL = small cell carcinoma of the lung; TTF-1 = thyroid transcription factor-1

The precise diagnosis of lung cancer depends on the pathologic examination of cytologic or tissue-based preparations of primary or metastatic tumor or malignant effusions. The pathologic identification of the tumor should be clinically and radiographically correlated to provide consistent diagnostic information, appropriate staging, and relevant prognostic information for management. The goal of pathologic examination is to provide a specific histologic diagnosis of the tumor. Other pathologic processes must be considered, and selected diagnostic tests should be initiated to eliminate tumor-like conditions such as infections, inflammatory masses, immunologic disorders, developmental anomalies, and pneumoco-

niosis. The routine cytologic and histologic preparations and examinations may be supplemented by histochemical and immunohistochemical assays, as well as by electron microscopic ultrastructural, cytogenetic, and molecular studies. The request for special tests should be communicated to the pathologist by the clinician so that special handling and processing techniques may be administered in a timely manner. Collaborative activities to establish tumor banks and setting aside tissue for research and protocol studies should be encouraged.

This chapter on the pathology of lung cancer focuses on newer developments in the classification of lung cancers, bringing together information on the histopathology, immunohistochemistry, and molecular biology of lung cancers. Challenges in diagnostic pathology are presented to demonstrate the role of basic and ancillary studies that are requisite for accurate diagnosis and provide prognostic information for clinical management.

Materials and Methods

For identifying and evaluating guidelines for the pathologic evaluation of lung cancers, a systematic search of the medical and scientific literature using MEDLINE, MDCONSULT, UpToDate, Cochrane Library, NCCN guidelines, and NCI/NIH search engines was performed for the years 1990 to 2006; the search was limited to literature on humans and articles in English. Recommendations developed in this chapter were graded by a standardized method (see "Methodology for Evidence Review and Guideline Development" chapter) and were critically assessed and reviewed by the entire lung cancer panel of authors, the Thoracic Oncology NetWork review committee, the Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.

Results

Pathologic Staging

The pathologic diagnosis of lung tumors has advanced beyond the recognition of benign or malignant neoplasms.[1,2] The designation of epithelial, mesothelial, hematopoietic, and mesenchymal tumors can usually be provided and the histologic subtyping can be accurately rendered. The precise histologic classification of the tumor is encouraged and may be achieved by routine techniques and special methods. The designation of carcinoma *not otherwise specified* should be relegated only to a minority of cases with an attempt to classify better each histologic tumor type. In addition to tumor histology, an assignment of the grade and extent of differentiation of the tumor is afforded by examination of the cellular maturation and physiologic differentiation, architectural pattern and arrangement, nuclear characteristics, cytoplasmic expression, mitotic and apoptotic activity, and extent of tumor necrosis. Gross and histologic examination provides diagnostic and prognostic information regarding the tumor size and location, infiltrative growth margin, the presence of lymphovascular and perineural invasion, permeation of the visceral pleura, and involvement of hilar and/or mediastinal lymph nodes (Table 1). Gross examination and complete histologic review of all bronchial and hilar lymph nodes are crucial for complete tumor staging. Mediastinal lymph nodes should be reported according to their location and surgical station. Histologic examination may also reveal additional pathologic conditions in the nontumorous areas of lung and assess the presence of underlying pathologic conditions, such as smoking-related injuries, pneumoconioses, parenchymal scarring, and secondary effects of the tumor, such as obstructive pneumonia. Special techniques such as immunohistochemistry, flow cytometry, *in situ* hybridization, and molecular biology can aid in the diagnosis of ambiguous cases or supply prognostic information for therapeutic management.[1] Routine cytology and surgical pathology along with special diagnostic studies may be seen as a multiparameter system that increasingly provides basic grading and staging of lung tumors, as well as additional prognostic and predictive information of tumor biology and clinical

Table 1—*Pathologic Staging of Lung Cancer

T stage
Histologic type
Histologic grade
Tumor size
Location
Pleural involvement
Lymphovascular invasion
Mediastinal or chest wall extension
Resection margins
N stage
Lymph nodes, hilar/bronchial
Lymph nodes, mediastinal station/location
Lymph nodes, distant
M stage
Metastases

*Refer to cancer protocols at www.cap.org.

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behavior. Proper staging of lung cancers provides patient stratification of tumor extent, prognostic information, criteria for patient inclusion and exclusion in protocol studies, treatment and management subgroups, and improved communication among members of the multidisciplinary team.[3,4]

Recommendation

1. When pathologically diagnosing patients with lung cancer, the reporting of histologic type, tumor size and location, tumor grade (if appropriate), lymphovascular invasion, involvement of pleura, surgical margins, and status and location of lymph nodes by station is recommended. Grade of recommendation, 1B

Precancerous Lesions

Of the four major types of lung cancer (squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell carcinoma), two have defined precursor lesions: squamous carcinoma and adenocarcinoma.[1,2,5] In general, preinvasive squamous cell lesions are usually found in bronchial lining epithelium and precursor lesions for adenocarcinomas occur more often in outlying pulmonary parenchyma.

In the lung, precancerous lesions are more common than invasive cancer. Careful examination often reveals that multiple precancerous lesions in different stages of development cooccur in the bronchial epithelium or parenchyma, especially in patients with cancer. The sequence of progression from bronchial squamous metaplasia through dysplasia and carcinoma *in situ* (CIS) and progressing to invasive squamous carcinoma represents the multistep carcinogenic pathway for these carcinomas.

Three precancerous lesions are recognized: squamous cell dysplasia, atypical adenomatous hyperplasia (AAH), and diffuse idiopathic pulmonary neuroendocrine hyperplasia. The last, a precursor for carcinoid, was included in the World Health Organization classification.[1] A fourth lesion, malignant mesothelioma *in situ*, has been proposed but remains controversial and was not included. Only the first two types are discussed in this chapter.

Dysplasia is the *sine qua non* of incipient neoplasia. Squamous cell dysplasia is seen primarily in bronchial lining epithelium most often in the lobar bronchi. It often is preceded by basal cell hyperplasia and squamous cell metaplasia, changes associated with chronic irritation. Squamous cell dysplasia is subcategorized by the pathologist as mild, moderate, or severe, which is an indirect assessment of the probability of progression. These mucosal epithelial lesions are histologically graded according to World Health Organization criteria[1] and characterized by increasing cellular atypia, nuclear enlargement, pleomorphism, hyperchromasia, and eventually loss of differentiation and stratification. High-grade dysplasia is considered an irreversible change that is neoplastic and the morphologic forerunner of bronchogenic carcinomas. Clinically, a diagnosis of high-grade, severe, or grade III dysplasia usually indicates persistence of the lesion or subsequent progression to invasive carcinoma in a high proportion of patients.

In squamous CIS, the full thickness of the bronchial epithelium is replaced by squamous cells with the cytologic features of cancer. The cells become hyperchromatic and pleomorphic and exhibit loss of stratification and orientation. The nucleoli are enlarged, and the nuclei are irregular in shape. There is no extension of tumor beyond the underlying basement membrane. These lesions may extend into submucosal glands, but unless the basement membrane is penetrated, they are still noninvasive. The finding of CIS within or adjacent to a cancer provides strong support that the cancer arose from the lung. In considering CIS, the pathologist needs to exclude invasive carcinoma, often using special stains as necessary. The presence of CIS opens the question of additional lesions within the bronchial epithelium, including invasive cancer or the subsequent development of invasive cancer.

Small adenomatous peripheral lesions have long been noted, especially in pulmonary resections for carcinoma. Originally described with a variety of terms, these lesions are now uniformly designated as AAH of the lung. Some previous terms have included *atypical alveolar hyperplasia*, *bronchioloalveolar adenoma*, and *alveolar epithelial hyperplasia*. These lesions are usually multiple, millimeters in size, and found in the peripheral fields often at a distance from central tumors. They have been noted in 5 to 20% of pulmonary resection specimens depending on the extent of search and diagnostic criteria. More benign-appearing forms are often designated as *alveolar cell hyperplasia*, which is considered a reactive lesion and not a preneoplastic change. AAH has been associated with adenocarcinomas, especially the nonmucinous bronchioloalveolar type. The evidence for this association is based on the frequent cooccurrence with cancer, immunohistochemical observations, and morphometric studies. These lesions are more common in lungs resected for adenocarcinoma or large cell undifferentiated carcinoma than for squamous cell carcinoma. Histologically, the involved alveoli and epithelium of the distal bronchioles are lined by atypical cuboidal to low columnar cells, more accurately type II pneu-

mocytes. The atypia is often more pronounced in larger lesions. For the most part, the lesions are not well demarcated; their periphery usually fades away, blending in with normal lung. The alveolar septae are thickened and often contain lymphocytes. The atypical cells are noninvasive with respect to the alveolar septae. Mitotic figures are rarely seen. In contrast to squamous dysplasia, pathologists ordinarily do not provide a grade or designation of mild, moderate, or severe for AAH.

The differentiation of AAH from early adenocarcinoma or bronchioloalveolar carcinoma (BAC) may be difficult.[1,5] It is particularly difficult to separate AAH from the nonmucinous variant of BAC. As yet, no reliable markers or patterns of marker expression have been found to separate the lesions. In general, AAH tends to show variable cytologic atypia, nonoverlapping cells, and blending into the adjacent lung. In contrast, BAC usually demonstrates considerable uniform cytologic atypia, overlapping cells, and an abrupt transition to adjacent normal lung. Diagnosis may rest only on size, with lesions > 0.5 cm often considered malignant. Because of their small size, location, and radiographic similarity to nonneoplastic lesions, such as granulomas, radiologic evaluation of AAH is often difficult.

Cytologic Screening for Cancer

For more than a century, sputum cytology has been used for the initial detection of lung cancer. In some suspected cases, cytology may even reveal early cancer. Although there are a variety of approaches for early detection, for example, spiral CT, sputum cytology is often used by clinicians because it is relatively inexpensive, convenient, and less invasive. Often the initial diagnosis of lung cancer is made on the basis of cytologic examination.

Cytologic diagnosis can be based on smears prepared from sputum, bronchial washing, BAL, scraping or brushing, and fine-needle aspiration.[6,7] All types of specimens should be submitted to the laboratory as expeditiously as possible or, in case of a delay, fixed in transport fluid or in 50 to 70% ethanol. Occasionally, cells may be smeared by the cytologists directly on a glass slide for a "dry-prep." More often, cytocentrifuge preparations are made and stained with the Papanicolaou method similar to the procedure in uterine cervical cytology. If a specimen is very large and contains plugs, then the material may be centrifuged and cell block prepared.

It is not possible, in nearly all cases, to determine the anatomic origin of malignant or atypical cells in sputum specimens. Consequently, further clinical evaluation is necessary to localize the lesion. Smears made from fine-needle aspiration should be fixed immediately to avoid drying artifacts, which may lead to a false-positive diagnosis.

Smears may reveal atypical squamous cells, suggestive of dysplasia, or overt neoplastic cells, indicative of invasive or *in situ* carcinoma. Of the four main types of lung cancer, invasive, or *in situ*, bronchogenic squamous cell carcinoma (a centrally located tumor) is most commonly detected by cytology. Most common, bronchogenic squamous carcinomas, similar to those of uterine cervical origin, desquamate and slough and may present within sputum. Small cells that are suggestive of small cell carcinoma are found in some cases.[8,9] These small cell carcinomas are invariably invasive when discovered through sputum cytology. Adenocarcinomas are usually not detected by sputum cytology, because these cancers tend to occur peripherally and the tumor cells ordinarily do not desquamate into the lumens of the bronchioles. Similarly, endobronchial salivary type tumors, such as mucoepidermoid carcinoma and adenoid cystic carcinoma, are present beneath the normal airway epithelium and are typically not sloughed into the sputum. Therefore, they are less likely to appear in sputum specimens but may be seen in smears made from lavage fluid because they erode the superficial mucosa. Adenocarcinomas are more accessible to fine-needle aspiration.

Sputum cytology is not recommended for screening. The sensitivity is $< 20\%$ in nearly all reported screening trials. Furthermore, because there has been an increase in the frequency of adenocarcinoma in the lung compared with squamous cell carcinoma, the sensitivity of sputum cytology has been decreasing because tumor cells from adenocarcinomas are not likely to appear in the sputum. In a general review[10] of practical applications, the pooled sensitivity for sputum cytology was 66% and the specificity was 99%. The pooled sensitivity is greater for central lesions (71%) than for peripheral lesions (49%). Sensitivity can be increased by using high-resolution image analysis of sputum specimens. For analysis, cells are stained by the Feulgen method for DNA and scanned; these techniques are typically used for research purposes and not available to most laboratories.

Sensitivity can be influenced by a number of factors. Cytology examination is more effective in patients who have symptoms, often with a productive cough and abnormal chest radiograph. Sensitivity can depend on time of specimen collection, number of specimens obtained, and adequacy of the sample. Specimens collected in the early morning and pooled are usually most rewarding. Results may be affected by the experience of the cytologist. However, a negative cytology report does not exclude the presence of cancer. If no or only a few cells are present,

then the specimen is not adequate. Specimens may show infectious agents or reveal other pathologic processes in the lung. A positive diagnosis of cancer on cytology should be followed by further evaluation, including histopathologic confirmation.

Invasion is occasionally difficult to assess in small bronchial biopsy specimens. The basement membrane may not be visible, may be fragmented, or may be covered by inflammatory cells. Invasion is recognized by the presence of tumor cells either singly or in clumps in the underlying stroma. Areas of microinvasion with penetration of a few millimeters may be found. Furthermore, CIS is more likely to be found through sputum cytology.

Adenocarcinomas are less likely to be detected by sputum cytology than by bronchial washes. These tumors are primarily found in the peripheral lung compartment, and malignant cells from adenocarcinomas are less likely to desquamate than malignant cells from squamous carcinomas. There are lesions that may be confused with CIS. These include atypical squamous cell metaplasia, usually associated with long-standing, chronic inflammation, and radiation- or chemotherapy-induced cellular changes.

Recommendation

2. In individuals who are at risk for lung cancer but do not have symptoms or history of cancer, use of single or serial sputum cytologic examinations to screen for the presence of lung cancer is of insufficient clinical benefit and is not recommended. Grade of recommendation, 1A

Malignant Mesothelioma vs Adenocarcinoma

Diffuse malignant mesothelioma is a pleural-based or peritoneal-based cancer that, in the American experience, is predominantly associated with asbestos fiber exposure.[11–15] The diagnosis often accompanies an occupational or environmental exposure history, typical radiographic appearances of an encasing pleural tumor with mediastinal extension, and specific pathologic features. The tumor can present with characteristic radiographic and gross findings and yet display a variety of histopathologic features and invasive growth patterns. These pathologic features may consist of a pure epithelial type, sarcomatoid type, or mixed epithelial and sarcomatoid type. Variant types have also been described, but they are unusual. When malignant mesothelioma shows the epithelial tubulopapillary glandular or nesting pattern merging with a sarcomatoid mesenchymal component, the diagnosis can readily be made. However, when the tumor contains only the epithelial type, its differential diagnosis with pleural-based primary adenocarcinoma or metastatic adenocarcinoma must be considered.

Malignant mesothelioma must also be distinguished from benign reactive counterparts, such a fibrosing pleuritis and mesothelial hyperplasia.[11,14] The pathologist distinguishes the benign reactive or inflammatory pattern of mesothelial hyperplasia from a mesothelioma by the infiltrative pattern of atypical mesothelial cells and the proliferation of densely packed spindle cells. Mesotheliomas have a minor component of inflammatory cells, but the overall architecture is infiltrative, haphazard, and irregular. In contrast, reactive and inflammatory conditions have a layered or zonal pattern of active inflammation with fibrin, granulation tissue, and organized layer of mesothelial proliferation. The reactive vasculature of benign inflammatory conditions seems to proliferate perpendicular to the pleural surface. Reactive mesothelial cells may have proliferative features but will lack cytologic atypia and the abnormal mitotic activity characteristic of malignant tumors. In cases of malignant mesothelioma, the cytokeratin (CK) immunoreactivity may highlight the presence of mesothelial invasion through adjacent stroma. Although these immunohistochemical techniques may be useful in some cases, there are situations that are ambiguous and an absent staining pattern is not helpful.

The differential diagnosis between malignant mesothelioma and adenocarcinoma requires ancillary pathologic studies such as histochemistry, immunohistochemistry, and ultrastructural analysis.[11,14,15] Adenocarcinomas are composed of malignant epithelial cells that contain epithelial-associated mucin, lacking in mesotheliomas that may produce connective tissue mucins. Therefore, adenocarcinomas and not mesotheliomas will be positive for histochemically stained mucicarmine. Mesotheliomas secrete a connective tissue mucin that contains hyaluronic acid. This substance reacts histochemically with Alcian Blue, and its staining properties will, as expected, be eliminated by previous treatment with the enzyme hyaluronidase.

Pathologists appreciate the importance of having a panel of both positive and negative markers for definitive diagnosis. Accordingly, a series of positive immunohistochemical markers for malignant mesotheliomas have been identified[14,15] (Table 2). Immunohistochemical markers that favor malignant mesothelioma include calretinin, CK5/6, and Wilms tumor antigen. Calretinin is an intracellular calcium-binding protein that is found in neural cells, steroid cells of the ovary, and mesothelial cells but absent in pulmonary epithelial cells. Investigators have found that calretinin is immunoreactive in $>75\%$ of me-

Table 2—*Immunohistochemical Profile

Immunohistochemical Marker	Malignant Mesothelioma	Adenocarcinoma
CEA B72.3 LeuM-1 (CD15) TTF-1	Absent†	Present
EMA CK	Present	Present
Calretinin CK5/6 WT1	Present	Absent‡

*EMA = epithelial membrane antigen; WT1 = Wilms tumor antigen.
†Malignant mesothelioma may show immunoreactivity in < 5% of cases.
‡Adenocarcinoma may show immunoreactivity in < 10 to 20% of cases.

sotheliomas and in < 5% of pulmonary adenocarcinomas. Similarly, CK5/6, a subtype of the large family of cytoplasmic keratins, shows strong diffuse immunoreactivity in malignant mesothelioma and absent or sparse positivity in adenocarcinomas. Wilms' tumor antigen may be identified in a variety of nonpulmonary adenocarcinomas; it is selectively immunoreactive in mesothelioma relative to pulmonary adenocarcinoma.

Immunohistochemical techniques that support the diagnosis of adenocarcinoma include carcinoembryonic antigen (CEA), B72.3, Leu-M1 (CD15), and thyroid transcription factor-1 (TTF-1).[14,15] CEA is a surface and cytoplasmic glycoprotein identified in adenocarcinomas from the lung and colon.[11,15] B72.3 is an antibody that reacts with another epithelial glycoprotein, TAG-72, that is present in lung and colon cancers. Leu-M1 belongs to the family of CD15 that is identified in a majority of lung and other visceral cancers. A recent marker, TTF-1 is present in certain lung cancers, such as adenocarcinoma and BAC, as well as in follicular and medullary thyroid cancers. It is nonreactive in mesotheliomas and in adenocarcinomas from other visceral organs. Adenocarcinomas demonstrate strong and diffuse reactivity to these markers in nearly 85 to 100% of cases, whereas < 5% of mesotheliomas will demonstrate only weak focal or sparsely positive reactivity. These markers, when significantly positive, are powerful indicators for eliminating the possibility of malignant mesothelioma.

The "gold standard" for differentiating malignant mesothelioma from adenocarcinoma is the ultrastructural features of the malignant cells identified on transmission electron microscopic examinations.[1] Mesotheliomas have abundant surface microvilli that are long, slender, and branched without filaments or terminal bars. The elongated microvilli are associated with peripheral cytoplasmic glycogen-rich vacuoles. Epithelial cells, conversely, have few short, blunted microvilli that cluster along the luminal border. The microvilli of mesotheliomas, in contrast to those in adenocarcinomas, have no core rootlets and lack glycocalyceal bodies at their base.

Sarcomatoid and desmoplastic mesotheliomas can be distinguished from other mesenchymal tumors of the pleura by a positive immunoreactivity to CK. Typically, mesenchymal sarcomas will be strongly reactive for vimentin, an intermediate cytoplasmic filament, and negative for CKs.

The optimal procedure for separating adenocarcinoma from mesothelioma begins with the routine hematoxylin-eosin sections. If a pleural-based biphasic tumor is identified to be composed of an epithelial tubulopapillary malignancy admixed with a sarcomatous component, then the diagnosis of diffuse malignant mesothelioma is readily made. Monophasic epithelial malignant mesothelioma may be distinguished from adenocarcinoma on the basis of a structured approach using a limited panel of histochemical and immunohistochemical assays. More challenging cases may need additional studies and, if available, ultrastructural analysis. Similarly, sarcomatoid mesothelioma may be diagnosed on a limited set of immunohistochemical phenotyping demonstrating immunoreactivity to CKs and vimentin.

Recommendation

3. In individuals with pleural-based tumors, when distinguishing between pleural adenocarcinoma and malignant mesothelioma, a structured approach using a limited panel of histochemical and immunohistochemical assays is recommended to increase the diagnostic accuracy. More challenging cases may need additional studies, including ultrastructural analysis. Grade of recommendation, 1B

Small Cell vs Non-small Cell Carcinoma

Small cell carcinomas of the lung (SCCL) are high-grade, mitotically active, undifferentiated carcinomas that derive from endogenous neuroendocrine cells and usually present as disseminated disease.[16–18] The tumor cells are smaller than those that compose other types of lung cancers and infiltrate in vague nesting or ribbon-like patterns with a predilection for perivascular invasion. The tumors are associated with geographic areas of tumor necrosis and lack any cytoplasmic features of glandular or squamous differentiation. These malignancies belong to the family of primary pulmonary neuroendo-

crine carcinomas, which are capable of secreting bioactive peptides and demonstrating dense core neurosecretory granules on ultrastructural examination. The cellular size of small cell carcinomas is small relative to that of the other bronchogenic carcinomas but is larger (approximately two to three times) than that of lymphocytes. The cells have a high nuclear/cytoplasmic ratio, minimal cytoplasm, absent or indistinct nucleoli, and a crowded cellular appearance with nuclear molding. Nuclear debris can be seen in the stroma and within vascular walls. The tumor cells are immunoreactive for neuroendocrine markers, such as synaptophysin, chromogranin, and CD56, but without the diffuse positive response seen in well-differentiated neuroendocrine carcinomas or carcinoid tumors. As primary tumors of the lung arising from endogenous neuroendocrine cells, the tumor cells are also immunoreactive for TTF-1.

Accurate diagnosis of SCCL may be rendered on cytologic preparations from fine-needle aspirations, transbronchial biopsies, or open-lung biopsies. The interobserver agreement is $> 95\%$ when the aforementioned criteria are satisfied.[19] On occasion, small cell carcinomas are mixed with large cell carcinoma or combined with other bronchogenic carcinomas and demonstrate the dual histopathologic features of these additional components.

Differentiating small cell carcinoma from other tumor types or pathologic conditions rests on the multiple histologic features and immunohistochemical reactivity described previously. Non-small cell carcinomas usually demonstrate some degree of cytoplasmic differentiation, larger cell and nuclear sizes with prominent nucleoli, lower nuclear/cytoplasmic ratio, and absent nuclear molding and nuclear debris. Other bronchogenic carcinomas will lack immunoreactivity to neuroendocrine markers and, conversely, small cell carcinoma will lack glandular features, cytoplasmic mucin, and extracellular keratin. Small cell carcinoma may be differentiated from non-Hodgkin lymphoma by identification of TTF-1 and neuroendocrine features in the former and their absence combined with immunoreactivity to lymphoid markers in the latter.

Distinguishing SCCL from other types of high-grade neuroendocrine carcinomas presents a challenging differential diagnosis.[17–19] The large cell neuroendocrine carcinoma may be identified by its large polygonal cell type, low nuclear/cytoplasmic ratio, and prominent nucleoli. It shares some features with SCCL, namely, its histopathologic invasive growth pattern, its immunoreactivity to chromogranin and synaptophysin, and its extensive mitotic activity and tumor necrosis. These two high-grade carcinomas may be separated from the intermediate-grade, moderately differentiated neuroendocrine carcinomas or atypical carcinoids by appreciation of the better defined histopathologic differentiation, fewer mitoses, and scant or focal necrosis in the latter group.

Recommendation

4. In individuals with parenchymal-based tumors, distinguishing between small cell carcinoma and non-small cell carcinoma of the lung is recommended. For challenging cases, a diagnostic panel of immunohistochemical assays is recommended to increase the diagnostic accuracy. More challenging cases may need additional studies, including ultrastructural analysis. Grade of recommendation, 1B

Adenocarcinoma vs BAC

Adenocarcinomas are malignant tumors characterized by glandular differentiation, papillary structures, or cytoplasmic mucin vacuoles.[20] The carcinomas may be graded according to the extent of tubular-glandular differentiation. Higher tumor stage at presentation correlates with decreasing degree of tumor differentiation and results in decreased overall survival. Adenocarcinomas are the most frequently diagnosed type of lung cancer. Although lung cancer is linked to smoking exposure, adenocarcinoma is also one of the leading carcinomas among nonsmokers. Adenocarcinomas may be associated with a malignant squamous component, so-called *adenosquamous carcinoma*; however, this subtype is unusual, and its biological progression and clinical behavior best correlate with the degree of differentiation of the adenocarcinoma component. Historically, adenocarcinomas were designated as *scar carcinomas* because they had a granular-cut surface and a fibrotic stromal background. Although some carcinomas may have arisen in scars of tuberculosis or in chronic interstitial fibrosis, research[20] indicates that adenocarcinomas can generate a desmoplastic pattern and induce the formation of a host collagenous stromal response, similar to that seen in breast or pancreatic carcinomas.

Adenocarcinomas often express a variety of epithelial glycoproteins, including CEA. Adenocarcinomas that involve the pleura must be distinguished from malignant mesothelioma as described previously. Grossly, primary adenocarcinomas that are adjacent to the pleura usually show puckering and thickening of the overlying pleura, in contrast to metastatic adenocarcinomas, which tend to show a bulging, stretched overlying pleura.

BAC is a subtype of adenocarcinoma that shows well-differentiated malignant cells that extend

along the luminal surface of alveolar septae in a so-called *lepidic* or *surface* growth without evidence of parenchymal, vascular, or pleural invasion or stromal desmoplasia.[1,21–24] The tumor cells may have a columnar, mucinous, goblet-like cellular pattern, or a hob-nailed, nonmucinous, serous-like cellular pattern. The mucinous pattern, present in a minority of cases, has a typical immunophenotypic profile with tumor cells that are CK7 negative, CK20 positive, and TTF-1 negative. The more common nonmucinous type is composed of type II alveolar pneumocytes or Clara cell differentiation. These tumor cells tend to have the reverse immunohistochemical phenotype, with CK7 and TTF-1 positivity and CK20 negativity. There is an abrupt separation of the BAC component from adjacent normal alveolar structures. Spread of the tumor continues along alveolar surfaces or by airway dissemination. Consequently, the carcinoma may present as a single peripheral mass, as a multicentric tumor, or in a pneumonic pattern.

Clinically and biologically, adenocarcinomas tend to be more aggressive and invasive than BACs. BACs tend to spread along airspaces with aerogenous dissemination, whereas typical adenocarcinomas show lymphatic, hematogenous spread and pleural extension. In select localized cases, surgery may be curative in BAC, similar to other cases of well-differentiated localized tumors with low proliferative rate, absent lymphovascular invasion, and indolent biological and clinical behavior. Extent of lymph node and metastatic spread is higher in adenocarcinomas; consequently, survival is poorer than in BACs. Separating adenocarcinoma from BAC depends on the presence of invasive growth pattern; range of cytologic differentiation; and presence of stromal response in the former and the lepidic growth pattern without invasion, uniform cytologic well-differentiated pattern, and lack of stromal fibrous response in the latter.[22–24] It must be appreciated that although some invasive adenocarcinomas, both primary and metastatic, may show a mixed subtype pattern or a marginal lepidic growth front to the adenocarcinoma, the presence of central tumor invasion and stromal desmoplasia supports the diagnosis of invasive adenocarcinoma and not that of BAC. A limited biopsy of an invasive adenocarcinoma may show the outer marginal bronchioloalveolar growth pattern, yet the true nature of the tumor will be appreciated only on greater examination of the central invasive glandular pattern. BAC can be diagnosed with certainty and distinguished from adenocarcinoma only when the lesion is completely excised and entirely submitted for histopathologic examination.

Recommendation

5. For individuals with glandular-producing tumors, distinguishing pure BAC from adenocarcinoma with or without BAC component is recommended. Grade of recommendation, 1C

Primary vs Metastatic Lung Cancer

Primary tumors of the lung may present in a typical clinical, radiologic, and pathologic pattern. Squamous cell carcinomas present as near hilar masses and are associated with bronchial metaplasia and squamous dysplasia. The cases are found in cigarette smokers and radiologic imaging of chronic obstructive lung disease, and histologic features of chronic bronchitis and emphysematous changes are seen. Adenocarcinomas tend to present in a peripheral location, show retraction or invasion of the visceral pleura, and are associated with tumor desmoplasia or scar. Large cell and small cell carcinomas of the lung also have their typical settings and presentations.

The difficult differential diagnosis occurs with the identification of a single metastatic site of adenocarcinoma or squamous cell carcinoma in the absence of a known primary carcinoma. Squamous cell carcinomas of the head and neck and adenocarcinomas of the gastrointestinal tract may mimic primary lung cancers. Gross and microscopic features of the tumor may provide clues to its primary origin. Lung tumors tend to bronchogenic, arise in bronchogenic squamous metaplasia and/or squamous dysplasia, show infiltrative rather than pushing growth margins, and retract rather than bulge the visceral pleura. Adenocarcinomas from other visceral sites, such as endometrial carcinoma, papillary thyroid carcinoma, clear cell (renal) carcinoma, and hepatocellular carcinoma, may have their own unique histopathologic features. These tumors may be suggested as metastatic on the basis of their cytologic and histologic patterns, and their primary diagnosis should be pursued. Overwhelmingly, lymphomas and sarcomas in the lung are metastatic tumors.

Immunohistochemical analysis has greatly assisted the surgical pathologist in the differential diagnosis of primary vs metastatic carcinoma and has increased the ability to identify metastatic tumors of unknown origin.[25–27] The preferred immunohistochemical marker for the identification of primary lung carcinoma is TTF-1. This factor is selectively expressed embryologically in the thyroid follicular cells and in airway and parenchymal cells of the lung. Papillary,

follicular, and medullary carcinomas of the thyroid show strong immunoreactivity for TTF-1. Primary lung cancers that have histologies of adenocarcinoma, BAC, small cell carcinoma, and carcinoid tumors (well-differentiated neuroendocrine carcinomas) show diffuse strong immunoreactivity. It is interesting that squamous cell carcinoma of the lung is nonimmunoreactive for TTF-1. Adenocarcinomas from other sites, such as the GI and the breast, are nonreactive for TTF-1. Although the carcinomas of the lung are immunoreactive for a set of cellular CKs, the specific CK components from the large family of these cytoplasmic filaments are somewhat unique to each tumor type. By identifying the immunoreactivity to the pair of CK7 and CK20, additional information may provide support for the differential diagnosis of primary vs metastatic carcinomas.[27] Typically, adenocarcinomas of the lung are CK7 positive and CK20 negative, with the subtypes of BAC and mucinous adenocarcinoma showing simultaneous CK7 and CK20 immunoreactivity. Small cell carcinomas and squamous cell carcinomas tend to be nonimmunoreactive for CK7 and CK20. Most helpful in the analysis is the differential between primary lung adenocarcinoma and metastatic adenocarcinoma of colorectal origin. These carcinomas may appear identical histologically yet have opposite immunohistochemical profiles. In the majority of cases, primary lung adenocarcinomas are TTF-1 positive, CK7 positive, and CK20 negative; colorectal adenocarcinomas have the opposite findings of TTF-1negative and CK7-negative and CK20-positive immunoreactivity. The diagnosis of tumors of unknown origin may also be elucidated by their selective expression of CK7 and CK20 immunohistochemistry. Carcinomas that tend to be CK7 and CK20 positive are those from the urinary bladder. Carcinomas that tend to be CK7 and CK20 negative are those from the liver, kidney, and prostate. In addition, some tumors have specific immunoidentifying markers, such as prostate-specific antigen for prostate carcinoma, thyroglobulin for thyroid carcinoma, alpha fetoprotein and human chorionic gonadotropin for certain germ cell tumors, Hepar-1 for hepatocellular carcinoma, estrogen receptor for some breast and gynecologic cancers, and MART-1 and Melan-A for malignant melanoma.

Recommendation

6. For individuals who have lung tumors and whose differential includes primary lung carcinoma vs metastatic carcinoma, a directed panel of immunohistochemical assays is recommended to increase the diagnostic accuracy. Grade of recommendation, 1C

Pathologic and Molecular Prognostic Markers

Lung cancers are associated with poor survival because of their relatively aggressive pathologic behavior, their advanced stage at presentation, and their limited response to chemotherapy. The availability of pathologic and molecular prognostic and predictive markers provides the clinician with information to stratify patients better according to treatment protocols and study designs. Screening for lung cancer with serum circulating biomarkers has a poor predictive value; however, the monitoring of the clinical course according to serum biomarkers has utility.[28]

The prognostic factors that are accepted or investigational relate to tumor and host factors. Tumor-related prognostic factors consist of disease extent, histopathologic typing and grading, and molecular expression and biological behavior. The host factors consist of clinical status (Karnofsky performance or Eastern Cooperative Oncology Group performance status), comorbid conditions, and presence of paraneoplastic syndromes. This brief review considers only the pathologic and molecular prognostic factors based on tissue analysis.

The standard pathologic prognostic markers relate to the tumor diagnosis, the presence of small cell carcinoma, and the anatomic distribution of the tumor (tumor staging). Molecular identification of mutated p53, a tumor suppressor gene, is considered a prognostic factor for poor survival among cases of nonsmall cell carcinoma and significant among adenocarcinoma and not squamous carcinoma histologic types.[29,30] The immunohistochemical assessment of microvessel density, a marker of tumor-associated angiogenesis, also shows statistical significance as a prognostic marker.[31] Tumors with high microvessel density correlate with a poor clinical outcome. Tumor grading, especially within the histologic type of adenocarcinoma, the presence of angiolymphatic invasion, perineural invasion, and peritumor lymphoid host response, seem intuitively to have prognostic importance; however, these markers are much less significant when compared with nodal status or metastases. As expected, tumors that are poorly differentiated with pleomorphic nuclear patterns tend to demonstrate aneuploid DNA content on flow cytometric analysis. There is a relative decrease in survival in cases with aneuploid DNA tumors as compared with diploid tumors, although the reduction in death is of lesser magnitude after 5 years.[32]

Tumors need a variety of growth factors, growth factor receptors, increase or overexpression of cell-cycle factors, and survival pathways for their proliferation and dissemination. Several reviews[33–35] have demonstrated that a combination of pathobiological

factors are prognostic for clinical behavior of tumor dissemination, recurrence, and overall survival. Prognostic information may be achieved by markers of several tumor pathways, such as cell-cycle regulation and proliferation, tumor cell survival and apoptosis, stromal and matrix modification for angiogenesis and invasion, and intercellular communication and metastasis. Multigene expression profiles have also been attempted with favorable results, improving the prognostic ability of tumor staging and pathologic features with respect to estimation of the relapse-free and overall survival of individuals with non-small cell lung cancer.[34,36] Chen et al,[36] using retrospective data, identified a five-gene signature and constructed a decision-tree analysis to stratify patients into low and high risk for relapse-free and overall survival.

The expression of growth factor receptors has potential as a marker of proliferative activity. The epidermal growth factor family (epidermal growth factor receptor, human epidermal growth factor receptor-2) has been studied by several authors, and systematic reviews[37,38] concluded that they are not recognized as a significant prognostic markers. The role of the antiapoptotic protein bcl-2 in governing the survival pathway has also been studied. Meta-analysis[39] shows that the hazard ratio favors bcl-2positive non-small cell carcinomas, yet the results are heterogeneous and mixed.

Molecular biological factors continue to be an area of great research activity, and molecular events seem to have significant treatment implications.[40–45] In this manner, the molecular markers have a predictive role in cancer management in that the molecular pattern is an indicator of response to therapy, in a similar way that expression of estrogen receptor predicts response to endocrine therapy in breast cancer. Prognostic markers, as discussed previously, are those that indicate biological and clinical behavior and may or may not be informative to therapeutic efficacy. Cases of BAC, especially in women never-smokers, seem to have a mutation in the tyrosine kinase domain that is susceptible to treatment with tyrosine kinase inhibitors.[40,42,43]

Molecular understanding of the pathogenesis of lung cancer, including genetic and epigenetic changes, modifications of tumor suppressor genes and oncogenes, and activation of autocrine and paracrine pathways, will provide targets for directed molecular drug development and avenues for screening and chemoprevention. Additional clinical implications of molecular studies include their ability for early detection and as an adjunct to histopathologic diagnosis. Molecular epidemiology will identify which patient cohorts are more susceptible to environmental carcinogens or to the toxicity of treatment chemotherapy.[45] Molecular studies will continue to complement and supplement histopathologic examinations of tumors and will act as multiparameter systems for prediction of treatment efficacy and clinical prognosis. In the newer studies,[46] however, investigational prognostic factors must integrate and correlate with accepted pathologic and molecular markers, robust patient groups with high statistical power must be included, appropriate and long-term end results must be selected, and there must be implications for improved patient care.

Recommendation

7. For individuals who have lung tumors and have had an assessment of pathologic features and staging parameters, the evaluation of pathobiological and molecular markers is appropriate for protocol investigations and is not routinely recommended for clinical management. Grade of recommendation, 1C

Micrometastases

The presence of metastatic carcinoma in hilar or mediastinal lymph nodes is a major component of lung cancer tumor staging and strongly correlates with increased tumor recurrence, especially at distant sites, and with decreased overall survival. The identification of metastatic tumor in specific nodal sites may be performed during preoperative staging assessment or during definitive surgery, and intraoperative determination of N2 or N3 nodal status may be requested. Data have indicated that not only the quality (presence or absence of metastatic cancer) but also the quantity (the total number of lymph nodes examined) is important.[47] The identification of $>$ 12 lymph nodes that are free of cancer is associated with an increase in survival of 26% relative to resection in which only 1 to 4 lymph nodes are sampled. Statistically, the increase sampling of lymph nodes ensures the N0 status and is associated with fewer staging errors of misclassifying stage II or IIIA as stage I.

For improving the intraoperative identity and sampling of lymph nodes, sentinel lymph node methods have been proposed.[48–53] These techniques use the physiologic draining pattern of a radionuclide tracer (^{99m}Tc) with or without a soluble dye. In cases in which both techniques were used, the quantity of nodal identification was concordant for both radioactivity and blue staining. Enhanced pathologic evaluation using immunohistochemical or molecular methods of designated sentinel lymph nodes increases the possibility of identifying the presence of micrometastases.[52,53] As expected, most sentinel

lymph nodes were graded as N1 with a minority graded as N2. The identification of positive sentinel lymph nodes was associated with increased tumor staging and reduced overall survival.

The complete resection of a stage I, organ-confined lung cancer would predict for an excellent survival. Despite this theoretical prognosis, between 25% and 40% of non-small cell lung cancers recur. Because invasive carcinomas have the ability to invade lymphovascular channels, the presence of early or initial malignant spread to regional lymph nodes would stratify those cases that are more likely to disseminate from those that lack this nodal involvement. Lymph nodes that initially were considered to be free of carcinoma may harbor malignant cells that are beyond the detection of routine histopathologic evaluation. Lymph nodes that have minimal or occult nodal metastases may be identified using enhanced pathologic or molecular techniques. Although there are several approaches to the pathologic or molecular identification of minimal metastatic tumor, descriptive characterization of minimal metastatic involvement is not clearly defined.[54–56] Occult metastases refer to cases in which the initial macroscopic examination and histologic sections fail to disclose the presence of malignancy, whereas continued and multiple sectioning of the lymph node reveals their presence. The distinction between micrometastases and isolated tumor cells has been proposed and incorporated by the staging manual of the American Joint Committee of Cancer.[57,58] Micrometastases refer to the presence of a nodal malignant focus $>$ 0.2 mm and $<$ 2 mm. The tumor deposit should demonstrate a proliferative and stromal reaction. Isolated tumor cells indicate a cluster of tumor cells, $<$ 0.2 mm, that do not show evidence of extravasation, cellular proliferation, or stromal response. Most investigators[59–63] have pursued enhanced pathology by probing the resected lymph nodes with immunohistochemical techniques that assay for CK markers. Others[64–66] have used more sophisticated and molecular techniques, such as flow cytometry and reverse transcriptase-polymerase chain reaction, to identify malignant epithelial cells within the lymph node. The techniques have also been allocated to the detection of malignant cells within the bone marrow as a marker of tumor dissemination.[67–69] Several studies[70–72] have also correlated the presence of micrometastatic carcinoma with tumor histology and small tumor size. As expected, micrometastatic carcinoma is more probable in invasive adenocarcinomas than in BACs, because BACs rarely enter lymphatic channels. In addition, micrometastatic spread is more probable in larger T1 tumors relative to smaller ones, tumors that have a micropapillary adenocarcinoma component, and adenocarcinoma relative to squamous carcinoma. In most studies, the presence of micrometastatic disease is associated with decreased disease-free survival and overall survival relative to cases in which enhanced pathologic or molecular techniques fail to identify occult or micrometastatic carcinoma. The issue, however, is not resolved. Several investigators[54,60,68,73] reported the identification of micrometastatic carcinoma with enhanced pathologic or molecular techniques but failed to demonstrate a clinical benefit. Some of these studies may not have been statistically powered sufficiently to identify a survival benefit with the existence of micrometastatic disease. Other considerations for the lack of clinical benefit may be due to the transport of tumor cells within lymphatic channels of the lymph node or vascular channels of the bone marrow, rather than true destructive invasion characteristic of a metastatic focus. The matter has not achieved consensus. The technique for finding minimal metastatic disease has clearly improved, yet it is still in need of large collaborative efforts with long follow-up periods to demonstrate its clinical relevance and importance.

Recommendation

8. For individuals who have lung tumors and have had an assessment of pathologic features and staging parameters, the determination of occult or micrometastatic disease, using enhanced pathologic or molecular techniques, is not of sufficient clinical utility and is not recommended. Grade of recommendation, 1C

Intraoperative Consultations

Intraoperative consultations during lung cancer cases provide the surgeon with immediate diagnostic information and response to management questions. The pathologist provides unique information to aid the surgeon in treatment and operative decisions. The indications for an intraoperative consultation are to identify the presence of a malignant vs a benign or reactive mass in the setting of an indeterminate radiographic lesion, to assess the extent of disease and the nodal staging of a lung cancer with assessment of N2 or N3 lymph nodes, to determine the adequacy of a surgical margin, to confirm the adequacy of a specimen directed for special molecular or chromosomal studies, and to diagnose an unexpected finding.[74–76] Achievement of best results occurs with optimum communication between surgeon and pathologist: awareness of the clinical history, the surgical procedure, the particular indication for the consultation, and the management conse-

quence of the intraoperative diagnosis. Given different settings and tissue specimens, a pathologist's diagnosis may in one situation initiate definitive surgical resection and in another be cause for the termination of an operative modality. Both the surgeon and the pathologist must also appreciate the inherent limitations of the intraoperative consultation and its time demand, inducible artifacts, restriction on extensive tissue sampling, and diagnostic accuracy. Factors that limit the accuracy of the intraoperative consultation include incomplete communication, inadequate sampling, technical artifacts, and diagnostic and interpretive errors.

Although frozen-section preparation and analysis have been a major approach to the intraoperative consultation, cytologic procedures have enhanced the modality and extended the range of the intraoperative consultation by complementing or, in some cases, replacing frozen-section techniques.[77] Cytologic procedures are faster, easier to prepare, less liable to damage delicate tissue, more amenable to small samples, and nearly as accurate as many frozen sections but are limited by the inability to allow the pathologist to assess and evaluate tissue architecture. Given strict cellular criteria for the determination of malignancy, the false-positive rate of intraoperative cytology should approach zero, similar to frozen-section analysis; however, the lack of histologic tissue orientation increases the chance for sampling error and the false-negative rate. Assessment of surgical margins by frozen-section analysis is consequently more accurate (improved sensitivity and specificity) than cytologic methods, although a cytologically identified positive margin strongly predicts determination of an involved margin by frozen-section techniques.[78]

In evaluating lymph nodes for metastatic tumor, cytologic preparation approaches the accuracy of frozen-section analysis without destroying or consuming necessary tissue for permanent evaluation. Both methods have a concordance that approaches 90%. In addition, cytologic techniques have the advantage of imprinting multiple surfaces of the sectioned lymph node, thereby enhancing tumor detection. The false-positive rate for both techniques is $< 2\%$. The false-negative rate for cytologic evaluation of metastatic disease is directly related to the extent of malignancy in the node, with a 25 to 50% false-negative rate (sensitivity of 50 to 75%) as the nodal tumor involvement approaches micrometastatic size (< 2 mm). Under optimal conditions, the sensitivity, specificity, and overall accuracy for the determination of nodal metastases by cytologic methods are 92.5, 98.2, and 96.7%, respectively.[79] Although sentinel lymph node evaluation is well accepted in breast cancer and melanoma staging, its role in lung cancer is still under exploration.[80,81] Intraoperative ^{99m}Tc sentinel lymph node mapping is effective and identifies lymph nodes that may show macro- or micrometastatic involvement by carcinoma.[81]

The frozen-section approach to the intraoperative diagnostic support has been reviewed by many authors. An audit[82] of 1,000 consecutive cases demonstrated an overall accuracy for all tissue types of 91%, false-negative rate of 2%, false-positive rate of 0.2%, and a deferral rate of 6%. The last group was generally correct in the pathologic process but not in the specific diagnosis. In thoracic cases, which represented $< 10\%$ of the overall tissue submissions, the false-positive and false-negative rates were approximately 1%.[82] The College of American Pathologists,[83] in a survey of 186 participating pathologists who evaluated 1,952 intraoperative consultations, disclosed a concordance rate of 96.5% between the operative frozen sections and the final diagnosis. Most errors were due to sampling insufficiency and, to a lesser extent, misinterpretation of the frozen-section findings. A larger interinstitutional study[84] of nearly 80,000 intraoperative consultations confirmed these results with an overall concordance rate of 98.3%, a deferral rate of 4.2%, and a diagnostic error rate of $< 2\%$. Intraoperative consultation for cases involving lung and mediastinum have the same indications of those for general surgery: specific diagnosis, especially between small cell and non-small cell carcinoma, nodal evaluation and extent of tumor spread for initial stage determination, and assessment of surgical margins of resection.[85,86] A collaborative interinstitutional program[87] of 174 laboratories affiliated with the College of American Pathologists demonstrated that the mean and median frozen-section/permanent-section discordant rates were 1.36 and 0.7%, respectively. The investigators also noted that when laboratories actively monitor their discordant rates, a progressive sustained improvement in performance is achieved. In a series[88] of 122 consecutive cases of lung cancer, intraoperative evaluation of nodal status had excellent results of 95% sensitivity, 100% specificity, and a false-negative rate of 1.6%. Given the testing parameters in this series of cases, the predictive value of a negative frozen section was 99%, indicating reliability for mediastinal evaluation of N2 nodal status. Additional retrospective studies[89–91] have demonstrated diagnostic accuracy regardless of whether the intraoperative technique was frozen sections or cytologic preparations. Frozen-section methods have a sensitivity of 99%, similar to the 97% sensitivity obtained with cytologic procedures. Once again, given the near 100% specificity, the predictive

value of an intraoperative finding (absent negative nodal tumor cells) approximated 99%.

Intraoperative diagnosis of specific lung cancers is also associated with excellent results. Intraoperative diagnosis has a near 98% accuracy in the diagnosis of malignant pulmonary tumors; the accurate diagnosis of benign lesions has a greater error and deferral rate. In an examination[92] of 183 cases of pulmonary tumors < 1.5 cm, the sensitivities for the diagnosis of neoplasia were 87% and 94%, respectively, for tumors that were < 1.1 cm and those that measured 1.1 to 1.5 cm. Well-differentiated tumors, such a carcinoids and BACs, were associated with the highest equivocal interpretations. There were no false-positive diagnoses in the evaluation of malignant tumors. In a study[93] of frozen-section diagnoses of CT-guided biopsies of the chest, 85% of the 55 lesions had sufficient tissue to render a diagnosis, and 74% of the malignant tumors were given a specific histologic diagnosis. Importantly, even in situations in which a definitive diagnosis is not rendered, the findings of the intraoperative consultation may eliminate certain pathologic conditions and enable the surgeon to pursue appropriate management.

Intraoperative evaluation of surgical resection margins ensures immediate pathologic confirmation of complete local excision of the primary tumor.[78,94,95] Bronchial resection margins that are > 30 mm from the primary tumor may be judged macroscopically to be uninvolved without the need for histopathologic confirmation. In a review[95] of frozen-section assessments of surgical margins from 268 cases, the overall accuracy of margin determination was near 97%, with 15% false-positive and 1.9% false-negative results. The pathologist should enhance communication with the surgeon and identify not only the presence or absence of tumor at the margin but also whether the tumor is located within lymphatic channels or other extrabronchial tissue.[94,95]

Conclusions

The proper approach to treating patients with lung cancer begins with a pathologic diagnosis that provides staging information and insights into the biological behavior of the tumor. The surgical pathology report should inform the treating clinician about the multiparameter aspect of the histopathologic features as well as the comorbid nonmalignant pathology of the lung. The presence of multifocal incipient neoplasia should be addressed. Challenging diagnostic issues and differential diagnostic problems, such as differentiating adenocarcinoma from malignant mesothelioma, separating small cell carcinoma from poorly differentiated non-small cell carcinoma, discriminating between classical adenocarcinoma and its unique subtype of bronchioloalveolar, and identifying primary vs metastatic carcinomas must be approached as a collaborative team effort. The pathologist should have the clinical information and radiographic findings, including the results from histochemical and immunohistochemical assays and, in select situations, electron microscopic ultrastructural features. The newer pathologic biological and molecular biological prognostic factors will amplify the pathologic conclusions and provide avenues toward directed therapy of proliferative activity, invasiveness, angiogenesis, and metastatic potential of a tumor.

Summary of Recommendations

1. When pathologically diagnosing patients with lung cancer, the reporting of histologic type, tumor size and location, tumor grade (if appropriate), lymphovascular invasion, involvement of pleura, surgical margins, and status and location of lymph nodes by station is recommended. Grade of recommendation, 1B

2. In individuals who are at risk for lung cancer but do not have symptoms or history of cancer, use of single or serial sputum cytologic examinations to screen for the presence of lung cancer is of insufficient clinical benefit and is not recommended. Grade of recommendation, 1A

3. In individuals with pleural-based tumors, when distinguishing between pleural adenocarcinoma and malignant mesothelioma, a structured approach using a limited panel of histochemical and immunohistochemical assays is recommended to increase the diagnostic accuracy. More challenging cases may need additional studies, including ultrastructural analysis. Grade of recommendation, 1B

4. In individuals with parenchymal-based tumors, distinguishing between small cell carcinoma and non-small cell carcinoma of the lung is recommended. For challenging cases, a diagnostic panel of immunohistochemical assays is recommended to increase the diagnostic accuracy. More challenging cases may need additional studies, including ultrastructural analysis. Grade of recommendation, 1B

5. For individuals with glandular-producing tumors, distinguishing pure BAC from adenocarcinoma with or without BAC component is recommended. Grade of recommendation, 1C

6. For individuals who have lung tumors and whose differential includes primary lung carcinoma vs metastatic carcinoma, a directed panel of immunohistochemical assays is recommended to increase the diagnostic accuracy. Grade of recommendation, 1C

7. For individuals who have lung tumors and have had an assessment of pathologic features and staging parameters, the evaluation of pathobiological and molecular markers is appropriate for protocol investigations and is not routinely recommended for clinical management. Grade of recommendation, 1C

8. For individuals who have lung tumors and have had an assessment of pathologic features and staging parameters, the determination of occult or micrometastatic disease, using enhanced pathologic or molecular techniques, is not of sufficient clinical utility and is not recommended. Grade of recommendation, 1C

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Evidence for the Treatment of Patients With Pulmonary Nodules: When Is It Lung Cancer?*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **The solitary pulmonary nodule (SPN) is a frequent incidental finding that may represent primary lung cancer or other malignant or benign lesions. The optimal management of the SPN remains unclear.**

Methods: **We conducted a systematic literature review to address the following questions: (1) the prevalence of SPN; (2) the prevalence of malignancy in nodules with varying characteristics (size, morphology, and type of opacity); (3) the relationships between growth rates, histology, and other nodule characteristics; and (4) the performance characteristics and complication rates of tests for SPN diagnosis. We searched MEDLINE and other databases and used previous systematic reviews and recent primary studies.**

Results: **Eight large trials of lung cancer screening showed that both the prevalence of at least one nodule (8 to 51%) and the prevalence of malignancy in patients with nodules (1.1 to 12%) varied considerably across studies. The prevalence of malignancy varied by size (0 to 1% for nodules < 5 mm, 6 to 28% for nodules 5 to 10 mm, and 64 to 82% for nodules > 20 mm). Data from six studies of patients with incidental or screening-detected nodules showed that the risk for malignancy was approximately 20 to 30% in nodules with smooth edges; in nodules with irregular, lobulated, or spiculated borders, the rate of malignancy was higher but varied across studies from 33 to 100%. Nodules that were pure ground-glass opacities were more likely to be malignant (59 to 73%) than solid nodules (7 to 9%). The sensitivity of positron emission tomography imaging for identifying a malignant SPN was consistently high (80 to 100%), whereas specificity was lower and more variable across studies (40 to 100%). Dynamic CT with nodule enhancement yielded the most promising sensitivity (sensitivity, 98 to 100%; specificity, 54 to 93%) among imaging tests. In studies of CT-guided needle biopsy, nondiagnostic results were seen approximately 20% of the time, but sensitivity and specificity were excellent when biopsy yielded a specific benign or malignant result.**

Conclusions: **The prevalence of an SPN and the prevalence of malignancy in patients with an SPN vary widely across studies. The interpretation of these variable prevalence rates should take into consideration not only the nodule characteristics but also the population at risk. Modern imaging tests and CT-guided needle biopsy are highly sensitive for identifying a malignant SPN, but the specificity of imaging tests is variable and often poor.** ***(CHEST 2007; 132:94S–107S)***

Key words: CT imaging; diagnosis; lung cancer; MRI; prevalence; solitary pulmonary nodule

Abbreviations: BAC = bronchioloalveolar carcinoma; HRCT = high-resolution CT; PET = positron-emission tomography; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SPN = solitary pulmonary nodule; VDT = volume doubling time

The solitary pulmonary nodule (SPN) is defined as a spherical radiographic opacity that measures up to 3 cm in diameter and is completely surrounded by lung tissue. Because of the widespread use of CT in the investigation of respiratory symptoms, the SPN is a frequent incidental finding. The cause of SPN ranges from lung cancer and metastases from an extrathoracic primary malignancy to infections, scar formation, and other benign lesions. As imaging techniques improve and more nodules are detected, the optimal management of SPN remains unclear. Current strategies include radiographic follow-up, tissue sampling, or surgical resection. Although surgical resection for early stage lung cancer offers potentially curative treatment and the best chance of survival, it is not free of complications and may not be necessary in a significant number of patients with benign SPNs. Evidence-based clinical decision making must incorporate data on the prevalence of SPNs and malignancy in a representative patient population, the radiographic characteristics of the nodule, and the demographic and clinical factors of the patient. We conducted a systematic review to address the following questions: (1) what is the prevalence of SPNs; (2) what is the prevalence of malignancy in nodules with varying characteristics (size, morphology, and type of opacity); (3) what are the relationships between growth rates, histology, and other nodule characteristics; and (4) what are the performance characteristics and complication rates of tests for SPN diagnosis?

Materials and Methods

The review methods were defined prospectively in a written protocol. The SPN Guideline Subcommittee, who authored the accompanying guideline, was consulted. Primary outcomes included prevalence of SPNs, stratified by smoking status, age, and other risk factors; prevalence of malignancy associated with specific nodule characteristics; histologic type and growth rates associated with specific nodule characteristics; diagnostic accuracy (sensitivity, specificity) of tests to determine whether a nodule is malignant; and complication rates of those diagnostic procedures. Secondary outcomes included changes in patient treatment or patient outcomes after diagnostic test or intervention.

Electronic database searches of MEDLINE (through August 19, 2005) and the Cochrane Library (through third quarter 2005) were conducted. The search was limited to English-language articles published since 1995. Additional and older citations were sought through consultations with experts and by identifying citations from included articles, review articles,[1,2] and practice guidelines.[3]

We sought observational studies as well as diagnostic test evaluation studies (question 4) and, when available, experimental studies, such as randomized, controlled trials, that compared the diagnostic interventions of interest. For studies of diagnostic accuracy, we sought single-arm trials that permitted computation of specificity and sensitivity in relation to a reference standard that included histopathologic verification of positive tests and at least clinical follow-up of negative lesions. These studies were required to have at least 10 patients, including at least 5 participants with malignant nodules. We included studies that enrolled patients with pulmonary nodules that measured up to 4 cm in diameter.

A single reviewer screened titles and abstracts for full-text retrieval, and a second reviewer reviewed citations marked as uncertain. Review of full-text articles was conducted in the same manner to determine inclusion in the systematic review. One reviewer performed primary data abstraction, and a second reviewer reviewed the evidence tables for accuracy. All disagreements were resolved by consensus. Findings were reviewed and approved by members of the lung cancer panel, Thoracic Oncology NetWork, Health and Science Policy Committee, and Board of Regents of the American College of Chest Physicians.

What Is the Prevalence of SPNs?

From the literature review, eight large studies[4–18] of lung cancer screening were identified (Table 1). It is important to note that nodules that are detected in screening studies differ in important ways from nodules that are detected in routine clinical practice. In screening studies, the nodules tend to be smaller, the prevalence of malignant nodules is much lower, and the tumor volume doubling times (VDTs) of malignant nodules are generally longer.

The included studies enrolled populations that are believed to be at high risk for lung neoplasm, usually as a result of tobacco use. Both the prevalence of SPNs (8 to 51%) and the prevalence of malignancy in participants with SPNs (1.1 to 12%) varied across studies. The results of these studies were reported in varying manners. Whereas some reported only the number of nodules detected, others provided the percentage of patients with SPNs. In addition, patients with multiple nodules were not clearly separated from those with SPNs, further complicating the attempt to pool data. Gohagan et al[6] reported a 20.5% "positivity rate" (*ie*, 20.5% of patients had a CT scan that was concerning for lung cancer), but the SPN prevalence rate was not reported. Li et al[7,8] reported that 7,847 patients underwent 17,892 screening low-dose and follow-up high-resolution CT (HRCT) scans; the number of patients with pulmonary nodules was not reported, but 819 of those CT scan findings were described as abnormal. In some cases, the same nodule could have appeared on several scans, but also a single patient could have had multiple nodules, making it difficult to estimate prevalence.

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Table 1—*Prevalence of SPNs in Studies of Lung Cancer Screening

Study/Year	Subjects, No.	Smoking Status	Detection Modality	Geographic Location	Prevalence of Any Abnormality	Prevalence of SPNs (Nodule < 3 cm)	Prevalence of Cancer in Patients With Nodules, % (No./Total)	Prevalence of Cancer in All Patients, % (No./Total)
Veronesi et al[4]/2006	5,189 (66% men)	80% current	LDCT	Italy	10% recall rate	NR (10% recall rate)	Approximately 10 (54/520)	1 (54/5,189)
Henschke et al[5]/2004	2,897		LDCT	New York, NY	NR	21.3% (616 of 2,897)	13 (81/616)	2.8 (81/2,897)
Gohagan et al[6]/2004	1,660 (58% men)	60% current; 42% former	LDCT	United States	20.5% (n = 325)	8% (26/1660)	3.8 (1/26)	
Li et al[7]/2004; Li et al[8]/2002; Takashima et al[9]/2003; Hasegawa et al[10]/2000; Sone et al[11]/2001	7,847 (55% men)	NR	LDCT	Nagano, Japan (1996–1999)	NR	NR (819 of 17,892 total scan results abnormal; 605 patients with 747 nodules received follow-up scans)	10.1 (76/747)	1% of nodules receiving follow-up scans (76/7,847)
Swensen et al[12]/2003; Swensen et al[13]/2002	1,520 (52% men)	All current or former (≥ 20 pack-yr)	LDCT	Minnesota	NR	51% (782 of 1,520)	1.1% of 2,244 nodules measured in serial CT; 3.5 (36/1,038) of participants with nodules ≤20 mm; 3.8 (40/1,049) of participants with nodules of any size; 1.4 (40/2,832) of nodules of any size	
Nawa et al[14]/2002	7,956 (79% men)	62% are current or former smokers	LDCT	Fukuoda, Japan	NR	26.3% (2,099 of 7,956)	1.7 (20/2,099)	0.44 (35/7,956)
Henschke et al[15]/2001 (republication of the original data by Henschke et al[16])	1,000 (54% men)	NS (all patients had at least a 10–pack-yr cigarette smoking history)	Single-slice helical CT	New York, NY	NR	23% (233 of 1,000; only noncalcified nodules reported; no size reported; solitary and multiple nodules included[17])	12 (27/233)	2.7 (27/1,000)
Diederich et al[18]/2000	> 700	All patients are heavy smokers (> 20 pack-yr)	LDCT	Munster, Germany	NS	20% for SPNs; 40% for SPNs and multiple nodules (precise numbers not reported)		1.1 (8/700)

*LDCT = low-density CT; NS = not specified; NR = not reported.

Table 2—*Prevalence of Malignancy in Nodules With Varying Size

Study/Year	Participants, No.	Nodules, No.	Overall Prevalence of Malignancy, %	Reference Test	Nodule Size	Nodules With Characteristic, % (No./Total)	Prevalence of Malignancy, %
Henschke et al[5]/2004	2,897	616	2.8	Histologic confirmation and radiographic stability	< 5 mm	61 (378/616)	0
					5–9 mm	39 (238/616)	6
Takashima et al[9]/2003	13,786	80	39	Cancers: tissue diagnosis; benign: 2-yr follow-up or tissue	< 10 mm	56 (45/80)	31
					10–15 mm	28 (22/80)	64
					16–20 mm	12 (10/80)	60
					> 20 mm	4 (3/80)	67
Henschke et al[19]/2002	233	233	12	Not mentioned in this study, but this is report from the ELCAP study	2–5 mm	58 (136/233)	0.7
					6–10 mm	30 (70/233)	20
					11–20 mm	9 (22/233)	45
					21–45 mm	2 (5/233)	80
Henschke et al[16]/1999	1,000	233	12	Cancers: tissue diagnosis; benign: 2-yr follow-up or tissue	2–5 mm	62 (99)	1
					6–10 mm	29 (46)	24
					11–20 mm	6 (9)	33
					21–45 mm	3 (5)	80
Suzuki et al[20]/1999	92	92	39	Histologic confirmation	< 5 mm	2 (2/92)	100
					5–< 10	32 (29/92)	21
					10–< 20	53 (49/92)	41
					≥ 20 mm	12 (11/92)	64
Zerhouni et al[21]/1986	369	384	60	Cancers: tissue diagnosis; benign: 2-yr follow-up	0–1 cm	25 (73/295)	55
					1–2 cm	32 (94/295)	51
					2–3 cm	17 (49/295)	82
					3–6 cm	12 (36/295)	97
					NR	3 (5)	65
Siegelman et al[22]/1986	720	720	56	Cancers: tissue diagnosis; benign: 2 yr follow-up	5–10 mm	18 (113/634)	28
					11–15 mm	31 (197/634)	44
					16–20 mm	19 (121/634)	51
					21–25 mm	11 (72/634)	82
					26–30 mm	10 (61/634)	82
					> 30 mm	11 (70/634)	93

*ELCAP = Early Lung Cancer Action Program. See Table 1 for expansion of abbreviation.

What Is the Prevalence of Malignancy in Nodules With Varying Characteristics?

We identified three nodule characteristics for analysis: size, morphology, and type of opacity (Tables 2–4). Seven studies[5,9,16,19–22] that assessed nodule size found a proportional increase in the risk for malignancy as the diameter of the nodule increased (Table 2). With the exception of one small retrospective study[20] in which two of two nodules < 5 mm in diameter were malignant, the prevalence of malignancy in nodules that measured < 5 mm was exceedingly low (range, 0 to 1%). The risk for malignancy was higher in nodules that measured between 5 and 10 mm (range, 6 to 28%), and it was very high in nodules that measured > 2 cm in diameter (range, 64 to 82%). It is not clear how many of these lesions were > 3 cm and therefore would qualify as pulmonary masses instead of nodules.

Data from six studies[9,21–25] of patients with incidental or screening-detected nodules showed that the risk for malignancy was approximately 20 to 30% in nodules with smooth edges, although one study[25] reported a prevalence of malignancy of 58% in nodules with smooth borders. In nodules with irregular, lobulated, or spiculated borders, the risk for malignancy was higher but varied across studies from 33 to 100% (Table 3).

SPN morphology may be classified as solid, partially solid, or ground glass. Some investigators use the term *nonsolid* to describe the traditional ground-glass morphology. Whereas two studies[7,9] found pure ground-glass opacities to be predominantly malignant (59 to 73%), another study[18] using different terminology found that partially solid nodules had a higher likelihood of malignancy (63%) as compared with nonsolid nodules (18%; Table 4). When partially solid and nonsolid nodules were pooled,[26] the aggregate prevalence of malignancy in such nodules was 32%. The prevalence of malignancy in solid nodules was generally lower (7 to 9%).

What Is the Histologic Type and Natural History (Growth Rate) of Small Pulmonary Nodules With Varying Characteristics?

Nine studies[9,10,27–33] analyzed the histology of pulmonary nodules with purely or primarily ground-glass attenuation on HRCT (Table 5). Bronchioloalveolar carcinoma (BAC) was the most common histologic subtype in such nodules (range, 70 to 100%).

Hasegawa et al[10] reported the VDT for malignant SPNs on the basis of their morphologic characteristics: 813 ± 375 days for pure ground-glass opacities, 457 ± 260 days for mixed or partial ground-glass opacities, and 149 ± 125 days for solid opacities. The same study[10] found the VDT for nodules < 10 mm in diameter to be nearly double that of nodules > 2 cm (536 ± 283 days vs 299 ± 273 days). A second study[33] reported VDT by tumor type but not by radiographic appearance.

Table 3—*Prevalence of Malignancy in Nodules With Varying Edge Characteristics*

Study/Year	Participants, No.	Nodules, No.	Overall Prevalence of Malignancy, %	Reference Test	Nodule Characteristic	Nodules With Characteristic, % (No./Total)	Prevalence of Malignancy, %
Tozaki et al[23]/2005	45	45	64	Histologic confirmation (2-yr follow-up for a few benign nodules)	Smooth	20 (9/45)	22
					Lobulated	27 (12/45)	58
					Irregular	53 (24/45)	83
Takashima et al[9]/2003	13,786	80	39	Cancers: tissue diagnosis; benign: 2-yr follow-up or tissue	Spiculation	38 (23/61)	35
					Lobulation	62 (38/61)	50
Swensen et al[24]/1997	629	629	23 malignant, 65 benign, 12 "indeterminate"	Cancers: tissue diagnosis; benign lesions: either path or 2-yr stability; indeterminate lesions did not meet above criteria	Smooth	33 (114/344)	17
					Spiculated	8 (29/344)	83
					Shaggy	38 (131/344)	33
					Spiculated and shaggy	7 (24/344)	50
					Lobulated	13 (46/344)	50
Swensen et al[25]/1995	163	163	68	Histologic confirmation (2-yr follow-up for a few benign nodules)	Infiltrating	13 (21/163)	76
					Lobulated	1 (2/163)	100
					Smooth	45 (73/163)	58
					Infiltrating, lobulated	11 (18/163)	78
					Lobulated, smooth	24 (39/163)	69
Siegelman et al[22]/1986	720	720	56	Cancers: tissue diagnosis; benign: 2-yr follow-up	Sharp and smooth	11 (66/634)	21
					Moderately smooth	55 (350/634)	42
					Slight spiculation	26 (165/634)	87
					Grossly irregular with complete spiculation	8 (53/634)	94
Zerhouni et al[21]/1986	369	384	60	Cancers: tissue diagnosis; benign: 2-yr follow-up	Infiltrating	31 (91/295)	88
					Lobulated	16 (48/295)	58
					Smooth	44 (130/295)	38
					Not recorded	9 (26/295)	73

What Are the Performance Characteristics of Tests for SPN Diagnosis?

An abundant body of evidence exists for the performance of positron emission tomography (PET) in the evaluation of SPN. Except for one study, the sensitivity of PET for identifying malignancy was consistently high (80 to 100%; Table 6).[34–50] In contrast, the specificity of PET was lower and highly variable (40 to 100%). The point on the summary receiver operating characteristic curve that corresponded to the median specificity reported in 17 studies of PET had a sensitivity of 87% and a specificity of 82.6%.

Other studies used a variety of radiographic techniques to differentiate benign from malignant SPNs, including HRCT and dynamic CT with nodule enhancement. The latter technology yielded the most promising results (sensitivity, 98 to 100%;

Table 4—*Prevalence of Malignancy in Nodules With Varying Morphology**

Study/Year	Participants, No.	Nodules, No.	Overall Prevalence of Malignancy, %	Reference Test	Nodule Characteristic	Nodules With Characteristic, % (No./Total)	Prevalence of Malignancy, %
Li et al[7]/2004	222	222	27	Histologic confirmation of malignant lesions, no histologic confirmation for benign nodules	Solid	25 (15/59)	9
					Mixed GGO	46 (27/59)	49
					Pure GGO	29 (17/59)	59
Takashima et al[9]/2003	13,786	80	39	Cancers: tissue diagnosis Benign: 2-yr follow-up or tissue	Predominant GGO	41 (33/80)	73
					Predominantly solid	59 (47/80)	26
Henschke et al[19]/2002	233	233	12	Subset of ELCAP study	Solid	81 (189/233)	7
					Partially solid	7 (16/233)	63
					Nonsolid	12 (28/233)	18

*GGO = ground-glass opacity. See Table 2 for expansion of abbreviation.

Table 5—*Histologic Type and Natural History (Growth Rate) of Small Pulmonary Nodules With Varying Characteristics

Study/Year	Participants, No.	Nodules, No.	Nodule Characteristic	Nodules With Characteristic, No.	Mean Size, mm	Histology, % (No./Total)	Growth Rate
Kishi et al[27]/2004	38	44	Ground-glass attenuation	36		22 (8/36) AAH; 78 (24/36) AD	NR
			Bubble-like attenuation	20		15 (3/20) Sq; 85 (17/20) AD	
			Lobulation	17		12 (2/17) Sq; 88 (15/17 AD	
			Convergence of peripheral vessels	21		5 (1/21) AAH; 14 (3/21) Sq; 81 (18/21) AD	
			Spiculation	17		18 (3/17) Sq; 82 (14/17) AD	
Nakamura et al[28]/2004	100	100	Pure GGO	27	9.3	100 (27/27) BAC	NR
			Nonpure GGO	73	21.2	29 (21/73) Sq; 32 (23/73) WD Ad; 21 (15/73) MD Ad; 15 (11/73)PD Ad	
Takashima et al[9]/2003	13,786	36	GGO	24	12.5 ± 4.5	21 (5/24) AAH; 71 (17/24) BAC; 8 (2/24) Ad	NR
			Air bronchogram	16		6 (1/16) AAH; 56 (9/16) BAC; 38 (6/16) Ad	
			Concave margin	9		33 (3/9) AAH; 44 (4/9) BAC; 23 (2/9) Ad	
Nakata et al[29]/2003			Pure GGO	33		70 (23/33) BAC; 27 (9/33) AAH; 3 (1/33) Ad	NR
			Mixed GGO	26		58 (15/26) BAC; 0 (0/26) AAH; 42 (11/26) Ad	
Suzuki et al[30]/2002	69	69	Pure GGO	38		84 (32/38) BAC; 16 (6/38) Ad	NR
			Complex GGO (mixed GGO)	31		48 (15/31) BAC; 52 (16/31) Ad	
Wantanabe et al[31]/2002	20	20	Pure GGO	20	7.9 ± 1.9 mm	15 (3/20) AAH; 85 (17/20) BAC	NR
Hasegawa et al[10]/2000	61	61	Pure GGO	19	9.9 ± 4.8	100 (19/19) WD Ad	VDT, 813 ± 375 d
			Mixed GGO	19	11.4 ± 4.4	74 (14/19) WD Ad; 26 (5/19) MD Ad	VDT, 457 ± 260 d
			Solid	23	15.6 ± 5.6	22 (5/23)WD Ad; 9 (2/23) MD Ad; 17 (4/23) PD Ad; 35 (8/23) Sq 17 (4/23) small cell	VDT, 149 ± 125 d
			Size < 10 mm	22		NR	VDT, 536 ± 283 d
			Size 10–15 mm	23		NR	VDT, 466 ± 481 d
			Size 16–20 mm	9		NR	VDT, 325 ± 353 d
			Size > 20 mm	7		NR	VDT, 299 ± 273 ds
Wang et al[32]/2000	12	12	Soft-tissue density (solid)	9		11 (1/9) WD Ad; 33 (3/9) MD Ad; 11 (1/9) PD Ad; 11 (1/9) Sq; 33 (3/9) small cell	NR
			GGO	3		100 (3/3) WD Ad	
			Smooth	7		29 (2/7) MD Ad; 14 (1/7) PD Ad; 14 (1/7) Sq; 43 (3/7) small cell	
			Irregular	5		80 (4/5) WD Ad; 20 (1/5) MD Ad;	
			Spiculation	6		17 (1/6) WD Ad; 17 (1/6) MD Ad; 17 (1/6) PD Ad; 17 (1/6) Sq; 33 (2/6) small cell	
			Lobulation	7		29 (2/7) MD Ad; 14 (1/7) PD Ad; 14 (1/7) Sq; 29 (3/7) small cell	

Table 5—*Continued*

Study/Year	Participants, No.	Nodules, No.	Nodule Characteristic	Nodules With Characteristic, No.	Mean Size, mm	Histology, % (No./Total)	Growth Rate
Aoki et al[33]/2000	34	34	Solid (no GGO)	12		58 (7/12) BAC; 42 (5/12) AD	VDT reported per tumor type, not by nodule characteristics; BAC range 42–1,486 AD; range 124–402; mean 252
			Minimal GGO (< 10%)	5		60 (3/5) BAC; 40 (2/5) AD	
			Moderate GGO (10–50%)	11		100 (11/11) BAC	
			Mostly GGO (> 50%)	6		100 (6/6) BAC	

*AAH = atypical adenomatous hyperplasia; Ad = adenocarcinoma; MD = moderately differentiated; PD = poorly differentiated; Sq = squamous cell carcinoma. See previous tables for other abbreviations.

specificity, 54 to 93%; Table 7).[25,51–56] The point on the summary receiver operating characteristic curve that corresponded to the median specificity reported in seven studies of dynamic CT with enhancement had a sensitivity of 96% and a specificity of 75%.

In 11 studies[38,57–66] of CT-guided needle biopsy, nondiagnostic results were recorded in 4 to 41% of cases (median, 21%). Nondiagnostic biopsy results were seen in approximately 44% of patients with benign nodules (range, 0 to 89%) and 8% of patients with malignant nodules (range, 0 to 22%). In patients with biopsy results that revealed a specific malignant or benign diagnosis, sensitivity ranged from 82 to 100% (median, 97.5%). However, when nondiagnostic biopsy results were included in the false-negative column, sensitivity ranged from 65 to 94% (median, 90%). Although all but one study reported perfect specificity, some studies assumed that all positive biopsy results were true positive (Table 8). In the 11 studies,[38,57–66] the risk for pneumothorax ranged from 15 to 43% (median, 26.5%), and 4 to 18% (median, 5%) of patients required chest tube placement.

In one study[67] of 118 patients with nodules that measured up to 4 cm in diameter, a combined strategy of tissue sampling (percutaneous and bronchoscopic) and radiographic observation with repeat sampling as needed yielded a sensitivity and a specificity of 100%. Further studies are needed to reproduce these promising results.

Results

What Is the Prevalence of SPNs?

The prevalence of SPNs (8 to 51%) and the prevalence of malignancy in patients with SPNs (1.1 to 12%) varied significantly across studies. This variation stems from the inconsistency among studies in method, enrolled population, and reporting of results.

What Is the Prevalence of Malignancy in Nodules With Varying Characteristics (Size, Morphology, and Type of Opacity)?

The prevalence of malignancy in SPNs increased in proportion to size: 0 to 1% for nodules < 5 mm, 6 to 28% for nodules 5 to 10 mm, and 64 to 82% for nodules > 20 mm. Data from six studies[9,21–25] of patients with incidental or screening-detected nodules showed that the risk for malignancy was approximately 20 to 30% in nodules with smooth edges; in nodules with irregular, lobulated, or spiculated borders, the rate of malignancy was higher but varied across studies from 33 to 100%. Nodules that were pure ground-glass opacities were more likely to be malignant (59 to 73%) than solid nodules (7 to 9%).

What Are the Relationships Between Growth Rates, Histology, and Other Nodule Characteristics?

BAC is the most common histologic subtype in nodules with purely or primarily ground-glass attenuation on HRCT (range, 70 to 100%). Limited data exist on the VDT of malignant SPNs.

Table 6—*Performance Characteristics and Complication Rates of Tests for SPN Diagnosis: PET With 18-Fluorodeoxyglucose

Study/Year	Participants, No.	Age, Mean ± SD, Range, Mean, or Mean (Range), yr	Pulmonary Nodules, No.	Lesion Diameter, Mean, Mean ± SD, or Mean (Range), cm	Prevalence of Malignancy in SPNs, %	Reference Test	Sensitivity for Malignancy, % (No./Total)	Specificity for Malignancy, % (No./Total)
Kubota et al[34]/ 1990†	22	35.0–75.0	13	0.5–6.0	46	Surgery, n = 8; bronchoscopy, n = 4; needle biopsy, n = 1	67 (4/6)	86 (6/7)
Gupta et al[35]/ 1992†	20	70.8 (39.0–85.0)	19	0.6–6.0	63	Thoracotomy, n = 9; needle biopsy, n = 8; bronchoscopy, n = 1; observation, n = 1	100 (12/12)	100 (7/7)
Dewan et al[36]/ 1993‡	30	65.3 (38.0–89.0)	31	0.6–3.0	68	Thoracotomy, n = 21; needle biopsy, n = 8; bronchoscopy, n = 1; observation, n = 1	90 (19/21)	80 (8/10)
Patz et al[37]/1993†	51	60.0 (19.0–80.0)	38	38 nodules < 4 cm; 5 masses > 4 cm; 8 poorly defined opacities	66	Bronchoscopy, n = 21; open lung biopsy, n = 14; needle biopsy, n = 14	100 (25/25)	100 (13/13)
Dewan et al[38]/ 1995†§	33	65.2 (41.0–88.0)	22	1–6	73	Thoracotomy or needle biopsy, n = 31; observation, n = 2	100 (16/16)	83 (5/6)
Duhaylongsod et al[39]/1995†‖	100	58.0 ± 4.0	47	2.2 ± 0.8 for 79 SPNs; 5.2 ± 0.8 for 11 masses; 10 ill-defined infiltrates	66	Bronchoscopy or needle biopsy, n = 49; open biopsy, n = 35	100 (31/31)	81 (13/16)
Duhaylongsod et al[40]/1995†	53	61.0 ± 4.0	39	39 nodules 4 cm; 14 masses > 4 cm	56		95 (21/22)	88 (15/17)
Gupta et al[41]/ 1996¶	61	65.0 (24.0–89.0)	42	0.6–3.0	79	Thoracotomy, n = 43; needle biopsy, n = 13; bronchoscopy, n = 4; observation, n = 1	91 (30/33)	78 (7/9)
Dewan et al[42]/ 1997#	52	63.6 ± 11.3	26	3	65	Thoracotomy, n = 36; needle biopsy, n = 9; bronchoscopy, n = 3; mediastinoscopy, n = 3; observation, n = 1	100 (17/17)	100 (9/9)
Gupta et al[43]/ 1998	19	32.0–78.0	19	1.0–3.5	63	Needle biopsy, n = 10; thoracotomy, n = 8; bronchoscopy, n = 1	100 (12/12)	100 (7/7)
Lowe et al[44]/ 1998†	89	63.0 ± 9.5	77	0.7–4.0	66	Needle biopsy or open-lung biopsy	98 (50/51)	69 (18/26)
Orino et al[45]/ 1998	23	64.6	23	1.0–2.8	74	VATS, n = 16; bronchoscopy, n = 4; needle biopsy, n = 3	88 (15/17)	67 (4/6)
Präuer et al[46]/ 1998**	50	59.0 (27.0–84.0)	54	1.8 ± 0.7 (0.3–3.0)	57	Surgery	90 (28/31)	83 (19/23)

Table 6—*Continued*

Study/Year	Participants, No.	Age, Mean ± SD, Range, Mean, or Mean (Range), yr	Pulmonary Nodules, No.	Lesion Diameter, Mean, Mean ± SD, or Mean (Range), cm	Prevalence of Malignancy in SPNs, %	Reference Test	Sensitivity for Malignancy, % (No./Total)	Specificity for Malignancy, % (No./Total)
Hung et al[47]/2001	26	60.0 (27.0–79.0)	26	2.5 ± 0.8	77	Pathology examinations n = 26	95 (19/20)	50 (3/6)
Croft et al[48]/2002	90	63.0 (34.0–86.0)	91	4.4 (0.7–17.0)	82	Mediastinoscopy, TBB, thoracoscopy, thoracotomy, or craniotomy, n = 90	93 (65/70)	40 (6/15)
Matthies et al[49]/2002	36	67.0 (36.0–88.0)	38	2.7 ± 1.2 (0.6–6.0)	53	Biopsy or resection, n = 19; no histology, n = 1	80 (16/20)	94 (15/16)
Herder et al[50]/2004	35	61.0 ± 0.0	36	< 3.0	67	Histology, n = 15; observation, n = 21	93 (13/14)	77 (17/22)

*TBB = transbronchial biopsy; VATS = video-assisted thoracoscopic surgery. See previous tables for other abbreviations.
†These studies included participants with pulmonary nodules and mass lesions; results presented are for pulmonary nodules.
‡Data include findings as reported for 30 nodules and a second nodule in patient 19 that was false positive but not initially reported, as described by Gould et al.[1]
§Data exclude four patients with SPNs (patients 17, 23, 27, and 28) for whom findings were reported previously in 1993 study.
‖Results presented for nodules ≤ 3 cm in diameter.
¶Data exclude 19 patients for whom findings were reported previously in 1992 study, as described by Gould et al.[1]
#Data exclude 26 patients for whom findings were reported previously in 1993 and 1995 studies.
**Four participants had two pulmonary nodules each.

What Are the Performance Characteristics and Complication Rates of Tests for SPN Diagnosis?

The sensitivity of PET imaging for identifying malignant SPNs was consistently high (80 to 100%), whereas specificity was lower and more variable across studies (40 to 100%). Dynamic CT with nodule enhancement yielded the most promising sensitivity (sensitivity, 98 to 100%; specificity, 54 to 93%) among imaging tests. In studies of CT-guided needle biopsy, sensitivity and specificity were excellent when biopsy yielded a specific benign or malignant results, but nondiagnostic results were seen approximately 20% of the time.

Discussion

In patients with incidentally detected SPNs, treatment goals include prompt identification of malignant nodules to permit timely surgical resection and avoidance of surgery (when possible) in patients with benign nodules. Patients with SPNs and their clinicians confront challenging treatment decisions and must weigh the risks and benefits of various treatment strategies. Our report sought answers to key questions that are frequently posed when an SPN is encountered.

Our first question addressed the prevalence of SPNs. Between-study variation in the prevalence of SPNs (Table 1) may be partially explained by the use of different radiographic techniques (*eg*, section thickness on CT), the varying percentage of smokers (former, current, and heavy) included in each study population, and the diverse geographic location of the studies (United States, Japan, Germany, and Italy). Other factors that can affect the prevalence of lung nodules include the technical quality of the scan and interobserver variation related to radiologists' interpretation of the images. On the basis of nodules found on follow-up scans, Swensen et al[12] reexamined baseline scans and retrospectively diagnosed new nodules in 26% of patients. Several studies commented on the appearance of new nodules and resolution of previously seen nodules during scheduled follow-up scans, further complicating the accurate determination of SPN prevalence.

Another important consideration is that these studies screened populations at higher risk for malignancy and therefore did not address the prevalence of SPN in the population at large. It remains unclear whether or how the prevalence of SPN is affected by age and smoking.

For obtaining reproducible information, it is important that future studies of SPN prevalence exclude patients with multiple nodules, as well as patients with masses that measure > 3 cm in diam-

Table 7—*Performance Characteristics and Complication Rates of Tests for SPN Diagnosis: Dynamic CT With Nodule Enhancement

Study/Year	Participants, No.	Nodules or Masses, No.	Prevalence of Malignancy, %	Reference Test	Definition of Positive Test Result (Malignancy)	Sensitivity for Malignancy, % (No./Total)	Specificity for Malignancy, % (No./Total)
Swensen et al[51]/1992†	52	30	73	Tissue diagnosis or observation	Enhancement > 19 HU	100 (23/23)	86 (6/7)
Swensen et al[25]/1995‡§	163	163	68	Tissue diagnosis, n = 132; observation, n = 31	Enhancement > 19 HU	100 (111/111)	77 (40/52)
Yamashita et al[52]/1995‖	32	32	56	Surgical resection or biopsy	Enhancement > 20 HU	100 (18/18)	93 (13/14)
Swensen et al[53]/1996¶	107	107	49	Tissue diagnosis, n = 63; observation, n = 44	Enhancement > 19 HU	98 (51/52)	73 (40/55)
Potente et al[54]/1997#	40	25	68	Thoracotomy, n = 18; needle biopsy, n = 6; bronchoscopy, n =1	Enhancement > 19 HU	100 (17/17)	75 (6/8)
Swensen et al[55]/2000**	356	356	48	Tissue diagnosis, n = 237; observation, n = 119	Enhancement > 15 HU	98 (167/171)	58 (107/185)
Yi et al[56]/2004	198	131	53 (70/131)	TTNB, n = 39; surgery, n = 70; observation, n = 22	Enhancement > 30 HU	99 (69/70)	54 (33/61)

*HU = Hounsfield units; TTNB = transthoracic needle biopsy. See previous tables for other abbreviations.
†Twenty-two nodules were excluded because the final diagnosis was not established (n = 22) or CT was technically inadequate (n = 3).
‡Includes 30 participants reported previously.[3]
§Fifty-five participants were excluded because the final diagnosis was not established (n = 34) or CT was technically inadequate (n = 21).
‖Fifteen participants were excluded because benign calcification was present on standard CT (n = 5), the final diagnosis was not established (n = 7), or CT was technically inadequate (n = 3).
¶Forty-nine participants were excluded because the final diagnosis was not established (n = 41) or CT was technically inadequate (n = 8).
#Fifteen participants were excluded because iodinated contrast material was contraindicated (n = 2), thin-section CT showed calcification (n = 8), CT was technically inadequate (n = 3), or plain CT was typical for acute granuloma (n = 2).
**A total of 169 participants were excluded because the final diagnosis was not established (n = 147), CT was technically inadequate (n = 19), needle biopsy was recently performed (n = 1), an incorrect dosage of contrast material was administered (n = 1), or the nodule diameter (3 mm) was the same size as the CT collimation (n = 1).

eter. For accurate calculation of SPN prevalence, the number of patients with at least one SPN must be reported, instead of the number of total nodules or the number of abnormal CT scans. An ideal study design would enroll a large cross-section of the population and analyze SPN rates in the overall population as well as subgroup of subjects with risk factors for lung cancer, such as smoking status, age, and sex. A study restricted to a specific geographic location would be of greatest interest to physicians in that area. Alternatively, a multicenter study could be stratified by location.

The prevalence of malignancy in detected nodules also varied across studies. A key factor that may account for these differences is the dissimilarity in the sizes of the pulmonary opacities included in each study, with larger nodules having a higher probability of malignancy.

Our second question dealt with the prevalence of malignancy in nodules with varying characteristics. A consistent finding among studies was the association between increasing nodule size and the likelihood of malignancy, as well as the exceedingly low incidence of malignancy in nodules < 5 mm in size. On the basis of this observation, the Fleischner Society[3] recommends that no follow-up is necessary in patients with nodules that measure up to 4 mm in size, provided that they have no risk factors for lung cancer.

On the basis of current data, the edge and morphology characteristics of a nodule are less instructive in determining the probability of malignancy. Although there is a trend toward a lower incidence of malignancy in smooth and solid nodules, no firm conclusions can be drawn, primarily because of the lack of a standardized terminology to describe SPN morphology and the resulting inconsistency between studies.

Our third question addressed the histologic type and growth rate of small pulmonary nodules with varying characteristics. Once again, definitions, classification systems, and results differed across studies. The pure ground-glass malignant pulmonary nodule stood out as an entity that has a long VDT and is predominantly caused by BAC.

The study by Hasegawa et al[10] showed that a lesion that has ground-glass attenuation and seems to be stable over a 2-year period could still be malignant,

Table 8—*Performance Characteristics and Complication Rates of Tests for SPN Diagnosis: CT-guided Needle Biopsy

Study/Year	Participants, No.	Procedures, No.	Prevalence of Malignancy, %	Reference Test	Nondiagnostic Biopsies, % (Malignant, No./Benign, No.)	Sensitivity of Diagnostic Biopsy for Malignancy, % (No./Total)	Specificity of Diagnostic Biopsy for Malignancy, % (No./Total)	Complications, %
van Sonnenberg et al[57]/1988	145†	107	78	NS	20 (7/8)‡	100 (76/76)	100 (10/10)	43 (pneumothorax)
García Río et al[58]/1994	84	84	80	Transbronchial biopsy, thoracotomy, mediastinoscopy, necropsy, response to therapy, or observation	20 (13/4)§	94 (51/54)	100 (13/13)	14 (pneumothorax)
Dewan et al[38]/1995	33‖	22	73	Needle biopsy or thoracotomy, n = 21; 2-yr clinical follow-up, n = 1	41 (4/5)	100 (12/12)	100 (1/1)	41 (pneumothorax); 18 (chest tube)
Li et al[59]/1996	27	27	85	Surgery or autopsy	26 (5/2)¶	83 (15/18)	100 (2/2)	22 (pneumothorax)
Santambrogio et al[60]/1997	Group A: 110#	Group A: 110	Group A: 62	Surgery (n = 217) and clinical follow-up over 15 mo (n = 3)	Group A: 0	Group A: 99 (67/68)	Group A: 100 (42/42)	Pneumothorax: (26, group A; 21, group B)
	Group B: 110#	Group B: 110	Group B: 65		Group B: 6	Group B: 90 (63/70)	Group B: 96 (26/27)	Chest tube: (6, group A; 5, group B)
Wescott et al[61]/1997	62**	75	67	Surgery, biopsy from other site, or clinical follow-up	19 (3/11)	100 (40/40)	100 (21/21)	27 (pneumothorax); 4 (chest tube); 9 (hemoptysis)
Yankelevitz et al[62]/1997	114	114	75	NS	27 (5/26)	100 (80/80)	100 (3/3)	20 (pneumothorax)
Hayashi et al[63]/1998	52	52	72	Surgery, biopsy from other site, autopsy, culture, or clinical follow-up	4 (0/2)	100 (35/35)	100 (15/15)	37 (pneumothorax)
Laurent et al[64]/2000	66††	67	71	Surgery or clinical follow-up	21 (4/10)	100 (43/43)	100 (9/9)	15 (pneumothorax)
Wallace et al[65]/2002	61	57	76	Surgery, biopsy, or clinical follow-up	23 (6/14)	82 (32/39)	100 (18/18)	31 (pneumothorax)
Yamagami et al[66]/2003	108	110	79	Surgery, biopsy, or clinical follow-up	6 (6/0)	95 (77/81)	100 (23/23)	34 (pneumothorax); 4 (chest tube); 6 (hemoptysis)

*See other tables for abbreviations.
†A total of 145 participants had 107 pulmonary lesions, 31 mediastinal lesions, and 12 pleural lesions; data presented are for pulmonary lesions.
‡The final diagnosis was not reported for six additional patients with nondiagnostic biopsies.
§Five of 13 nondiagnostic (malignant) biopsies were suspicious for malignancy.
‖Thirty-three participants had 22 pulmonary nodules ≤ 3 cm, 9 masses > 3 cm, 3 hilar lesions, and 1 case of multiple pulmonary nodules; data presented are for SPNs.
¶In five cases, needle biopsy results were suspicious for malignancy but not diagnostic.
#In group A (n = 110), a cytologist assessed sample adequacy and the biopsy was repeated when necessary; in group B (*n* = 110), immediate cytologic assessment was not performed.
**Sixty-two participants with 64 nodules underwent 75 biopsy procedures; 5 procedures were performed under fluoroscopic guidance.
††Sixty-seven biopsy procedures were performed in 66 participants; results reported for 66 procedures.

challenging the time-honored rule of 2-year radiographic stability as a sign of a benign process. Whether such lesions represent clinically important cases of lung cancer or "overdiagnosed" cases of indolent lung cancer is a question that has not been resolved.

Our last question addressed the performance characteristics and complication rates of tests for SPN diagnosis. The accurate measurement of the sensitivity and specificity of a diagnostic test requires the use of an appropriate reference standard and depends on disease prevalence. Surgical excision of a suspected malignant nodule remains the "gold standard," but the associated risk and expense demand a search for an alternative diagnostic test that is minimally invasive and accurate. At present, the most extensively studied diagnostic test is the PET scan. Data convincingly showed that PET imaging was relatively sensitive for identifying malignancy, but specificity was more variable and often poor to fair. CT-guided tissue sampling yields specific malignant diagnoses but suffers from sampling bias, which dictates additional workup if biopsy results are nondiagnostic in patients with a high pretest probability of malignancy. The associated pneumothorax rate, albeit high, infrequently leads to significant morbidity.

Conclusions

Our report sought evidence related to the prevalence of SPNs, the prevalence of malignancy in patients with SPNs, characteristics of SPNs associated with malignancy, and accuracy of tests that are used for SPN diagnosis. It is clear that further research is needed to address vital questions such as the prevalence of SPNs in the population at large, the characteristics that indicate malignancy, and the best management strategy. Essential steps toward more rigorous research must include the establishment of consensus on classification schema for radiographic opacities, especially with regard to size and morphology, and collaboration among researchers to conduct large-scale clinical trials.

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Evaluation of Patients With Pulmonary Nodules: When Is It Lung Cancer?*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **Pulmonary nodules are spherical radiographic opacities that measure up to 30 mm in diameter. Nodules are extremely common in clinical practice and challenging to manage, especially small, "subcentimeter" nodules. Identification of malignant nodules is important because they represent a potentially curable form of lung cancer.**

Methods: **We developed evidence-based clinical practice guidelines based on a systematic literature review and discussion with a large, multidisciplinary group of clinical experts and other stakeholders.**

Results: **We generated a list of 29 recommendations for managing the solitary pulmonary nodule (SPN) that measures at least 8 to 10 mm in diameter; small, subcentimeter nodules that measure < 8 mm to 10 mm in diameter; and multiple nodules when they are detected incidentally during evaluation of the SPN. Recommendations stress the value of risk factor assessment, the utility of imaging tests (especially old films), the need to weigh the risks and benefits of various management strategies (biopsy, surgery, and observation with serial imaging tests), and the importance of eliciting patient preferences.**

Conclusion: **Patients with pulmonary nodules should be evaluated by estimation of the probability of malignancy, performance of imaging tests to characterize the lesion(s) better, evaluation of the risks associated with various management alternatives, and elicitation of patient preferences for treatment.**

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Key words: emission CT; granulomas; lung metastasis; lung neoplasms; needle biopsy; pulmonary coin lesion; radiograph CT; thoracic radiography; thoracic surgery

Abbreviations: ACCP = American College of Chest Physicians; CXR = chest radiography; FDG = F-18 fluorodeoxyglucose; HU = Hounsfield unit; NSCLC = non-small cell lung cancer; OR = odds ratio; PET = positron emission tomography; SCLC = small cell lung cancer; SPN = solitary pulmonary nodule; TTNA = transthoracic needle aspiration/biopsy

Pulmonary nodules are small, focal, radiographic opacities that may be solitary or multiple. By definition, the solitary pulmonary nodule (SPN) is a single, spherical, well-circumscribed, radiographic opacity that measures ≤ 3 cm in diameter and is surrounded

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completely by aerated lung. There are no associated atelectasis, hilar enlargement, or pleural effusion.[1,2] The term *coin lesion* should be discouraged because nodules are spherical and not coin shaped. Patients with solitary nodules typically have no symptoms. Focal pulmonary lesions that are > 3 cm in diameter are called *lung masses* and are presumed to represent bronchogenic carcinoma until proved otherwise. The diagnosis and management of lung masses and symptomatic nodules are discussed in other chapters in these guidelines.

We further distinguish small, subcentimeter nodules from the classical SPN because, compared with larger nodules, nodules that measure < 8 to 10 mm in diameter are much less likely to be malignant, typically defy accurate characterization by imaging tests, and are often difficult to approach by needle biopsy. Throughout this chapter, we reserve the term *SPN* for nodules that measure at least 8 to 10 mm in diameter and use the term *subcentimeter* to refer to smaller nodules. We use the term *indeterminate* to describe a nodule that is not calcified in a benign pattern and that has not been shown to be stable after > 2 years of follow-up. We do not distinguish screen-detected nodules from nodules that are detected incidentally or distinguish nodules that are detected by chest radiography (CRX) vs chest CT. When treating patients with lung nodules, it is more important to consider the number (solitary vs multiple), size, and morphology of the lesion(s), as well as the presence of symptoms and risk factors for malignancy. In contrast to the patient with an SPN, patients with multiple lung nodules often have symptoms and typically require systemic therapy for an underlying infectious, inflammatory, or neoplastic diseases.

We begin this chapter by discussing recommendations for the patient with an SPN that measures at least 8 to 10 mm in diameter. Next, we discuss recommendations for managing the increasingly common problem of the subcentimeter nodule. Finally, we discuss patients with multiple lung nodules and other special circumstances. Most of the interventions described in this chapter are diagnostic tests. Although there have been many high-quality studies of diagnostic accuracy, few randomized, controlled trials or outcomes studies have been performed. As a result, many of the recommendations in this chapter are based on evidence that is relatively low in quality.

Materials and Methods

To update previous recommendations on the evaluation of patients with pulmonary nodules,[3] guidelines on lung cancer diagnosis and management that were published between 2002 and May 2005 were identified by a systematic review of the literature (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter). Those guidelines, which include recommendations that are specific to the treatment of patients with pulmonary nodules, were identified for inclusion in this chapter. Supplemental material that is appropriate to this topic was obtained by literature search of a computerized database (MEDLINE), as described in the chapter of these guidelines by Wahidi et al.[4] In addition, we identified articles by searching our own files and by reviewing reference lists provided by the Thoracic Oncology NetWork of the American College of Chest Physicians (ACCP). A multidisciplinary writing committee composed of three pulmonologists, two thoracic surgeons, and two radiologists developed the recommendations and graded the strength of the recommendations and the quality of the supporting evidence by using a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter). The resulting guideline was reviewed by all members of the lung cancer guidelines panel before approval by the Thoracic Oncology NetWork, the Health and Science Policy Committee, and the Board of Regents of the ACCP.

Results

SPNs

The SPN is commonly encountered in both primary care and specialty settings. Most lung nodules are detected incidentally on CXRs or CT scans that are obtained for some other purpose. In one study[5] from the 1950s, an SPN was found in 1 of 500 CXRs (0.2%) that were obtained in community settings. More recently, almost 7% of 1,000 healthy volunteers in New York who participated in the Early Lung Cancer Action Project[6] were found to have between one and three nodules on baseline screening CXR. In most of these volunteers (76%), the largest nodule measured < 1 cm in diameter. Perhaps not surprising, an even larger number of the participants in this study (almost 25%) were found to have between one and six lung nodules (many of which were subcentimeter nodules) on a low-dose spiral CT scan of the chest. Of note, more than half of the nodules that were detected by CXR were false-positive findings; the presence of the nodule was not confirmed by low-dose CT. In other studies[4] of screening with low-dose CT, nodules were identified in 8 to 51% of participants at the time of baseline screening.

The prevalence of malignancy in patients with SPN varies widely across studies. In studies[4] of positron emission tomography (PET) with F-18 fluorodeoxyglucose (FDG), the prevalence of malignancy ranged from 46 to 82%. In screening studies,[4] the prevalence of malignant SPN was much lower, roughly 2 to 13% in those with nodules. Most of the screening-detected nodules measured < 10 mm in diameter. In a study[4] of patients with either screening-detected or incidentally detected lung nodules, the prevalence of malignancy was 33 to 60% in nod-

ules that measured 11 to 20 mm in diameter and 64 to 82% in nodules that measured > 20 mm in diameter.

The SPN is important because malignant nodules represent a potentially curable form of bronchogenic carcinoma. In stark contrast to patients who present with more advanced lung cancer, > 60% of patients with clinical stage IA (T1N0M0) tumors will still be alive 5 years after they receive treatment.[7] It is not clear to what extent the malignant SPN represents "early" lung cancer vs "slowly growing" lung cancer, but it should be acknowledged that many patients who present with a malignant SPN probably have tumors that are less aggressive biologically than tumors in patients who present with more advanced stages of lung cancer.[8] Despite this, many cancerous SPNs clearly do not behave in a "benign" or indolent manner: up to 20% of patients with clinical stage IA tumors will have occult mediastinal lymph node metastasis identified by mediastinal biopsy or thoracotomy.[9,10]

Differential Diagnosis: In studies[11–20] of PET imaging, most of which were performed in the United States, the most common causes of benign SPN were healed or nonspecific granulomas, accounting for 25% of all benign causes. Another 15% of benign nodules were caused by active granulomatous infections, including tuberculosis, coccidioidomycosis, histoplasmosis, cryptococcosis, and aspergillosis. Hamartomas comprised an additional 15% of benign lesions. Less common miscellaneous causes of benign nodules included nonspecific inflammation and fibrosis, lung abscesses, round pneumonia, round atelectasis, bronchogenic cysts, healed pulmonary infarcts, focal hemorrhage, hemangiomas, and arteriovenous malformations. Because bronchopneumonia is a very uncommon cause of SPN and unnecessary use of antibiotics encourages the development of resistant strains of bacteria, we strongly discourage the use of empirical antibiotics in patients who have lung nodules with no symptoms. In addition, a trial of antibiotics contributes to avoidable delays in the diagnosis and treatment of patients with malignant nodules.

The most common causes of malignant SPN in studies[11–20] of PET imaging were adenocarcinoma (47%), squamous cell carcinoma (22%), solitary metastasis (8%), undifferentiated non-small cell carcinoma (NSCLC) [7%], small cell lung cancer (SCLC) [4%], and bronchioloalveolar cell carcinoma (4%). Less common causes of malignant SPN included large cell carcinoma, carcinoid tumors, intrapulmonary lymphomas, adenosquamous carcinoma, adenoid cystic carcinoma, and malignant teratomas.

Pretest Probability: Although clinical and radiographic characteristics cannot reliably distinguish between benign and malignant nodules in most patients, it nevertheless is important to estimate the clinical "pretest" probability of malignancy before ordering imaging tests or biopsy procedures. Estimating pretest probability facilitates the selection and interpretation of subsequent diagnostic tests. Common sense suggests that different management approaches are called for in a 30-year-old nonsmoker with a 1-cm, smooth-bordered nodule, and a 70-year-old heavy smoker with a 2.5-cm spiculated nodule. Most patients with SPNs have characteristics that fall somewhere between these two extremes. Although many clinicians estimate pretest probability intuitively, several quantitative models[21–23] have been developed to assist in this task. One validated model[22,24] was developed by investigators at the Mayo Clinic, who used multiple logistic regression analysis to identify six independent predictors of malignancy in 419 patients with noncalcified nodules that measured between 4 and 30 mm in diameter on CXR. Independent predictors of malignancy included older age (odds ratio [OR], 1.04 for each year), current or past smoking (OR, 2.2), history of extrathoracic cancer > 5 years before nodule detection (OR, 3.8), nodule diameter (OR, 1.14 for each millimeter), spiculation (OR, 2.8), and upper-lobe location (OR, 2.2). The prediction model is described by the following equations:

$$\text{Probability of malignancy} = e^x/(1 + e^x)$$

$$x = -6.8272 + (0.0391 \times \text{age}) + (0.7917 \times \text{smoke}) + (1.3388 \times \text{cancer}) + (0.1274 \times \text{diameter}) + (1.0407 \times \text{spiculation}) + (0.7838 \times \text{location})$$

where e is the base of natural logarithms, age is the patient's age in years, smoke = 1 if the patient is a current or former smoker (otherwise = 0), cancer = 1 if the patient has a history of an extrathoracic cancer that was diagnosed > 5 years ago (otherwise = 0), diameter is the diameter of the nodule in millimeters, spiculation = 1 if the edge of the nodule has spicules (otherwise = 0), and location = 1 if the nodule is located in an upper lobe (otherwise = 0).

Of note, the accuracy of this model for predicting malignancy was similar to the accuracy of expert clinicians.[25] Other investigators have attempted to predict malignancy by using the likelihood ratio form of Bayes theorem[21,23] and neural networks.[26–28]

Recommendation

1. In every patient with an SPN, we recommend that clinicians estimate the pretest probability of malignancy either qualitatively by using clinical judgment or quantitatively by using a validated model. Grade of recommendation, 1C

Imaging Tests: Pulmonary nodule diagnosis begins with imaging studies. CXR and CT are useful and widely available. Recent attention has focused on contrast-enhanced CT and FDG-PET. MRI plays a limited role, if any, in most patients.

CXR: SPN diagnosis should begin with a careful review of the CXR. Nodules located within the chest should be seen in more than one radiographic view, although it is sometimes difficult to visualize nodules in the lateral projection. Occasionally, nipple shadows or articular surfaces of ribs can masquerade as pulmonary nodules. In these cases, the use of nipple markers or apical lordotic projections may help to distinguish normal anatomic structures from abnormal nodular parenchymal lesions.

Depending on the location of the lesion and the sharpness of its borders, nodules as small as 5 to 6 mm in diameter can sometimes be visualized by plain CXR.[29] However, many larger solitary nodules are often missed by even experienced chest radiologists. For example, in the Mayo Lung Project,[30] 45 of 50 screening-detected peripheral carcinomas were visible on previous radiographs when reviewed in retrospect. All but one of the tumors measured at least 1 cm in diameter. In another study,[31] 19% of NSCLCs were identified retrospectively on previous CXRs that were interpreted as being normal. Patients with missed lesions had smaller nodules, more superimposing structures, and more indistinct border edges than patients with tumors that were not missed. In a more recent retrospective study[32] of 40 patients with NSCLCs that initially were missed on CXR, the median diameter was 1.9 cm, and 85% of the lesions were peripheral in location. Missed cancers were most commonly located on the right side and in the upper lobes, especially in the apical and posterior segments. A clavicle obscured 22% of the missed lesions.

The recent introduction of dual-energy subtraction digital CXR systems substantially increases the ability to detect nodules. This technique provides markedly enhanced contrast resolution, especially in previously difficult-to-evaluate regions of the lung, including behind the heart and below the diaphragms.[33] It is also possible, by use of both single- and dual-exposure techniques, to vary radiation exposure (kilovolt peak) and thereby facilitate detection of noncalcified nodules.[34] As the use of these newer techniques becomes more widespread in clinical practice, it is likely that fewer lung nodules will escape detection.

In all patients with an SPN, it is essential to compare the current CXR with previous chest films. This point cannot be emphasized strongly enough because nodules that have been stable for at least 2 years usually do not require further evaluation. If the nodule is seen with the benefit of hindsight on the previous CXR, then growth rate of it can be estimated. The growth rate is typically expressed in terms of the doubling time, or the time it takes for the nodule to double in volume. Because the volume of a sphere equals $4\Pi r^3/3$, one doubling in tumor volume corresponds approximately to an increase in nodule diameter of 26%. The doubling time can be calculated by using the formula $dt = (t \times \log 2)/\{3 \times [\log (d_2/d_1)]\}$, where dt is the doubling time in days, t is the time in days between CXRs, d_2 is the diameter of the nodule at the time of the current CXR, and d_1 is the diameter of the nodule at the time of the previous CXR.[35] Doubling times for malignant nodules are highly variable but are generally thought to fall between 20 and 300 days.[36–38] However, older studies of lung cancer growth rates selectively enrolled patients who were more likely to have benign-appearing nodules or nodules that initially escaped detection, biasing the results in favor of longer doubling times. Indirect epidemiologic evidence suggests that most malignant nodules encountered in clinical practice have tumor doubling times that are well < 100 days.[39] Malignant nodules with longer doubling times can grow for many years before symptoms develop. For example, assuming exponential growth, a malignant nodule that measures 10 mm in diameter and has a tumor volume doubling time of 300 days will require > 4 years (approximately five doubling times) to reach a size that is commonly associated with symptoms (32 mm).

Because doubling times for malignant SPN rarely are > 300 days (except in screening studies), 2-year radiographic stability strongly suggests a benign etiology. Some authors[40] have questioned the validity of this rule, especially as it relates to smaller, screening-detected nodules, which may have longer doubling times when cancerous. Many of these nodules have a pure ground-glass appearance, which often represents slowly growing bronchioloalveolar cell carcinoma. Because some ground-glass opacities eventually take on a more aggressive phenotype, longer follow-up for patients with these lesions should be considered.[41,42] However, there is no evidence that extending follow-up beyond 2 years identifies a sizable number of malignant nodules or improves patient outcomes.

Occasionally, a presumptive benign diagnosis can be established when a characteristic pattern of calcification is noted on the CXR. Diffuse, central, laminated, and popcorn patterns of calcification are considered to be benign,[43,44] although the presence of intranodular fat density is more sensitive for identifying a hamartoma than popcorn calcification.[45] If one of these patterns of calcification is clearly evident on the CXR, no additional evaluation is necessary. However, other patterns of calcification, including the stippled and eccentric patterns, do not exclude malignancy. Further evaluation of these nodules is mandatory. Studies[46] have documented that, compared with routine CXR and standard digital radiography, dual-energy digital subtraction radiography improves detection of intranodular calcification.

Recommendations

2. In every patient with an SPN that is visible on CXR, we recommend that previous CXRs and other relevant imaging test be reviewed. Grade of recommendation, 1C

3. In patients who have an SPN that shows clear evidence of growth on imaging tests, we recommend that tissue diagnosis be obtained unless specifically contraindicated. Grade of recommendation, 1C

4. In a patient with an SPN that is stable on imaging tests for at least 2 years, we suggest that no additional diagnostic evaluation be performed, except for patients with pure ground-glass opacities on CT, for whom a longer duration of annual follow-up should be considered. Grade of recommendation, 2C

5. In a patient with an SPN that is calcified in a clearly benign pattern, we recommend no additional diagnostic evaluation. Grade of recommendation, 1C

Chest CT: Because of lack of superimposition of normal structures, CT is both more sensitive and more specific than CXR for detecting nodules. The likelihood of nodule detection increases with use of thinner slice thickness. Single-arm prospective studies[6,47] of CT screening in high-risk participants found one or more nodules in approximately 25% of participants when 10-mm collimation was used. In contrast, approximately 50% of participants were found to have one or more nodules when 1.25- to 5-mm collimation was used for screening.[48–50]

As is true for nodules identified by CXR, all previous CT scans should be reviewed when a nodule is first identified by CT. Chest CT provides more specific information about the location, density, and edge characteristics of nodules that have been detected. In addition, CT sometimes identifies unsuspected lymphadenopathy, synchronous parenchymal lesions, or invasion of the chest wall or mediastinum. Selected morphologic characteristics are described next. We discuss nodule size and attenuation characteristics (solid vs semisolid vs ground-glass) in greater detail in a subsequent section on small, subcentimeter nodules.

Morphologic characteristics on chest CT that suggest malignancy include spiculated margins,[51–53] vascular convergence (which suggests vascular and/or lymphatic invasion),[54] and the finding of either a dilated bronchus leading into the nodule[55] or the presence of pseudocavitation, a "bubbly" appearance thought to represent air bronchiolograms.[53] True cavitation, especially when associated with a thick and irregular wall, is a strong predictor of malignancy. One study[56] found that whereas only 5% of all cavitated nodules with thin walls (< 5 mm) were malignant, the probability of malignancy was $> 85\%$ when maximum wall thickness was > 15 mm.

Morphologic clues can sometimes lead to a presumptive benign diagnosis. For example, arteriovenous fistulas often demonstrate the presence of a feeding artery and a draining vein. A fungus ball can be identified as a solitary nodule within a cavity, although this appearance does not exclude the possibility of malignancy. Acute pulmonary infarcts typically appear on CT as wedge-shaped densities that abut the pleura, involve the lower lobes, and contain air bronchograms, but chronic infarcts may be more difficult to distinguish from a peripheral carcinoma. Rounded atelectasis is characterized by a quartet of CT features, including volume loss, a juxtapleural location, associated pleural thickening, and a dense "comet tail" of bronchovascular structures that points toward the hilum. Although classically associated with asbestos-related pleural disease, this entity may be the result of any process that causes marked focal pleural fibrosis.[57]

Initially described in severely immunocompromised patients with marked neutropenia, the CT halo sign (defined as a zone of ground-glass attenuation surrounding a solid dense core) is strongly associated with the presence of an invasive fungal infection, with the halo caused by hemorrhage surrounding a focal pulmonary infarct.[58] It should be emphasized, however, that other infectious and noninfectious entities may be associated with a positive halo sign, including mycobacterial infections.[59–61]

In the past, CT densitometry was performed by comparing the density of a given nodule with the density of a standardized "reference phantom."[52,62] Relatively sensitive but not specific, this technique is no longer used because of limited reliability.

However, smaller (< 20 mm in diameter), smooth-bordered nodules that contain fat density (< 25 Hounsfield units [HU]) can be confidently diagnosed as a hamartoma, provided appropriate caution is taken to avoid misinterpreting partial volume artifacts as actual fat.[63]

CT with dynamic contrast enhancement has proved to be highly sensitive but nonspecific for identifying malignant nodules.[4] A multicenter study[64] enrolled 356 participants with normal renal function and noncalcified nodules that measured 0.5 to 4 cm in diameter, 48% of which were malignant. Using a threshold for enhancement of 15 HU, the sensitivity and specificity of contrast-enhanced CT were 98% and 58%, respectively. Absence of lung nodule enhancement was strongly predictive of a benign diagnosis; the negative predictive value was 96.5%. Allowing for slight differences in technique, nearly identical results have been reported by others.[65–69]

Risks associated with CT include radiation exposure and adverse effects as a result of administration of iodinated contrast material. The magnitude of the risk associated with radiation exposure from a single CT scan is likely to be small, but in patients who require multiple follow-up scans, low-dose techniques should be used whenever possible to minimize the uncertain risk associated with repeated radiation exposure.[70] IV contrast should not be used in patients with renal insufficiency or allergy to iodine, and it is usually not necessary to administer contrast when performing follow-up CT scans to identify growth.

Recommendations

6. In every patient with an indeterminate SPN that is visible on CXR, we recommend that CT of the chest be performed, preferably with thin sections through the nodule. Grade of recommendation, 1C

7. In every patient with an indeterminate SPN that is visible on chest CT, we recommend that previous imaging tests be reviewed. Grade of recommendation, 1C

8. In a patient with normal renal function and an indeterminate SPN on CXR or chest CT, we recommend that CT with dynamic contrast enhancement be considered in centers that have experience performing this technique. Grade of recommendation, 1B

MRI: MRI has a very limited role in the evaluation of the SPN. Dynamic gadolinium-enhanced MRI of lung nodules has been shown to be nearly comparable to contrast-enhanced CT for differentiating benign from malignant nodules: however, this technique remains experimental because of a lack of consensus regarding standardization.[71,72] Consequently, MRI is not indicated in the workup of the SPN outside investigational settings.

FDG-PET: In this chapter, recommendations address the use of FDG-PET for characterizing SPNs. Recommendations regarding the related issue of when to use FDG-PET for lung cancer staging are presented in these guidelines in the "Noninvasive Staging of Non-small Cell Lung Cancer" chapter.

FDG-PET is a noninvasive functional imaging test that is widely used in clinical oncology for tumor diagnosis, disease staging, and evaluation of treatment response.[73,74] FDG is taken up selectively by malignant tumor cells, which overexpress the glucose transporter protein. FDG subsequently accumulates within the cell because the radiolabeled glucose analog is phosphorylated once but not metabolized further. FDG is a positron-emitting radionuclide that undergoes an annihilation reaction after colliding with a nearby electron, resulting in the simultaneous release of two high-energy (511 kiloelectron volts) photons in opposite directions. Annihilation photons are coincidentally detected by a ring of crystals in the PET scanner. Electronic circuits and computer software subsequently localize the abnormality, register the intensity of uptake, and reconstruct cross-sectional images for display.[75]

In 17 studies[4] of diagnostic accuracy identified in the evidence chapter for this guideline, PET characterized pulmonary nodules with fairly high sensitivity (80 to 100%) and variable specificity (40 to 100%); using a summary receiver operating characteristic curve method, point estimates for pooled sensitivity and specificity were 87% and 83%, respectively. Slightly more favorable estimates were reported in a previous metaanalysis.[76] PET seems to be less sensitive for nodules that measure < 8 to 10 mm in diameter,[77] so its use in such nodules should be discouraged outside investigational settings. Preliminary evidence suggests that FDG-PET can help characterize screening-detected nodules that measure at least 8 to 10 mm in diameter, but a troubling number of false-negative and occasional false-positive findings have been reported in this situation.[78–80]

False-negative findings on PET can be seen in patients with bronchioloalveolar cell carcinoma, carcinoid tumors, and mucinous adenocarcinomas.[18,81] In theory, uncontrolled hyperglycemia may also cause false-negative results,[82] but the influence of hyperglycemia in clinical settings is uncertain. False-positive findings are often the result of infections or inflammatory conditions, including (but not limited to) endemic mycoses, tuberculosis, rheumatoid nod-

ules, and sarcoidosis.[11,83] Paradoxically, false-positive PET results can be helpful sometimes because they alert the clinician to the presence of an active infectious or inflammatory condition that might require specific treatment. In some circumstances, FDG-PET can be helpful by directing tissue biopsy.[84] As a "metabolic biopsy tool," PET can identify which lesions or portions of lesions are metabolically active and most likely to yield a definitive tissue result.

Use of FDG-PET may be most cost-effective when clinical pretest probability and CT results are discordant, especially when pretest probability is relatively low and CT characteristics are indeterminate (*ie*, not clearly benign).[85] In patients with indeterminate nodules (by CT) and high pretest probability, negative PET results do not reliably exclude malignancy. However, patients with nonhypermetabolic malignant tumors may have a favorable prognosis even when definitive surgical treatment is delayed by a period of observation as long as 238 days.[86,87] Hence, patients with negative PET results should be followed up with serial imaging tests for at least 2 years to confirm a benign diagnosis. A more cautious approach would be to perform needle biopsy in high-probability patients with negative PET results.

Integrated PET-CT scanners combine CT and FDG imaging capability in a single patient gantry, facilitating the precise localization of areas of FDG uptake to normal structures or abnormal soft-tissue masses. Accordingly, PET-CT can help to distinguish between hilar and mediastinal lymph nodes and identify invasion of the chest wall or mediastinal structures, but the role of PET-CT scanners in the management of SPN has not been well defined.[88,89] FDG-PET imaging is associated with minimal risk to the patient, because radiation doses are extremely low.

Recommendations

9. In patients with low-to-moderate pretest probability of malignancy (5 to 60%) and an indeterminate SPN that measures at least 8 to 10 mm in diameter, we recommend that FDG-PET imaging be performed to characterize the nodule. Grade of recommendation, 1B

10. In patients with an SPN that has a high pretest probability of malignancy (> 60%) or patients with a subcentimeter nodule that measures < 8 to 10 mm in diameter, we suggest that FDG-PET not be performed to characterize the nodule. Grade of recommendation, 2C

Management Strategies: Once imaging tests have been performed, management alternatives include surgery, transthoracic needle or bronchoscopic biopsy, and observation with serial radiographs, or "watchful waiting." Each of these approaches has advantages and disadvantages. Surgery is the diagnostic "gold standard" and the definitive treatment for malignant nodules, but surgery should be avoided in patients with benign nodules. Biopsy often establishes a specific benign or malignant diagnosis, but biopsy is invasive, potentially risky, and frequently nondiagnostic. Observation with serial imaging tests avoids unnecessary surgery in patients with benign nodules, but observation delays diagnosis and treatment in cases of malignancy. A decision analysis found that the choice of management strategy was "a close call" across a range of probabilities for malignancy.[90] In this analysis, observation was favored when the probability of malignancy was $< 3\%$, and surgery was preferred when the probability was $> 68\%$. Biopsy was the recommended strategy when the probability of malignancy fell between 3% and 68%. A generic management algorithm that is based on this analysis and a subsequent cost-effectiveness analysis[85] is presented in Figure 1. More specific recommendations are outlined next.

Patients with SPN may have underlying comorbidities that preclude surgical intervention. Preoperative risk assessment is discussed in detail in the chapter on "Physiologic Evaluation of the Patient With Lung Cancer Being Considered for Resectional Surgery" in these guidelines, and evaluation of patients who refuse surgery or who are poor candidates for surgery is discussed later in this chapter.

Shared Decision Making and Patient Preferences: Because different management strategies are associated with similar expected outcomes in many patients with lung nodules, patient preferences should be elicited and used to guide decisions. Some patients may be uncomfortable with adopting a strategy of observation when told that a potentially cancerous lung nodule is present. Others are similarly risk averse about undergoing surgery unless they are certain that cancer is present. All patients should be provided with an estimate of the probability of cancer and informed about the specific risks and benefits associated with alternative management strategies. Clinicians should elicit preferences for management and be sensitive to the preferred participatory decision-making style of the patient.[91,92]

Recommendation

11. In every patient with an SPN, we recommend that clinicians discuss the risks and ben-

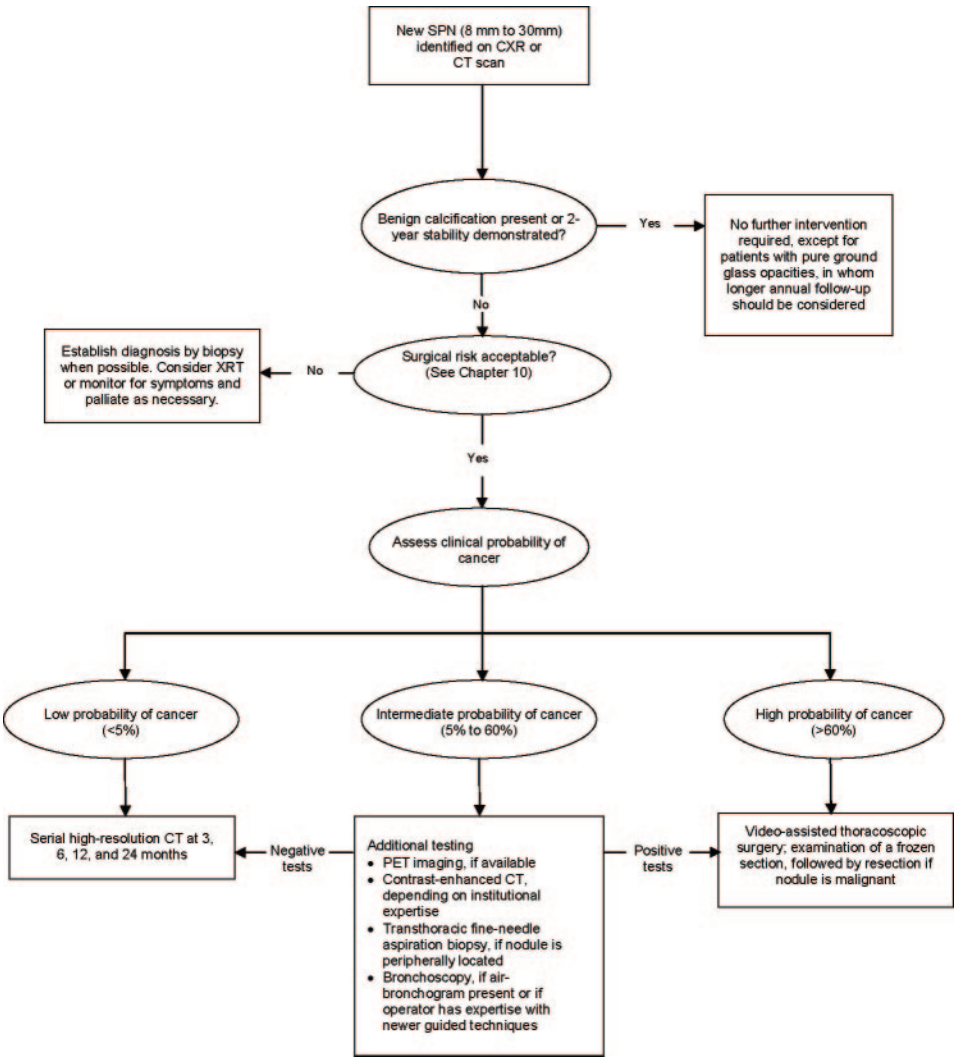

FIGURE 1. Recommended management algorithm for patients with SPNs that measure 8 to 30 mm in diameter. Adapted from Ost et al.[2]

efits of alternative management strategies and elicit patient preferences. Grade of recommendation, 1C

Observation or Watchful Waiting: In some patients with lung nodules, observation with serial imaging tests may be used as a diagnostic tool. When this strategy is used, detection of growth at any time is presumptive evidence of malignancy, and surgical resection should be performed in patients who are operative candidates. Two-year radiographic stability is strong presumptive evidence of a benign cause. Because it may be difficult to detect growth in nodules on plain CXRs, CT is usually preferred. Although it may be possible to detect growth on serial CXRs when the nodule is large (> 1.5 to 2 cm) and has sharp, clearly demarcated borders, the observation strategy is seldom used in operative candidates with nodules of this size, because of the relatively high probability of malignancy. The optimal time interval between imaging tests has not been determined for patients with SPN, but the standard clinical practice is to obtain follow-up CT scans at least at 3, 6, 12, and 24 months. More frequent follow-up may be considered in patients who are at higher risk for malignancy. Less frequent follow-up is indicated in patients with small, subcentimeter nodules.

The disadvantage of the observation strategy is that it potentially delays diagnosis and treatment in patients with malignant nodules. Depending on the growth rate and metastatic potential of the nodule and the length of observation, some malignant tumors will progress from resectable to unresectable disease during the observation period, and opportunities for surgical cure will be missed. Empirical data relevant to the hazard of delay

are scarce, although a Scottish study[93] found that maximum cross-sectional tumor area increased by > 50% in almost 25% of patients who had delays in radiotherapy treatment lasting between 18 and 131 days. Therefore, the observation strategy should be selected with caution. It is most appropriate in patients with a very low risk for malignancy and/or those who are at high risk for complications of surgical resection and/or nonsurgical biopsy.

Recommendations

12. In patients who have an indeterminate SPN that measures at least 8 to 10 mm in diameter and are candidates for curative treatment, observation with serial CT scans is an acceptable management strategy in the following circumstances: (1) when the clinical probability of malignancy is very low (< 5%); (2) when clinical probability is low (< 30 to 40%) and the lesion is not hypermetabolic by FDG-PET or does not enhance > 15 HU on dynamic contrast CT; (3) when needle biopsy is nondiagnostic and the lesion is not hypermetabolic by FDG-PET; (4) when a fully informed patient prefers this nonaggressive management approach. Grade of recommendation, 2C

13. In patients who have an indeterminate SPN that measures at least 8 to 10 mm in diameter and undergo observation, we suggest that serial CT scans be repeated at least at 3, 6, 12, and 24 months. Grade of recommendation, 2C

Transthoracic Needle Aspiration Biopsy: Needle biopsy of the SPN is usually performed under the guidance of fluoroscopy or, more common, CT. Few studies of needle biopsy have been performed under fluoroscopic guidance and limited enrollment to participants with pulmonary nodules. In one study[94] with a very high prevalence of malignancy, a diagnosis was made by fluoroscope-guided needle biopsy in 84% of patients with nodules that measured 2 to 4 cm in diameter. However, in two other studies[95,96] with a lower prevalence of malignancy, the diagnostic yield was only 36 to 43%.

Several studies of CT-guided needle biopsy limited enrollment to patients with pulmonary nodules that measured < 4 cm in diameter.[4] As expected, the specificity of needle biopsy for identifying malignancy was very high. However, nondiagnostic biopsy results were seen in 4 to 41% of patients (median, 21%). It is interesting that nondiagnostic biopsies were more common in nodules that proved to be benign (approximately 44% of all benign nodules) than in those that were malignant (approximately 8% of all malignant nodules). The sensitivity of transthoracic needle aspiration biopsy (TTNA) depends on the size of the nodule, the size of the needle (especially for identifying lymphoma or benign disease), the number of needle passes, and the presence of on-site cytopathology examination. Complications include minor pneumothorax in approximately 25% of procedures and major pneumothorax that requires chest tube drainage in approximately 5% of procedures. Identified risk factors for pneumothorax include smaller lesion size, deeper location, proximity to fissures, the presence of emphysema, lateral pleural puncture site, and a smaller angle of entry between the needle and the pleura. Risk factors for chest tube drainage include emphysema, proximity to fissures, and the need to traverse aerated lung.[97–99]

Use of needle biopsy is probably most appropriate when there is discordance among the clinical probability of cancer, imaging test results, patient preferences, and/or the risk for surgical complications, as described in recommendation 14. It is important to emphasize that a nondiagnostic needle biopsy result does not rule out the possibility of malignancy.

Bronchoscopy: Bronchoscopy is an excellent tool for sampling central airway lesions, mediastinal nodes, and parenchymal masses. Traditionally, bronchoscopy has played a limited role in SPN management outside investigational settings. Diagnostic yields with fluoroscope-guided bronchoscopy for malignant, peripheral pulmonary nodules that measure < 2 cm in diameter have consistently been in the range of 10 to 50%.[100–103] The likelihood of obtaining a specific benign diagnosis is even lower. The presence of an air bronchogram in a pulmonary nodule is associated with an increased yield, especially if this provides a specific road map as to the bronchial location.[104,105] Likewise, bronchoscopy with multiplanar CT or endobronchial ultrasound guidance seems to be an improvement over bronchoscopy under standard fluoroscopic guidance.[105–108]

A newer technique, electromagnetic navigation, combines simultaneous CT virtual bronchoscopy with real-time fiberoptic bronchoscopy and shows promise as another tool for guiding biopsy of peripheral nodules.[109,110] Although these new methods seem to improve diagnostic yields over fluoroscopic guidance, results still do not compare favorably with those from a recent series that evaluated TTNA in patients with small peripheral nodules.[111] Until further progress is made in guidance of bronchoscopy, peripheral nodules that do not have a CT-bronchus sign should be pursued with TTNA. In addition, routine preoperative bronchoscopy is not recom-

mended in the patient with an SPN, because it has been shown rarely to change stage and obviate the need for surgery.[112]

Older retrospective series[113] reported major complications of bronchoscopy in < 1% of procedures, including bleeding, respiratory depression, cardiorespiratory arrest, arrhythmia, and pneumothorax. Mortality has been considered rare, with a reported death rate of 0.01 to 0.03% in > 70,000 procedures.[114,115] However, a more recent prospective, multicenter study[116] suggested that complications and mortality are more frequent than previously recognized. Bechara et al[116] reported adverse events in 35% of 300 bronchoscopies performed that included at least two endobronchial biopsies. Severe adverse events occurred in 10% of patients, 4 of whom died (2%). However, two of the deaths occurred 1 week after the procedure and seemed to be unrelated.

Recommendation

14. In patients who have an indeterminate SPN that measures at least 8 to 10 mm in diameter and are candidates for curative treatment, it is appropriate to perform a transthoracic needle biopsy or bronchoscopy in the following circumstances: (1) when clinical pretest probability and findings on imaging tests are discordant; for example, when the pretest probability of malignancy is high and the lesion is not hypermetabolic by FDG-PET; (2) when a benign diagnosis that requires specific medical treatment is suspected; (3) when a fully informed patient desires proof of a malignant diagnosis before surgery, especially when the risk for surgical complications is high. In general, we suggest that transthoracic needle biopsy be the first choice for patients with peripheral nodules, unless the procedure is contraindicated or the nodule is inaccessible. We suggest that bronchoscopy be performed when an air bronchogram is present or in centers with expertise in newer guided techniques. Grade of recommendation, 2C

Surgery: Surgical resection is the "gold standard" diagnostic test and can often be therapeutic. However, only one flawed and inconclusive randomized, controlled trial[117–119] has compared surgery alone with an alternative treatment in patients with resectable lung cancer. The decision to include surgery as part of the diagnostic strategy for the SPN must take into account the benefits of definitive diagnosis and treatment when compared with the surgical risk. Video-assisted thorascopic surgery, thoracotomy, and mediastinoscopy may be used alone or in combination in patients with SPNs, depending on the clinical circumstances. Video-assisted thorascopic surgery is commonly used to diagnose peripheral SPN. Thoracotomy is sometimes necessary to make the diagnosis. If the nodule proves to be a primary lung malignancy, then therapeutic resection and staging are often completed in a single operative procedure.

Thoracoscopy is usually the favored surgical approach for nodules located in the peripheral third of the lung. It is a minimally invasive technique with a sensitivity and specificity approaching 100%,[120–122] with an associated mortality of approximately 1%.[123–128] The rate of conversion to thoracotomy is approximately 12%. As thorascopic techniques mature, resection of smaller nodules (< 5 mm) is becoming possible. Localizing techniques can be used to aid the surgeon in finding these lesions. Wire localization, methylene dye injection, fluoroscopy, and intrathoracic and extrathoracic ultrasound each have been reported as useful allies in locating small nodules.[129–134]

The diagnosis is most often established by intraoperative consultation with pathology. Frozen-section analysis is sensitive and specific for diagnosis of malignancy; however, the technique has limitations that the surgeon should understand. In one recent study,[135] the sensitivity for identifying malignancy was 86.9% for nodules that measured < 1.1 cm in diameter and 94.1% for nodules that measured between 1.1 and 1.5 cm. The specificity of frozen-section analysis was 100%. The technique has limitations in distinguishing bronchioloalveolar carcinoma from atypical adenomatous hyperplasia and reactive pneumocyte hyperplasia. It is limited in establishing a specific cell type in NSCLC. It is limited in recognizing small peripheral carcinoid tumors. Lesions that measure < 5 mm should probably not be used for frozen-section analysis unless there is other material available for permanent studies.[135]

For the surgical candidate with an SPN that is proved to be NSCLC, lobectomy and systematic mediastinal lymph node dissection are the standard of care for complete oncologic resection and staging.[136] Thoracotomy is the standard approach for resection, with a morbidity and mortality of approximately 34% and 4%, respectively.[137–145] Thoracoscopic resection and lymph node dissection for staging is an option in experienced hands.[143,146–148] For patients with marginal cardiac performance or limited pulmonary reserve, limited resection can be considered acceptable treatment, although limited resection is associated with a higher rate of local recurrence and a statistically nonsignificant trend toward reduced 5-year survival.[149,150]

An oncologic resection is not complete without staging the mediastinum. Recommendations for intraoperative staging can be found in the "Treatment of Non-small Cell Lung Cancer-Stage IIIA" in these guidelines.

Recommendations

15. In surgical candidates with an indeterminate SPN that measures at least 8 to 10 mm in diameter, surgical diagnosis is preferred in most circumstances, including the following: (1) when the clinical probability of malignancy is moderate to high (> 60%); (2) when the nodule is hypermetabolic by FDG-PET imaging; (3) when a fully informed patient prefers undergoing a definitive diagnostic procedure. Grade of recommendation, 1C

16. In patients who have an indeterminate SPN in the peripheral third of the lung and choose surgery, we recommend that thoracoscopy be performed to obtain a diagnostic wedge resection. Grade of recommendation, 1C

17. In a patient who chooses surgery for an indeterminate SPN that is not accessible by thoracoscopy, bronchoscopy, or TTNA, we recommend that a diagnostic thoracotomy be performed. Grade of recommendation, 1C

18. In patients who undergo thoracoscopic wedge resection for an SPN that is found to be cancer by frozen section, we recommend that anatomic resection with systematic mediastinal lymph node sampling or dissection be performed during the same anesthesia. Grade of recommendation, 1C

19. In patients who have an SPN and are judged to be marginal candidates for lobectomy, we recommend definitive treatment by wedge resection/segmentectomy (with systematic lymph node sampling or dissection). Grade of recommendation, 1B

Patients Who Are Not Surgical Candidates: Management is uncertain in patients who have an SPN and refuse surgery or are judged to be at unacceptably high risk for complications from even a limited pulmonary resection. No randomized trials have compared early treatment before the development of symptoms vs later treatment when symptoms develop. Discussion of potential risks and benefits with patients is limited by the paucity of data. For patients who prefer treatment, the diagnosis of lung cancer should first be confirmed by biopsy whenever possible. Although external-beam radiation therapy with curative intent is the current standard of care, experimental alternatives for these patients include stereotactic radiosurgery and radiofrequency ablation.

Recommendations

20. For the patient who has an SPN and is not a surgical candidate and prefers treatment, we recommend that the diagnosis of lung cancer be confirmed by biopsy, unless contraindicated. Grade of recommendation, 1C

21. For the patient who has a malignant SPN and is not a surgical candidate and prefers treatment, we recommend referral for external-beam radiation or to a clinical trial of an experimental treatment such as stereotactic radiosurgery or radiofrequency ablation. Grade of recommendation, 2C

Small Subcentimeter Pulmonary Nodules

Subcentimeter nodules measure < 8 to 10 mm in diameter, can be solitary or multiple, and are usually detected incidentally on a CT scan that has been ordered for some other reason. As is true for larger nodules, the likelihood of malignancy depends on patient risk factors, nodule size, and certain morphologic characteristics.

Predictors of Malignancy: Patient characteristics have been incompletely studied as predictors of malignancy in individuals with subcentimeter nodules. In the Lung Screening Study,[151] abnormal findings on a single low-dose CT screening examination were more common in current smokers and individuals who were at least 65 years of age. The likelihood of malignancy is probably highest in current smokers and lowest in nonsmokers who have nodules that are comparable in size. Extrapolation from studies in patients with larger nodules would suggest that the risk for malignancy probably increases with age.[21–23]

Size: Studies of CT screening in volunteers at risk for lung cancer confirm a strong association between nodule diameter and the likelihood of malignancy.[4] Data from baseline screening in three US trials[49,151,152] of low-dose CT show that the probability of malignancy is extremely low (< 1%) in prevalent nodules that measure < 5 mm in diameter. For nodules that measure 5 to 9 mm in diameter, the prevalence of malignancy varies from 2.3 to 6%.[151,152] In one Japanese study,[130] the prevalence of malignancy in subcentimeter nodules was > 20%, considerably higher than in the US studies.

Similar results have been reported in nonscreened populations evaluated by CT. One retrospective review[153] of 3,446 consecutive chest CT scans at a single institution identified 87 patients with non–screening-detected lung nodules that measured < 10 mm in diameter and definitive 2-year follow-up. Whereas 10 of these nodules were malignant (11%), 9 nodules proved to be metastases in patients with known extrathoracic malignancies (who composed 56% of the study population). More recently, in a retrospective review[154] of 414 patients with no history of neoplasm, infection, fibrosis, or immune deficiency and one or more noncalcified lung nodules that measured < 5 mm, none of the nodules was observed to grow at > 3 to 24 months of follow-up. The upper boundaries of the 95% confidence intervals for the probability of growth in these small nodules were 0.9, 1.0, and 1.3% at 3, 6, and 12 months, respectively.

Morphology: In the past decade, we have witnessed a remarkable change in CT terminology to describe the morphology of lung nodules. Morphologic characteristics of small nodules can be visualized by high-resolution CT with thin (approximately 1 mm) slices through the target nodule. On the basis of observations from recent lung cancer screening trials,[4] it is now appreciated that nodules may be characterized as solid, partly solid, or pure ground-glass opacities (defined as focal densities in which underlying lung morphology is preserved). These categories can help to distinguish benign from malignant nodules. In two small studies,[155,156] almost 60% of pure ground-glass opacities were malignant, although the percentage was lower (18%) in another study.[42] The likelihood of malignancy was similarly high in partly solid lesions but much lower (< 10%) in solid nodules.[42,156]

Ground-glass nodules often represent either atypical adenomatous hyperplasia or true bronchoalveolar cell carcinoma.[54,157–164] When malignant, partly solid or solid nodules usually represent adenocarcinoma but can also be caused by squamous cell carcinoma or small cell carcinoma. Of note, observed growth rates are often very slow for malignant ground-glass opacities, intermediate for partly solid nodules, and relatively fast for solid nodules.[4]

Management Strategies: The optimal approach to the management of subcentimeter nodules remains problematic. Expert consensus-based guidelines for radiographic follow-up in patients with small pulmonary nodules were published by members of the Fleischner Society,[165] who concluded that the follow-up should be less frequent and often shorter in duration than in patients with larger nodules.

Decisions about the frequency and duration of follow-up for patients with subcentimeter nodules need to weigh multiple considerations, including clinical risk factors (*eg*, age, smoking history, exposure to secondhand smoke and other lung carcinogens); nodule size; the probable rate of nodule growth as reflected by CT morphology[41,158,163]; the limited accuracy of available techniques for establishing growth by cross-sectional and/or volumetric measurements, especially for nodules that measure < 5 mm in size[166–168]; concerns regarding radiation dose[70,169,170]; risk factors for surgical complications; and cost. There is no evidence that early identification of subcentimeter malignant lung nodules improves lung cancer mortality rates (see "Screening for Lung Cancer"), providing additional justification for a less aggressive management approach. In patients who are not considered to be surgical candidates (especially those with limited life expectancy), the utility of follow-up is questionable, and even less aggressive management alternatives (including no follow-up) should be considered.

In general, we agree with the consensus recommendations of the Fleischner Society that are outlined in Recommendations 22 to 25 and in Figure 2, although more frequent follow-up of small lung nodules should be considered in fully informed patients who prefer a more aggressive approach. It should also be noted that controversy remains regarding how long follow-up should be continued for both partly solid and especially pure ground-glass nodules.[41,158,163] As a consequence, longer follow-up extending over years may be appropriate in some patients, especially when there is an antecedent history of lung cancer. Follow-up studies should be performed with the lowest possible radiation dose (ideally between 40 and 100 mA) to minimize cumulative radiation exposure in individuals who require multiple follow-up CT examinations.

Recommendations

22. For surgical candidates who have subcentimeter nodules and no risk factors for lung cancer, the frequency and duration of follow-up (preferably with low-dose CT) should depend on the size of the nodule. We suggest the following: (1) that nodules that measure up to 4 mm in diameter not be followed up, but the patient must be fully informed of the risks and benefits of this approach; (2) that nodules that measure > 4 to 6 mm be reevaluated at 12 months without additional follow-up if unchanged; (3) that nodules that measure > 6 to 8 mm be followed up sometime between 6 and 12

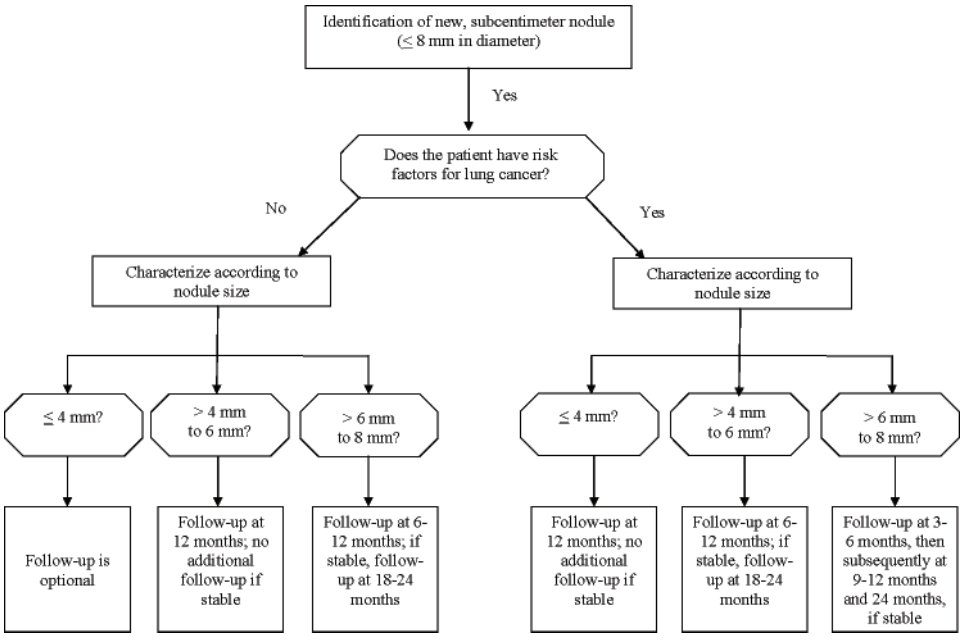

FIGURE 2. Recommended management algorithm for patients with subcentimeter pulmonary nodules that measure ≤ 8 mm in diameter.

months and then again between 18 and 24 months if unchanged. Grade of recommendation, 2C

RECOMMENDATIONS

23. For surgical candidates who have subcentimeter nodules and one or more risk factors for lung cancer, the frequency and duration of follow-up (preferably with low-dose CT) should depend on the size of the nodule. We suggest the following: (1) that nodules that measure up to 4 mm in diameter be reevaluated at 12 months without additional follow-up if unchanged; (2) that nodules that measure > 4 to 6 mm be followed up sometime between 6 and 12 months and then again between 18 and 24 months if unchanged; (3) that nodules that measure > 6 to 8 mm be followed up initially sometime between 3 and 6 months then subsequently between 9 and 12 months and again at 24 months if unchanged. Grade of recommendation, 2C

24. For surgical candidates with subcentimeter nodules that display unequivocal evidence of growth during follow-up, we recommend that definitive tissue diagnosis be obtained by surgical resection, transthoracic needle biopsy, or bronchoscopy. Grade of recommendation, 1C

25. For individuals who have subcentimeter nodules and are not candidates for curative treatment, we recommend limited follow-up (in 12 months) or follow-up when symptoms develop. Grade of recommendation, 1C

Multiple Nodules

Multiple nodules and the solitary nodule have similar causes, although for multiple nodules, metastatic disease is the most likely malignant diagnosis and active infectious or inflammatory granulomatous disease is the most likely benign cause. A detailed discussion of diagnosis and treatment in these patients is beyond the scope of this chapter; however, the diagnosis can usually be established by a combination of serologic testing, sputum analysis, bronchoscopy with biopsy or bronchoalveolar lavage, transthoracic needle biopsy, and/or open surgical biopsy. Treatment should be directed at the specific underlying cause. An inherent assumption in the evaluation of many patients with multiple nodules is that all of the nodules identified represent the same diagnosis. This is usually true in a patient with multiple nodules that measure ≥ 1 cm in diameter but often not the case when a dominant nodule and one or more additional diminutive nodules are present.

Patients With One or More Additional Nodules Detected During SPN Evaluation: In patients with a known or suspected lung cancer on CXR, CT will frequently identify one or more additional nodules.

Studies indicate that most of these additional nodules are benign. A study[171] from Japan showed that 10% of patients with suspected lung cancer had a second nodule detected during subsequent evaluation, and 60% of these were benign at surgery. Similarly, Keogan et al[172] reported that CT detected a second, indeterminate nodule in 16% of patients with clinically operable stage I to IIIA NSCLC. The nodules ranged in size from 4 to 12 mm, and although many of the nondominant nodules were unavailable for follow-up, > 85% of those with a definite diagnosis were benign.

Screening studies provide additional evidence that patients with a malignant nodule will not uncommonly have additional benign nodules. In the Early Lung Cancer Action Project,[6] 30% of the participants with cancer identified during baseline (prevalence) screening had one or more additional nodules at the time of detection. None of these was reported to be malignant after follow-up.[173] In the Mayo Clinic screening study,[174] > 50% of the 31 participants with prevalent cancers had other nodules detected, and all but one (a carcinoid tumor) proved to be benign by absence of growth during follow-up. In these studies, the majority of "secondary" nodules measured < 4 mm, which suggests a very low risk for malignancy. Therefore, although the likelihood of finding one or more additional nodules increases with the use of smaller slice thickness on CT, the vast majority of additional nodules will be benign.

When confronted with one or more additional nodules during SPN evaluation, it is prudent to consider each nodule individually, rather than assuming that the additional nodules are either metastatic or benign. Preoperative PET scanning may help to decide whether more than one nodule is likely malignant and guide further evaluation, although many of these nodules will be too small to be reliably characterized by PET. Above all, candidates for curative treatment who have known or suspected malignant nodules and have one or more additional nodules present should not be denied curative therapy unless metastasis is confirmed by histopathology. The evaluation and treatment of a synchronous cancer in a separate lobe, satellite cancers in the same lobe, and metachronous cancers is discussed in the "Bronchioloalveolar Lung Cancer" chapter in these guidelines.

Recommendation

26. In patients who are candidates for curative treatment for a dominant SPN and one or more additional small nodules, we recommend that each nodule be evaluated individually, as necessary, and curative treatment not be denied unless there is histopathologic confirmation of metastasis. Grade of recommendation, 1C

Solitary Metastasis

In patients with an active or previous extrapulmonary cancer, the SPN can represent a metastasis, a primary lung cancer, or benign disease. Determining the cause of the nodule is important so that appropriate therapy can be offered.

Pulmonary metastasectomy has been offered to selected patients who have an SPN in the setting of an extrapulmonary malignancy because of the potential for cure.[175–184] In this group, 60 to 80% of nodules will be malignant, and 20 to 50% will be due to bronchogenic carcinoma.[185–187] Distinguishing patients with metastatic disease from those with a primary lung cancer is the task, and treatment for cure is the goal. Chronic benign processes and infectious causes are a consideration; however, malignancy must be aggressively pursued, and tissue diagnosis is required.

The site and histology of the primary tumor influence both the likelihood of metastasis[188–192] and the prognosis after metastasectomy.[183,193,194] Of 5,206 procedures included in the International Registry of Lung Metastases, the most common malignant diagnoses were sarcoma (42%), colon cancer (14%), breast cancer (9%), renal cell carcinoma (8%), germ cell tumors (7%), melanoma (6%), and head and neck cancer (5%). In a combined series,[183] 5-year survival after metastasectomy was 80% for patients with germ cell tumors, 53% for gynecologic cancers, 44% for head and neck tumors, 43% for renal cell carcinoma, 38% for colon cancer, 34% for sarcoma, 34% for breast cancer, and 16% for melanoma. Overall survival after metastasectomy ranges from 25 to 45%.[188,195] Prognosis is best for patients with longer disease-free intervals (> 36 months), solitary metastases, and germ cell or Wilms tumors. A diagnosis of melanoma confers the worst prognosis.[196,197]

Metastasectomy should be considered in surgical candidates who have disease that is otherwise controlled without evidence of extrapulmonary involvement, for whom no better therapy is available. If these criteria are met, then the surgical strategy must be directed at completeness of resection with minimal morbidity and mortality. The "gold standard" is argued to be complete resection with an approach that will allow thorough palpation of the lung.[198,199] Thoracotomy is appropriate for this approach. It has been reported that 30 to 50% of metastases will present as bilateral disease that is not apparent on CT scan, and exploration of both lungs may be justified.[198,199] This approach would require bilateral thoracotomies, median sternotomy, or bilateral ante-

rior thoracotomy with transverse sternotomy (clamshell incision) to explore both lungs completely. However, some believe that equal benefits can be achieved when only radiographically visible disease is resected. Thoracoscopy can be used to achieve this objective.[200–202]

Recommendation

27. In surgical candidates with a solitary pulmonary metastasis, we recommend that pulmonary metastasectomy be performed when there is no evidence of extrapulmonary malignancy and there is no better available treatment. Grade of recommendation, 1C

Solitary Nodule Caused by Small Cell Carcinoma

SCLCs represent approximately 15 to 20% of all primary lung cancers,[203] and 90% of these patients have regional lymph node involvement or metastatic disease at initial presentation.[204] Infrequently, surgical resection of an undiagnosed lung nodule reveals the presence of SCLC. Surgery should also be considered in patients who have known SCLC and present with an SPN and no evidence of regional or distant metastasis. In one older study,[205] multimodality treatment with surgery and adjuvant chemotherapy resulted in a 5-year survival rate of 59% in patients with T1N0M0 tumors caused by small cell carcinoma. Other series[206–210] confirmed that cure was possible in surgically resected, limited-stage small cell carcinoma. Three factors contributed to favorable outcomes: small tumor size, no lymph node involvement, and candidacy for lobectomy.[211] A patient who has small cell carcinoma and presents with an SPN falls into this category and should be considered for surgery.

Recommendations

28. In surgical candidates with an SPN that has been diagnosed as SCLC, we recommend surgical resection with adjuvant chemotherapy, provided that noninvasive and invasive staging exclude the presence of regional or distant metastasis. Grade of recommendation, 1C

29. In patients who have an SPN and in whom SCLC is diagnosed intraoperatively, we recommend anatomic resection (with systematic mediastinal lymph node sampling or dissection) under the same anesthesia when there is no evidence of nodal involvement and when the patient will tolerate resection. Surgery should be followed by adjuvant chemotherapy. Grade of recommendation, 1C

Conclusions

The classical SPN is a common and vexing problem. Patients with an SPN should be evaluated by review of old films, estimation of the probability of malignancy, performance of imaging tests to characterize the nodule better, evaluation of the risks associated with various treatment alternatives, and elicitation of patient preferences for treatment. Subcentimeter nodules are becoming increasingly prevalent, and we still have much to learn about their biology and behavior, although it is already apparent that the growth rates of small malignant nodules vary widely and that morphologic characteristics provide clues about the likelihood of malignancy and the rate of growth. In this guideline, we endorsed recent expert consensus-based recommendations for performing follow-up CT scans in patients with subcentimeter nodules that balance the potential benefits of careful follow-up with the potential risks associated with radiation exposure from CT. In the future, as imaging tests and other diagnostic technologies improve, the prevalence of pulmonary nodules will likely increase, as will our ability to distinguish malignant from benign nodules before surgery.

Summary of Recommendations

1. In every patient with an SPN, we recommend that clinicians estimate the pretest probability of malignancy either qualitatively by using their clinical judgment or quantitatively by using a validated model. Grade of recommendation, 1C

2. In every patient with an SPN that is visible on CXR, we recommend that previous CXRs and other relevant imaging tests be reviewed. Grade of recommendation, 1C

3. In patients who have an SPN that shows clear evidence of growth on imaging tests, we recommend that tissue diagnosis be obtained unless specifically contraindicated. Grade of recommendation, 1C

4. In a patient with an SPN that is stable on imaging tests for at least 2 years, we suggest that no additional diagnostic evaluation be performed, except for patients with pure ground-glass opacities on CT, in whom a longer duration of annual follow-up should be considered. Grade of recommendation, 2C

5. In a patient with an SPN that is calcified in a clearly benign pattern, we recommend no additional diagnostic evaluation. Grade of recommendation, 1C

6. In every patient with an indeterminate SPN that is visible on CXR, we recommend that CT of the chest be performed, preferably with thin sections through the nodule. Grade of recommendation, 1C

7. In every patient with an indeterminate SPN that is visible on chest CT, we recommend that previous imaging tests be reviewed. Grade of recommendation, 1C

8. In a patient with normal renal function and an indeterminate SPN on CXR or chest CT, we recommend that CT with dynamic contrast enhancement be considered in centers that have experience performing this technique. Grade of recommendation, 1B

9. In patients with low-to-moderate pretest probability of malignancy (5 to 60%) and an indeterminate SPN that measures at least 8 to 10 mm in diameter, we recommend that F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging be performed to characterize the nodule. Grade of recommendation, 1B

10. In patients with an SPN that has a high pretest probability of malignancy (> 60%) or patients with a subcentimeter nodule that measures < 8 to 10 mm in diameter, we suggest that FDG-PET not be performed to characterize the nodule. Grade of recommendation, 2C

11. In every patient with an SPN, we recommend that clinicians discuss the risks and benefits of alternative management strategies and elicit patient preferences. Grade of recommendation, 1C

12. In patients who have an indeterminate SPN that measures at least 8 to 10 mm in diameter and are candidates for curative treatment, observation with serial CT scans is an acceptable management strategy in the following circumstances: (1) when the clinical probability of malignancy is very low (< 5%); (2) when clinical probability is low (< 30 to 40%) and the lesion is not hypermetabolic by FDG-PET or does not enhance > 15 Hounsfield units (HU) ondynamic contrast CT; (3) when needle biopsy is nondiagnostic and the lesion is not hypermetabolic by FDG-PET; (4) when a fully informed patient prefers this nonaggressive management approach. Grade of recommendation, 2C

13. In patients who have an indeterminate SPN that measures at least 8 to 10 mm in diameter and undergo observation, we suggest that serial CT scans be repeated at least at 3, 6, 12, and 24 months. Grade of recommendation, 2C

14. In patients who have an indeterminate SPN that measures at least 8 to 10 mm in diameter and are candidates for curative treatment, it is appropriate to perform a transthoracic needle biopsy or bronchoscopy in the following circumstances: (1) when clinical pretest probability and findings on imaging tests are discordant; for example, when the pretest probability of malignancy is high and the lesion is not hypermetabolic by FDG-PET; (2) when a benign diagnosis that requires specific medical treatment is suspected; (3) when a fully informed patient desires proof of a malignant diagnosis before surgery, especially when the risk for surgical complications is high. In general, we suggest that transthoracic needle biopsy be the first choice for patients with peripheral nodules, unless the procedure is contraindicated or the nodule is inaccessible. We suggest that bronchoscopy be performed when an air bronchogram is present or in centers with expertise in newer guided techniques. Grade of recommendation, 2C

15. In surgical candidates with an indeterminate SPN that measures at least 8 to 10 mm in diameter, surgical diagnosis is preferred in most circumstances, including the following: (1) when the clinical probability of malignancy is moderate to high (> 60%); (2) when the nodule is hypermetabolic by FDG-PET imaging; (3) when a fully informed patient prefers undergoing a definitive diagnostic procedure. Grade of recommendation, 1C

16. In patients who have an indeterminate SPN in the peripheral third of the lung and choose surgery, we recommend that thoracoscopy be performed to obtain a diagnostic wedge resection. Grade of recommendation, 1C

17. In a patient who chooses surgery for an indeterminate SPN that is not accessible by thoracoscopy, bronchoscopy, or transthoracic needle aspiration, we recommend thata diagnostic thoracotomy be performed. Grade of recommendation, 1C

18. In patients who undergo thoracoscopic wedge resection for an SPN that is found to be cancer by frozen section, we recommend that anatomic resection with systematic mediastinal lymph node sampling or dissection be performed during the same anesthesia. Gradeof recommendation, 1C

19. In patients who have an SPN and are judged to be marginal candidates for lobectomy, we recommend definitive treatment by wedge resection/segmentectomy (with systematic lymph node sampling or dissection). Grade of recommendation, 1B

20. For the patient who has an SPN and is not a surgical candidate and prefers treatment, we recommend that the diagnosis of lung cancer be confirmed by biopsy, unless contraindicated. Grade of recommendation, 1C

21. For the patient who has a malignant SPN and is not a surgical candidate and prefers treatment, we recommend referral for external-beam radiation or to a clinical trial of an experimental treatment such as stereotactic radiosurgery or radiofrequency ablation. Grade of recommendation, 2C

22. For surgical candidates who have subcentimeter nodules and no risk factors for lung cancer, the frequency and duration of follow-up (preferably with low-dose CT) should depend on the size of the nodule. We suggest the following: (1) that nodules that measure up to 4 mm in diameter not be followed up, but the patient must be fully informed of the risks and benefits of this approach; (2) that nodules that measure > 4 to 6 mm be reevaluated at 12 months without additional follow-up if unchanged; (3) that nodules that measure > 6 to 8 mm be followed up sometime between 6 and 12 months and then again between 18 and 24 months if unchanged. Grade of recommendation, 2C

23. For surgical candidates who have subcentimeter nodules and one or more risk factors for lung cancer, the frequency and duration of follow-up (preferably with low-dose CT) should depend on the size of the nodule. We suggest the following: (1) that nodules that measure up to 4 mm in diameter be reevaluated at 12 months without additional follow-up if unchanged; (2) that nodules that measure > 4 to 6 mm be followed up sometime between 6 and 12 months and then again between 18 and 24 months if unchanged; (3) that nodules that measure > 6 to 8 mm be followed up initially sometime between 3 months and 6 months then subsequently between 9 and 12 months and again at 24 months if unchanged. Grade of recommendation, 2C

24. For surgical candidates with subcentimeter nodules that display unequivocal evidence of growth during follow-up, we recommend that definitive tissue diagnosis be obtained by surgical resection, transthoracic needle biopsy, or bronchoscopy. Grade of recommendation, 1C

25. For individuals who have subcentimeter nodules and are not candidates for curative treatment, we recommend limited follow-up (in 12 months) or follow-up when symptoms develop. Grade of recommendation, 1C

26. In patients who are candidates for curative treatment for a dominant SPN and one or more additional small nodules, we recommend that each nodule be evaluated individually, as necessary, and curative treatment not be denied unless there is histopathologic confirmation of metastasis. Grade of recommendation, 1C

27. In surgical candidates with a solitary pulmonary metastasis, we recommend that pulmonary metastasectomy be performed when there is no evidence of extrapulmonary malignancy and there is no better available treatment. Grade of recommendation, 1C

28. In surgical candidates with an SPN that has been diagnosed as SCLC, we recommend surgical resection with adjuvant chemotherapy, provided that noninvasive and invasive staging exclude the presence of regional or distant metastasis. Grade of recommendation, 1C

29. In patients who have an SPN and in whom SCLC is diagnosed intraoperatively, we recommend anatomic resection (with systematic mediastinal lymph node sampling or dissection) under the same anesthesia when there is no evidence of nodal involvement and when the patient will tolerate resection. Surgery should be followed by adjuvant chemotherapy. Grade of recommendation, 1C

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Initial Diagnosis of Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **Lung cancer is usually suspected in individuals who have an abnormal chest radiograph finding or have symptoms caused by either local or systemic effects of the tumor. The method of diagnosis of suspected lung cancer depends on the type of lung cancer (*ie*, small cell lung cancer [SCLC] or non-SCLC [NSCLC]), the size and location of the primary tumor, the presence of metastasis, and the overall clinical status of the patient.**

Objectives: **To determine the test performance characteristics of various modalities for the diagnosis of suspected lung cancer.**

Methods: **To update previous recommendations on the initial diagnosis of lung cancer, a systematic search of MEDLINE, Healthstar, and Cochrane Library databases to July 2004, and print bibliographies was performed to identify studies comparing the results of sputum cytology, bronchoscopy, transthoracic needle aspiration (TTNA), or biopsy with histologic reference standard diagnoses among at least 50 patients with suspected lung cancer. Recommendations were developed by the writing committee, graded by a standardized method, and reviewed by all members of the lung cancer panel prior to approval by the Thoracic Oncology Network, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physician.**

Results: **Sputum cytology is an acceptable method of establishing the diagnosis of lung cancer with a pooled sensitivity rate of 0.66 and specificity rate of 0.99. However, the sensitivity of sputum cytology varies by location of the lung cancer. For central, endobronchial lesions, the overall sensitivity of flexible bronchoscopy (FB) for diagnosing lung cancer is 0.88. The diagnostic yield of bronchoscopy decreases for peripheral lesions. Peripheral lesions smaller or larger than 2 cm in diameter showed a sensitivity of 0.34 and 0.63, respectively. In recent years, endobronchial ultrasound (EBUS) has shown potential in increasing the diagnostic yield of FB while dealing with peripheral lesions without adding to the risk of the procedure. In appropriate situations, its use can be considered before moving on to more invasive tests. The pooled sensitivity for TTNA for the diagnosis of lung cancer is 0.90. A trend toward lower sensitivity was noted for lesions < 2 cm in diameter. The accuracy in differentiating between SCLC and NSCLC cytology for the various diagnostic modalities was 0.98, with individual studies ranging from 0.94 to 1.0. The average false-positive rate and FN rate were 0.09 and 0.02, respectively.**

Conclusions: **The sensitivity of bronchoscopy is high for the detection of endobronchial disease and poor for peripheral lesions < 2 cm in diameter. Detection of the latter can be aided with the use of EBUS in the appropriate clinical setting. The sensitivity of TTNA is excellent for malignant disease. The distinction between SCLC and NSCLC by cytology appears to be accurate.**

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Key words: bronchoscopy; endobronchial ultrasound; esophageal ultrasound; lung neoplasm; needle aspiration; sensitivity and specificity; sputum cytology; transthoracic needle aspiration

Abbreviations: CI = confidence interval; EBUS = endobronchial ultrasound; EUS = esophageal ultrasound; FB = flexible bronchoscopy; FDG = fluoro-18–2-deoxyglucose; FN = false negative; FNA = fine-needle aspiration; FP = false positive; NA = needle aspiration; NSCLC = non-small cell lung cancer; PET = positron emission tomography; SCLC = small cell lung cancer; TBNA = transbronchial needle aspiration; TTNA = transthoracic needle aspiration; US = ultrasound

The findings of CT scans of the chest and clinical presentation usually allow a presumptive differentiation between small cell lung cancer (SCLC) and non-SCLC (NSCLC). Massive lymphadenopathy and direct mediastinal invasion are well-recognized phenomena in patients with small cell carcinoma.[1,2] A mass in or adjacent to the hilum is a particular characteristic of small cell cancer and is seen in about 78% of cases.[1,2] Not infrequently, SCLC presents with paraneoplastic syndromes.[3] These include the syndrome of inappropriate antidiuretic hormone, ectopic adrenocorticotropic hormone production, and the Lambert-Eaton syndrome. If SCLC is suspected, the diagnosis should be achieved by whatever means is easiest (*ie*, sputum cytology, thoracentesis if an accessible pleural effusion is present, fine-needle aspiration [FNA] of a supraclavicular node or metastatic site, and bronchoscopy with or without transbronchial needle aspiration [TBNA] of mediastinal nodes or submucosal process). If the diagnosis of SCLC is established in a biopsy specimen of the primary lesion, the distinction between limited or extensive disease is then made radiographically. Routine staging of SCLC includes a CT scan of the chest and abdomen or a CT scan of the chest with cuts going through the entire liver and adrenal glands, a CT scan or MRI scan of the brain, and a bone scan. The reader is referred to the "Management of Small Cell Lung Cancer" chapter for a more detailed discussion of the staging and management of SCLC.

In patients suspected of having NSCLC, the method of achieving a diagnosis is usually dictated by the presumed stage of the disease. Patients with suspected lung cancer who present with a pleural effusion should undergo thoracentesis first in order to differentiate between a malignant effusion (due to malignant involvement of the pleura) and a paramalignant effusion (due to other factors such as lymphatic blockade, atelectasis, or hypoproteinemia). Distinction between the two is important because the finding of malignant cells in the pleural fluid alters the stage and treatment of the particular patient. Pleural metastases are more common in the visceral pleura[4] and tend to be focal when there is involvement of the parietal pleura. Because of this, pleural fluid cytology is a more sensitive diagnostic test than percutaneous pleural biopsy, with the latter being a blind sampling procedure.[5–7] When three separate pleural fluid specimens from a patient with malignant pleural disease are submitted to an experienced cytologist, one should expect a positive diagnosis in about 80% of patients.[7,8] Percutaneous, closed pleural biopsy is reported to be diagnostic for malignancy in about 50% of cases.[6] Thoracoscopic biopsy of the pleura is safe and can provide a definitive diagnosis with a high degree of accuracy and minimal risk to the patient.[9,10] The reported sensitivity rate ranges between 0.80 and 0.99, the specificity rate ranges between 0.93 and 1, and the negative predictive value ranges between 0.93 and 0.96.[9,11–13] False-negative (FN) results are more common with mesothelioma than primary lung carcinoma.[11]

Patients with metastatic NSCLC (stage IV disease) usually present with constitutional symptoms (*eg*, fatigue and weight loss), organ-specific symptoms (*eg*, bone pain and neurologic symptoms), and/or abnormal laboratory findings (*eg*, anemia, elevated alkaline phosphatase levels, and/or elevated liver enzyme levels). In many of these patients, FNA or a needle biopsy of a site of metastasis represents the most efficient way to both make a diagnosis and to confirm the stage of disease. In some cases, however, the metastatic site may be technically difficult to biopsy. If metastatic disease can be predicted with a high degree of accuracy on the basis of radiographic findings (*ie*, multiple brain, liver, or bone lesions), it may be more efficient to achieve a diagnosis of the primary lung lesion by whatever method is easiest for the patient (*eg*, sputum cytology, bronchoscopy, or transthoracic needle aspiration [TTNA]). This decision must be made by weighing the technical considerations involved in each approach as well as the reliability of diagnosing an extrathoracic lesion as a site of metastasis based on radiographic appearances alone (see "Noninvasive Staging of Non-small Cell Lung Cancer" chapter). A joint decision among a radiologist, pulmonologist, and medical or radiation oncologist is the desirable approach.

NSCLC can present with extensive infiltration of the mediastinum, which is defined as a mass that infiltrates and encases the mediastinal structures where no discrete mediastinal lymph nodes are visible. In such patients, the diagnosis should be achieved by the method that has the most favorable risk/benefit ratio. Bronchoscopy with TBNA for cytologic or histologic examination of mediastinal

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lymph nodes has been shown to be a safe procedure.[14–17] Technical aspects that are frequently emphasized to be important in achieving a high success rate include accurate preparation of the specimen, rapid on-site evaluation by a cytopathologist, and using the larger 19-gauge needles, which provide better tissue samples for histologic evaluation.[18,19] The overall sensitivity of TBNA is 0.76, and the specificity is 0.96.[14–22] (See the "Invasive Clinical Staging of Non-small Cell Lung Cancer" chapter for a more detailed review of the performance characteristics of TBNA for staging the mediastinum.) The negative predictive value of TBNA is not high enough (0.71) to obviate the need for further confirmation of negative results. Mediastinoscopy is warranted in patients with nondiagnostic results.

TTNA (CT scan-guided) of mediastinal masses can be performed safely.[23] The role of TTNA in patients with extensive mediastinal disease (defined as such extensive mediastinal tumor growth that discrete lymph nodes can no longer be discerned) is usually to confirm the presence of SCLC or NSCLC who are not surgical candidates because of the extent of mediastinal disease.

In the case of a small (< 3 cm), solitary, peripheral lung lesion that is suspicious for lung cancer in a patient who appears to have early-stage disease and is a surgical candidate, the diagnostic dilemma generally centers around whether or not to obtain a biopsy specimen to confirm the diagnosis of cancer before surgical resection is carried out. When the lesion is moderately to highly suspicious for lung cancer, an excisional biopsy performed via thoracoscopy has a much higher sensitivity than TTNA and is the most definitive method of establishing a definitive diagnosis. (See the "Solitary Pulmonary Nodule" chapter for a more detailed review of the diagnostic approach to the solitary pulmonary nodule.)

Recommendations

1. In patients suspected of having SCLC based on the radiographic and clinical findings, it is recommended that the diagnosis be confirmed by the easiest method (*eg*, sputum cytology, thoracentesis, FNA, bronchoscopy including TBNA, endobronchial ultrasound [EBUS]-needle aspiration [NA], and esophageal ultrasound [EUS]-NA), as dictated by the patient's presentation. Grade of recommendation, 1C

2. In patients suspected of having lung cancer who have an accessible pleural effusion, thoracentesis is recommended to diagnose the cause of the pleural effusion. Grade of recommendation, 1C

3. In patients suspected of having lung cancer who have an accessible pleural effusion, if the pleural fluid cytology finding is negative (after at least two thoracenteses), thoracoscopy is recommended as the next step if establishing the cause of the pleural effusion is thought to be clinically important. Grade of recommendation, 1C

4. In patients suspected of having lung cancer who have a solitary extrathoracic site that is suspicious of a metastasis, it is recommended that tissue confirmation of the metastatic site be obtained if an FNA or biopsy of the site is feasible. Grade of recommendation, 1C

5. In patients suspected of having lung cancer, who have lesions in multiple distant sites that are suspected of metastases, but in whom biopsy of a metastatic site would be technically difficult, it is recommended that the diagnosis of the primary lung lesion be obtained by the easiest method (*eg*, sputum cytology, bronchoscopy, or TTNA). Grade of recommendation, 1C

6. In patients suspected of having lung cancer, who have extensive infiltration of the mediastinum based on radiographic studies, it is recommended that the diagnosis of lung cancer be established by the easiest and safest method (*eg*, bronchoscopy with TBNA, EBUS-NA, EUS-NA, TTNA, or mediastinoscopy). Grade of recommendation, 1C

Diagnosis of Primary Tumor

A variety of techniques (*eg*, sputum cytology, flexible bronchoscopy [FB], and TTNA) are available as methods of achieving a definitive diagnosis. Positron emission tomography (PET) scanning has emerged as a helpful adjunct in both the diagnosis and staging of lung cancer.

The main goals in selecting a specific diagnostic modality are to (1) maximize the yield of the selected procedure for both diagnosis and staging and (2) to avoid unnecessary invasive tests for the patient, with special attention to the projected treatment plan. Four key questions to determine the test performance characteristics of various modalities for the diagnosis of lung cancer were formulated. A systematic search of the MEDLINE, Healthstar, and Cochrane Library databases to July 2001 and print bibliographies was performed by the Duke University Center for Clinical Health Policy Research. Studies of at least 50 patients with suspected lung cancer or radiographic follow-up of at least 1 year were selected. The following diagnostic tests were considered: sputum cytologic examination (expecto-

rated or aspirated, spontaneous or induced); FB (including any of biopsy, brushing, washing, TBNA, or BAL); and TTNA. Studies were required to report sufficient data to permit the completion of a 2-×-2 table comparing test results with a reference standard diagnosis. If too few studies met this criterion, then studies that described the diagnostic yield (sensitivity) among patients with lung cancer were considered. When possible, diagnostic performance was estimated separately for patients with central (endobronchial) lesions, peripheral lesions > 2 cm in diameter, and peripheral lesions < 2 cm in diameter. The systematic search was published in the Lung Cancer Guidelines published by the American College of Chest Physicians in 2003.[24]

An updated literature review from July 2001 to July 2004 that compared the results of sputum cytology, FB, and TTNA with histologic reference standard diagnoses among at least 50 patients with suspected lung cancer was performed. The previously published reviews and the current systematic reviews were analyzed and the data were compiled to generate updated tables. Recommendations based on a critical review of the published evidence are provided.

Sputum Cytology

Key Question 1: What are the performance characteristics of sputum cytology for the diagnosis of lung cancer with special consideration for the location of the tumor?

Sputum cytology is the least invasive means of obtaining a diagnosis in a patient who is suspected of having lung cancer. The diagnostic accuracy of sputum cytology, however, is dependent on rigorous specimen sampling (at least three specimens) and preservation techniques, as well as on the location (central vs peripheral) and size of the tumor. Unfortunately, many institutions do not have an established program for sputum collection and processing, and therefore present data with a much lower sensitivity than the data presented here (which come from institutions with well-established sputum analysis programs). Patient characteristics associated with positive cytologic diagnosis on sputum include the following: bloody sputum; low FEV_1 values; large lung tumors (> 2.4 cm); centrally located tumors; and squamous cell cancers.[25]

Sputum cytology is particularly useful in patients who present with centrally located tumors (*ie*, SCLC or squamous call carcinoma) and in those who present with hemoptysis. The sampling of sputum specimens should certainly be considered in a patient who presents with a central lesion with or without radiographic evidence of metastatic disease, in whom a semi-invasive procedure such as bronchoscopy or TTNA might pose a higher risk. The previously published[24] and the more recently performed systematic literature reviews found 17 studies[26–42] providing data on the performance characteristics of sputum cytology for the diagnosis of suspected lung cancer (Table 1). Sensitivity ranged from 0.42 to 0.97; specificity ranged from 0.68 to 1.0. The pooled sensitivity was 0.66, and the pooled specificity was 0.99. The single study conducted in patients evaluated for suspected lung cancer[27] had a sensitivity of 0.87 and a specificity of 0.90. Pooling all studies, regardless of the indication for sputum testing, the false-positive (FP) rate was 0.09 and the FN rate was 0.06.

Böcking et al[26] have shown that the sensitivity of sputum cytology for detecting lung cancer is highly dependent on the number of sputum specimens collected per patient, ranging from approximately 0.68 for a single specimen, to 0.78 for two specimens, to 0.85–0.86 for three or more specimens. Studies of the accuracy of sputum cytology for the diagnosis of lung cancer are difficult to summarize because of a variety of methodological problems.[24] The studies show highly variable estimates of sensitivity and no clear reasons for the variation. There is evidence to suggest that the number of sputum samples and the specimen adequacy are strongly related to the sensitivity of the technique. There is insufficient detail about these features to determine whether these factors explain the heterogeneity of the test accuracy results.

Recommendation

7. In patients suspected of having lung cancer, who present with a central lesion with or without radiographic evidence of metastatic disease, in whom a semi-invasive procedure such as bronchoscopy or TTNA might pose a higher risk, sputum cytology is recommended as an acceptable method of establishing the diagnosis. However, the sensitivity of sputum cytology varies by the location of the lung cancer. It is recommended that further testing be performed with a nondiagnostic sputum cytology test if the suspicion of lung cancer remains. Grade of recommendation, 1C

FB

Key Question 2: What are the performance characteristics of FB and its ancillary procedures for the diagnosis of central (endobronchial) as opposed to peripheral tumors and to peripheral tumors < 2 cm and > 2 cm in size?

Table 1—*Sensitivity and Specificity of Sputum Cytology for Diagnosis of Bronchogenic Carcinoma*

Study/Year	Patients, No.	Indication	Sensitivity	Specificity	FP Rate	FN Rate	Prevalence
Erkilic et al[42]/2003	697	Lung mass	0.69	0.99	0.04	0.04	0.12
Böcking et al[26]/1992	1,888	Mixed	0.86	1.00	0.04	0.02	0.12
Kern[28]/1988	1,289	Mixed	0.97	0.68	0.20	0.06	0.57
Risse et al[29]/1985	1,830	Mixed	0.60	0.98	0.11	0.08	0.17
Johnston and Bossen[30]/1981	9,892	Mixed	0.44	1.00	0.03	0.03	0.05
Jay et al[27]/1980	224	Lung mass	0.87	0.90	0.21	0.06	0.31
Yoneyama and Canlas[31]/1978	547	Mixed	0.83	1.00	0.04	0.02	0.12
Gagneten et al[32]/1976	506	Mixed	0.57	0.99	0.01	0.30	0.50
Rosa et al[33]/1973	1,003	Mixed	0.71	1.00	0.01	0.15	0.38
Dahlgren and Lind[34]/1972	121	Mixed	0.42	0.95	0.02	0.76	0.83
Koss et al[35]/1964	1,307	Mixed	0.71	0.98	0.12	0.06	0.17
Hinson and Kuper[36]/1963	528	Mixed	0.60	0.97	0.06	0.24	0.43
Russell et al[37]/1963	3,440	Mixed	0.51	1.00	0.02	0.07	0.13
Allen and Whittlesey[38]/1960	254	Mixed	0.90	1.00	0.00	0.06	0.41
Koss[39]/1958	607	Mixed	0.60	0.98	0.07	0.11	0.24
Spujt et al[40]/1955	4,933	Mixed	0.53	1.00	0.00	0.04	0.09
Liebow et al[41]/1948	108	Mixed	0.43	0.95	0.12	0.33	0.45
Total	29,245		0.66	0.99	0.09	0.06	0.15

FB with its attendant procedures is a valuable diagnostic procedure in the workup of a patient suspected of having lung cancer. A comprehensive literature search on studies published from 1970 to 2001 was performed[24] to determine the sensitivity of FB for the diagnosis of bronchogenic carcinoma. Studies with < 50 patients and those that reported exclusively on interoperator performance variabilities or focused on technical aspects (*eg*, needle size or cytology preparation) were excluded. Forty-four studies[14,43–85] met the inclusion criteria. An additional nine studies[86–94] using the same inclusion criteria were found during the updated literature review. Most of the studies identified were limited to patients with pathologically confirmed bronchogenic carcinoma and provided data only on the diagnostic yield (test sensitivity). The data were further analyzed with respect to the diagnosis of central disease with an endobronchial component and peripheral disease beyond the segmental level.

The decision about whether to pursue a diagnostic bronchoscopy for a lesion that is suspicious for lung cancer largely depends on the location of the lesion (central vs peripheral). Central lesions can present as an exophytic endobronchial mass, submucosal spread, or a peribronchial tumor causing extrinsic compression. Thirty-five studies[14,44–48,50–72,86–90] of patients with central disease were identified (Table 2). Among a total of 4,507 patients, the overall sensitivity of FB was 0.88. Direct forceps biopsy of visible central lesions is the technique used most frequently, and the sensitivity of this test by itself was 0.74. At least three forceps biopsies of the visible lesion are recommended. The sensitivity from washings and brushings is somewhat lower (0.48 and 0.59, respectively), but these tests are often combined with forceps biopsies. The addition of TBNA to obtain cytology or histology samples when there is submucosal tumor spread or peribronchial tumor causing extrinsic compression increases the sensitivity of bronchoscopy.[95,96]

Peripheral lesions are defined in most studies as lesions that are not visible beyond the visual segmental bronchi; thus, it is not surprising that the sensitivity of FB for diagnosing peripheral lung cancers is lower than for central lesions. Thirty-four studies[43,46,49,50,51,58,59–62,64,65,68–85,91–94] reported on the sensitivity of FB for peripheral lesions (Table 3). Transbronchial biopsies provided the highest sensitivity (0.57; 21 studies), followed by brush biopsy (0.54; 18 studies) and BAL/washings (0.43; 14 studies). Although TBNA showed a high sensitivity (0.65; seven studies), the data deserve cautious interpretation because of the limited number of studies and the large differences in sample size.[24] The overall sensitivity for all modalities in the diagnosis of peripheral disease was 0.78 (16 studies).

A few points must be made in order to interpret the results of bronchoscopy in the diagnosis of peripheral lung cancers. First, most of the studies used fluoroscopy routinely for peripheral lesions, which increases the reported sensitivity of bronchoscopy.[97] Second, the number of transbronchial biopsy samples taken is important, with a sensitivity of 0.45 for one sample and 0.70 for six samples being reported in one study.[98] And last, the sensitivity of bronchoscopy is reported to be higher if the CT scan

Table 2—*Sensitivity of FB Diagnostic Procedures for Central Bronchogenic Carcinoma

Study/Year	Patients,† No.	Sensitivity				
		All Methods	Endobronchial Biopsy	Brush	Wash	EBNA/TBNA
Hsu et al[86]/2004	24					0.71
Win et al[87]/2003	78	0.85	0.61	0.27	0.45	0.42
Gaber et al[88]/2002	39	0.90	0.79	0.74	0.54	
Karahalli et al[89]/2001	98	0.90	0.83	0.68	0.32	0.69
Jones et al[90]/2001	514	0.89	0.72	0.72	0.48	
Baaklini et al[51]/2000	22	0.82				
Bungay et al[52]/2000	24	0.92				
Dasgupta et al[53]/1999	32	0.97				0.78
Govert et al[54]/1999	57	0.95	0.74		0.63	0.82
McLean et al[55]/1998	71		0.82			
Bilaceroglu et al[56]/1997	68	0.96		0.66		0.90
Sing et al[43]/1997	53			0.64		
Govert et al[57]/1996	177	0.85	0.81	0.48	0.43	
Castella et al[58]/1995	39					0.87
Utz et al[14]/1993	88					0.36
Buccheri et al[59]/1991	708		0.80	0.35	0.31	
Popp et al[60]/1991	99		0.93	0.79		
Mak et al[61]/1990	125	0.87	0.76	0.52	0.50	
Gay and Brutinel[62]/1989	53					0.23
Saita et al[63]/1989	105		0.48	0.30		
Wagner et al[44]/1989	72	0.67	0.58	0.39	0.35	0.36
Schenk et al[45]/1987	91	0.71	0.56	0.40	0.29	0.45
Cox et al[64]/1984	33	0.94	0.84	0.83	0.76	
Lam et al[65]/1983	329	0.94	0.82	0.74	0.76	
Zisholtz and Eisenberg[66]/1983	51	0.73	0.67	0.65	0.44	
Gellert et al[67]/1982	218		0.78			
Pilotti et al[46]/1982	286			0.78		
McDougall and Cortese[68]/1981	16		0.50	0.23		
Radke et al[69]/1979	15	0.87				
Chaudhary et al[47]/1978	95		0.76	0.53	0.78	
Chopra et al[48]/1977	51		0.66	0.72	0.51	
Stringfield et al[70]/1977	78		0.85			
Kvale et al[71]/1976	71		0.71	0.77	0.63	
Zavala[72]/1975	193	0.94	0.97	0.93		
Oswald et al[50]/1971	434		0.61			
Summary	4,507	0.88	0.74	0.61	0.47	0.56

*EBNA = endobronchial needle aspiration.

†Represents the maximum number of patients included in sensitivity calculations for any one method.

shows a bronchus extending to the peripheral lesion (0.60 vs 0.25, respectively).[99,100]

The sensitivity of bronchoscopy for diagnosing peripheral lesions is most affected by the size of the lesion. Ten studies[49,51,68–70,84–86,92,93] were identified that reported on the sensitivity of bronchoscopy (brush and/or biopsy) for peripheral lesions with a size < 2 cm or > 2 cm in diameter (Table 4).The sensitivity for peripheral lesions of < 2 cm in diameter was 0.34. Peripheral tumors with a diameter of > 2 cm resulted in a sensitivity of 0.63. Six studies[47,48,75,77,79,83] reported on the sensitivity of post-bronchoscopy sputa as an adjunct to the above-mentioned bronchoscopic techniques, which was 0.35 (Table 5).

Following in the footsteps of the gastroenterologists, pulmonologists have started using ultrasound (US) technology in the diagnosis and staging of bronchogenic carcinoma. Of the two kinds of ultrasonic probes (*ie*, convex and radial), the radial probe is used to locate the peripheral lesion, which was previously thought to be inaccessible by conventional bronchoscopy.[101,102] A flexible double-hinged curette or an electromagnetic device is used, if necessary, to maneuver an extended working channel to the area of interest, under fluoroscopic guidance. The latter is used to facilitate the probe as well as the sampling tools. Due to the steep learning curve associated with the device, its use is limited to tertiary care centers.

Kurimoto et al[103] carried out an open-label, prospective, nonrandomized trial using a radial probe in

Table 3—*Sensitivity of FB Diagnostic Procedures for Peripheral Bronchogenic Carcinoma*

Study/Year	Patients,* No.	Sensitivity				
		All Methods	Transbronchial Biopsy	Brush	BAL	TBNA
Kawaraya et al[91]/2003	1,372	0.88	0.77	0.57		0.35
Trkanjec et al[92]/2003	50	0.86	0.62	0.16	0.29	
Bandoh et al[93]/2003	97	0.60				
Baba et al[94]/2002	87	0.75	0.53	0.44		0.67
Baaklini et al[51]/2000	129	0.61				
Gasparini et al[73]/1999	480	0.76	0.50			0.70
Reichenberger et al[74]/1999	103		0.39	0.36	0.28	0.47
Aristiazabal et al[75]/1998	64		0.34			
Bilaceroglu et al[76]/1998	92	0.64				
Wongsurakiat et al[77]/1998	30	0.50	0.17		0.47	
Sing et al[43]/1997	22			0.22		
Castella et al[58]/1995	45					0.69
Debeljak et al[78]/1994	39		0.77	0.59	0.36	
de Gracia et al[79]/1993	55				0.33	
Torrington and Kern[80]/1993	91		0.20			
Utz et al[14]/1993						
Pirozynski[81]/1992	145		0.33	0.30	0.65	0.58
Buccheri et al[59]/1991	337		0.75	0.44	0.33	
Popp et al[60]/1991	87		0.80	0.83		
Mak et al[61]/1990	63	0.56	0.37	0.29	0.38	
Rennard et al[82]/1990	730				0.47	
Gay and Brutinel[62]/1989	20					0.65
Wagner et al[44]/1989						
Mori et al[83]/1989	85	0.84		0.84	0.42	
Naidich et al[84]/1988	65	0.48				
Cox et al[64]/1984	22	0.36	0.29	0.22	0.36	
Lam et al[65]/1983	155	0.86	0.61	0.52	0.52	
Pilotti et al[46]/1982	84			0.29		
Wallace and Deutsch[85]/1982	143		0.19			
McDougall and Cortese[68]/1981	130	0.62	0.48	0.36	0.36	
Radke et al[69]/1979	82	0.51				
Stringfield et al[70]/1977	29		0.48			
Kvale et al[71]/1976	29		0.27	0.21	0.12	
Zavala[72]/1975	137	0.71	0.69	0.70		
Hattori et al[49]/1971	208			0.83		
Oswald et al[50]/1971	435		0.28			
Summary	5,742	0.78	0.57	0.54	0.43	0.65

*Represents the maximum number included in sensitivity calculations for any one method.

150 patients with peripheral lung lesions. A final diagnosis was established in all patients with a variety of means. US-guided sampling established the diagnosis in 77% of cases; 69% of lesions were benign, and 82% of lesions were malignant. There was no difference in the diagnostic yield (range, 69 to 77%) based on the size of the lesion (< 10 mm, 10 to 14 mm, 15 to 20 mm, and 20 and 29 mm), except when the lesion was > 3 cm in size (yield, 92%). There were no complications. The authors concluded that sampling guided by the radial US probe significantly increases the diagnostic yield of FB while dealing with peripheral lung lesions < 20 mm in size. In another study,[104] information from a multiplaner volume reformation of the CT scan images were used to guide the endobronchial accessories to sample peripheral lesions. The study[104] demonstrated that the diagnostic yield of FB could be increased up to at least 82%, irrespective of the size and location of the lesion.

A convex US probe is mainly used for the sampling of the mediastinal lymph nodes to aid in disease staging and is discussed in more detail in the "Invasive Staging of Lung Cancer" chapter. A number of newer modalities such as ultrathin bronchoscopy, CT fluoroscopy, multiplanar volume reformation, and electromagnetic navigation are being studied for their impact on the diagnostic yield of FB for lung cancer, yet no recommendation can be made based on the preliminary results

The FN rate for bronchoscopy has not yet been defined. Most clinicians would pursue the diagnosis

Table 4—*Sensitivity of FB Diagnosis of Bronchogenic Carcinoma by Size of Lesion

Study/Year	Lesion < 2 cm				Lesion > 2 cm			
	Patients, No.	Pos	Neg	Sens	Patients, No.	Pos	Neg	Sens
Trkanjec et al[92]/2003	17	9	8	0.53	33	27	6	0.82
Bandoh et al[93]/2003	25	8	17	0.32	72	50	22	0.69
Baaklini et al[51]/2000	16	4	12	0.25	135	93	42	0.69
Gasparini et al[73]/1999	195	82	113	0.42	300	169	131	0.56
Naidich et al[84]/1988	15	4	11	0.27	46	26	20	0.57
Wallace and Deutsch[85]/1982	65	3	62	0.05	78	24	54	0.31
McDougall and Cortese[68]/1981	9	1	8	0.11	36	21	15	0.58
Radke et al[69]/1979	21	6	15	0.29	76	49	27	0.64
Stringfield et al[70]/1977	3	1	2	0.33	26	13	13	0.50
Hattori et al[49]/1971	17	13	4	0.76	182	150	32	0.82
Summary	383	131	252	0.34	984	622	362	0.63

*Neg = negatives; Pos = positives; Sens = sensitivity.

further in the case of a nondiagnostic bronchoscopy of a visible endobronchial abnormality. The FN rate can be estimated to be fairly high in the case of peripheral lesions, especially smaller ones, because of the relatively low sensitivity in this setting. Bronchoscopy has an important role in the diagnosis of benign conditions, but the chance of finding a benign condition in a patient who is clinically suspected of having lung cancer is only 1%.[105]

Recommendations

8. In patients suspected of having lung cancer who have a central lesion, bronchoscopy is recommended to confirm the diagnosis. However, it is recommended that further testing be performed if bronchoscopy results are nondiagnostic and suspicion of lung cancer remains. Grade of recommendation, 1C

9. In expert hands, a radial probe US device can increase the diagnostic yield of FB while dealing with peripheral lesions of < 20 mm in size. Its use can be considered prior to referring the patient for TTNA. Grade of recommendation, 2B

TTNA

Key Question 3: What are the performance characteristics for TTNA as a diagnostic modality with particular emphasis on the size and location of the suspected cancer?

In the previously published lung cancer guidelines, Schreiber and McCrory[24] analyzed data from a metaanalysis[106] of 46 studies and an additional 19 studies[107–125] that focused on the performance characteristics of TBNA or biopsy for the diagnosis of localized pulmonary lesions. The metaanalysis by Lacasse et al[106] encompassed a comprehensive search (up to 1995) of reports published in the English language on the use of NA or biopsy for the evaluation of solitary or multiple pulmonary lesions. At least 90% of the study populations had parenchymal pulmonary lesions as opposed to mediastinal, hilar, or pleural lesions. All diagnoses were verified by surgical biopsy, biopsy of an adjacent site with tumor involvement, culture results, or clinical follow-up for at least 1 year. Cytology findings alone, even when confirmed by findings from another site, was not accepted as a reference standard. At least 90% of patients in each study had a histologic reference standard diagnosis. Forty-two[86,125–166] of the 46 studies in the metaanalysis were used for the final analysis. Five studies with < 50 patients included in the metaanalysis were excluded.[24] In the reanalysis of the data, Schreiber and McCrory[24] considered only the following cut point: definite malignancy or suspicion of malignancy as test-positive, and all other test results, including nondiagnostic, benign, nonspecific, and specific benign diagnoses, as test-negative (this corresponded to cut point "b" in the published metaanalysis).

Five studies,[166–170] published from 2001 to 2004 were identified and incorporated into the reanalysis for this current chapter (Table 6). The pooled sensitivity of TTNA for the diagnosis of peripheral bronchogenic carcinoma was 0.90 (95% confidence interval [CI], 0.88 to 0.91). Individual study estimates ranged from 0.62 to 0.99. There was little difference in specificity for any group of studies analyzed. Overall, only a few studies described the test performance data (*ie*, sensitivity and specificity) according to location of lesion; thus, there were limited data with which to address the question of differences in test performance based on lesion location.[24]

TTNA of a peripheral lung lesion can be per-

formed under either fluoroscopic or CT scan guidance. Lacasse et al[106] did not find any differences in test-operating characteristics between CT scan and fluoroscopic guidance of TTNA in their original metaanalysis. However, with substantially more data from CT scan-guided TTNA studies, the analysis by Schreiber and McCrory[24] found that studies using CT scan guidance showed higher sensitivity than those using fluoroscopy guidance. Using a random-effects model, the pooled sensitivities were 0.92 (95% CI, 0.90 to 0.94) and 0.88 (95% CI, 0.85 to 0.90), respectively, for studies of CT scan-guided and fluoroscopy-guided TTNA. Two studies[108,125] reported direct comparisons between aspiration cytology and cutting needle biopsy histologic diagnosis. Both studies found that transthoracic needle core biopsy when compared with FNA showed similar sensitivity for malignancy (Bilaceroglu et al,[76] 86% vs 92%, respectively; Bandoh et al,[93] 98% vs 98.4%, respectively) and better ability to determine a specific diagnosis for nonmalignant lesions (Bilaceroglu et al,[76] 100% vs 44%, respectively; Bandoh et al,[93] 100% vs 50%, respectively).

In summary, for peripheral lung lesions the sensitivity of TTNA is higher than that of bronchoscopy. In patients who have lung cancer, TTNA has approximately a 90% chance of providing confirmation of the diagnosis. Furthermore, given the FP rate of 0.01 to 0.02, a positive TTNA finding for cancer is reliable. On the other hand, the FN rate of TTNA is high (range, 0.20 to 0.30)[171]; thus, TTNA is generally not useful in ruling out cancer. In patients with lesions that are even moderately suspicious for lung cancer, and who appear to have early-stage disease and are candidates for surgical resection, the high FN rate of TTNA makes reliance on a negative result untenable; therefore, further testing to establish a definitive diagnosis is necessary.

Establishing a specific benign diagnosis such as tuberculosis, fungal infection, or hamartoma on TTNA results is quite valuable, particularly in patients in whom the clinical and radiologic findings strongly suggest a benign diagnosis. In such cases, a specific benign diagnosis based on TTNA findings further decreases the risk of missing a cancer.

PET scanning using fluoro-18–2-deoxyglucose (FDG) has proven to be an excellent modality for evaluating solitary pulmonary nodules. In a meta-analysis[172] of the available data on FDG-PET scanning, the average sensitivity and specificity of FDG-PET scanning for detecting a malignancy was reported to be 0.97 and 0.78, respectively. Like any test, PET scanning has some limitations. The current generation of PET scanners can miss lesions that are < 1 cm in size,[172–174] and FN results can occur when dealing with carcinoid tumors or bronchoalveolar carcinomas.[172,174,175] FP results may be seen with certain inflammatory or infectious lesions such as tuberculomas, histoplasmomas, and rheumatoid nodules.[180,182] (The reader is referred to the chapter on "Solitary Pulmonary Nodules" for a more detailed discussion of FDG-PET scanning in the evaluation of the solitary pulmonary nodule.)

Recommendation

10. In patients suspected of having lung cancer who have a small (< 2 cm) peripheral lesion, and who require tissue diagnosis before further management can be planned, TTNA is recommended. However, it is recommended that further testing be performed if TTNA results are nondiagnostic and suspicion of lung cancer remains. Grade of recommendation, 1B

Cell Type Accuracy

Key Question 4: What is the diagnostic error when differentiating between NSCLC and SCLC generated by various diagnostic techniques (*eg*, bronchoscopy, TTNA, and sputum cytology)?

In a patient with lung cancer, distinguishing between SCLC and NSCLC is of paramount importance as each of these cancers is treated in a radically different manner. The distinction between SCLC

Table 5—*Sensitivity of Postbronchoscopy Sputum for Diagnosis of Bronchogenic Carcinoma*

Study/Year	Patients, No.	Postbronchoscopy Sputum		
		Positive	Negative	Sensitivity
Wongsurakiat et al[77]/1998	26	2	24	0.08
de Gracia et al[79]/1993	43	13	30	0.30
Mori et al[83]/1989	81	17	64	0.21
Chaudhary et al[47]/1978	114	58	56	0.51
Chopra et al[48]/1977	51	24	27	0.47
Kvale et al[71]/1976	22	3	19	0.14
Summary	337	117	220	0.35

Table 6—*Sensitivity and Specificity of TTNA and/or Transthoracic Needle Biopsy for Diagnosis of Peripheral Bronchogenic Carcinoma

Study/Year	Patients, No.	Type of Needle	Radiologic Assistance	Sensitivity	Specificity	FP Rate*	FN Rate*	Prevalence
Geraghty et al[166]/2003	846	C	CT scan	0.91	0.99	0	0.19	0.74
Yamagami et al[167]/2003	110	C	CT scan	0.95	1	0	0.15	0.78
Arslan et al[168]/2002	121	A	CT scan	0.89	1	0	0.27	0.78
Tan et al[169]/2002	100	A	Fluo, CT scan	0.93	0.96	0.01	0.18	0.76
Wallace et al[170]/2002	57	A, C	CT scan	0.82	1	0	0.28	0.68
Lopez Hanninen et al[114]/2001	79	C	CT scan	0.96	1.00	0	0.06	0.63
Laurent et al[115]/2000	202	C	CT scan	0.94	1.00	0	0.18	0.80
Hirose et al[116]/2000	50	C	CT scan	0.83	1.00	0	0.19	0.58
Charig and Phillips[117]/2000	185	C	CT scan	0.93	1.00	0	0.48	0.93
Swischuk et al[118]/1998	612	C	Fluo, CT scan	0.96	0.99	0	0.13	0.76
Lucidarme et al[119]/1998	89	C	CT scan	0.93	1.00	0	0.26	0.84
Larscheid et al[120]/1998	130	A, C	CT scan	0.91	1.00	0	0.26	0.80
Yankelevitz et al[121]/1997	114	A	CT scan	0.94	1.00	0	0.16	0.76
Westcott et al[122]/1997	62	A, C	Fluo, CT scan	0.93	1.00	0	0.12	0.67
Santambrogio et al[123]/1997	220	A	CT scan	0.93	0.99	0.01	0.11	0.64
Cattelani et al[124]/1997	119	A	CT scan	0.93	1.00	0	0.13	0.67
Li et al[107]/1996	97	A	CT scan	0.89	1.00	0	0.43	0.88
Klein et al[108]/1996	129	A, C	CT scan	0.95	1.00	0	0.08	0.64
Milman et al[109]/1995	103	A	Fluo	0.69	1.00	0	0.49	0.76
Böcking et al[125]/1995	371	A, C	CT scan	0.99	0.94	0.02	0.04	0.79
Zakowski et al[110]/1992	176	A	Fluo, CT scan	0.84	1.00	0	0.47	0.84
Yang et al[111]/1992	120	A	US	0.62	1.00	0.00	0.63	0.82
Cristallini et al[112]/1992	390	A, B	Fluo, CT scan	0.94	0.99	0.00	0.16	0.77
Calhoun et al[113]/1986	197	A	Fluo	0.87	1.00	0.00	0.35	0.81
Knudsen et al[127]/1996	128	A	US	0.95	0.95	0.02	0.09	0.68
Gasparini et al[73]/1999	589	A, C	Fluo, CT scan	0.93	0.99	0.00	0.15	0.72
Garcia Rio et al[128]/1994	84	A	CT scan	0.84	1.00	0.00	0.39	0.80
Burbank et al[129]/1994	60	C	CT scan	0.95	1.00	0.00	0.11	0.72
Targhetta et al[130]/1993	64	B	US	0.91	1.00	0.00	0.31	0.83
Grode et al[131]/1993	219	A, B, C	Fluo	0.89	1.00	0.00	0.31	0.80
Collins et al[132]/1992	129	B, C	Fluo, CT scan	0.94	1.00	0.00	0.39	0.91
Veale et al[133]/1988	100	A	Fluo	0.84	1.00	0.00	0.52	0.87
Simpson et al[134]/1988	227	B	Fluo	0.82	1.00	0.00	0.73	0.93
Lovett et al[135]/1988	92	A	Fluo	0.90	1.00	0.00	0.38	0.86
Levine et al[136]/1988	58	NR	Fluo	0.71	1.00	0.00	0.30	0.60
Balslov et al[137]/1988	284	C	Fluo	0.78	1.00	0.00	0.37	0.73
Weisbrod et al[138]/1987	133	C	Fluo	0.78	1.00	0.00	0.36	0.71
Stanley et al[139]/1987	440	A	Fluo, CT scan	0.97	0.97	0.01	0.09	0.73
Winning et al[140]/1986	165	A	Fluo	0.77	1.00	0.00	0.43	0.76
Nahman et al[141]/1985	120	B	Fluo	0.98	0.94	0.01	0.11	0.86
Lees et al[142]/1985	86	A, B	Fluo, CT scan, US	0.85	1.00	0.00	0.42	0.83
Greene et al[143]/1985	150	B	Fluo	0.97	1.00	0.00	0.13	0.81
Crosby et al[144]/1985	180	A	Fluo, CT scan, US	0.82	1.00	0.00	0.69	0.93
Stevens and Jackman[145]/1984	348	A, B, C	Fluo	0.92	0.99	0.00	0.13	0.64
Harrison et al[146]/1984	89	C	Fluo	0.96	1.00	0.00	0.14	0.78
McEvoy et al[147]/1983	81	C	Fluo	0.87	1.00	0.00	0.45	0.86
Johnson et al[148]/1983	200	A, B	Fluo, CT scan	0.95	0.98	0.01	0.09	0.68
Vine et al[149]/1982	91	C	Fluo	0.87	1.00	0.00	0.22	0.69
Samuelsson et al[126]/1982	367	A	Fluo	0.97	0.96	0.02	0.06	0.67
Pilotti et al[150]/1982	130	A	Fluo	0.92	0.93	0.01	0.39	0.88
Jamieson et al[151]/1981	82	A, B	Fluo	0.94	1.00	0.00	0.19	0.80
Allison and Hemingway[152]/1981	147	B	Fluo	0.89	1.00	0.00	0.15	0.62
Westcott[153]/1980	400	B	Fluo	0.98	0.94	0.02	0.05	0.73
Taft et al[154]/1980	100	B	Fluo	0.83	0.95	0.01	0.42	0.80
Poe and Tobin[155]/1980	95	B	Fluo	0.90	0.94	0.01	0.32	0.81
Pak et al[156]/1981	52	A, B	Fluo	0.98	0.00	0.18	1.00	0.83
Flower and Verney[157]/1979	282	B	Fluo	0.87	0.96	0.02	0.25	0.72
Sagel et al[158]/1978	1,153	B	Fluo	0.96	0.99	0.00	0.13	0.78

(*Continued*)

Table 6—*Continued*

Study/Year	Patients, No.	Type of Needle	Radiologic Assistance	Sensitivity	Specificity	FP Rate*	FN Rate*	Prevalence
Lalli et al[159]/1978	1,204	B	Fluo	0.85	0.99	0.00	0.36	0.78
House and Thomson[160]/1977	88	B	Fluo	0.96	0.97	0.02	0.06	0.65
Francis[161]/1977	244	B	Fluo	0.82	0.95	0.03	0.29	0.68
Pavy et al[162]/1974	59	B	Fluo	0.86	1.00	0.00	0.54	0.89
Stevens et al[163]/1968	100	B	Fluo	0.90	0.95	0.03	0.14	0.62
Nasiell[164]/1967	144	B	Fluo	0.72	1.00	0.00	0.29	0.60
King and Russell[165]/1967	59	A	Fluo	0.88	1.00	0.00	0.35	0.81
Summary				0.90 (0.88 0.91)	0.97 (0.96 0.98)			

*A = aspiration needle; B = aspiration biopsy needle; C = cutting biopsy needle; Fluo = fluoroscopy; NR = not reported.
†The FP rate is 1 − the positive predictive value of the test; the FN rate is defined here as 1 − the negative predictive value of the test. Both are highly dependent on the prevalence of disease.

and NSCLC on sputum cytology, TTNA cytology, and bronchoscopic washings, brushings, and BAL cytology is quite reliable. Table 7 summarizes 21 studies, some of which address several diagnostic modalities (TTNA, 14 studies; expectorated sputa, 5 studies; bronchoscopy brush sample, 2 studies; TBNA, 4 studies).[29,44,46,50,116,122,127,131,136,139,148,154,157,162,175–185] The studies selected for reviews of the diagnostic accuracy of TTNA and bronchoscopy were systematically reviewed to find data on differences in diagnosis between SCLC and NSCLC based on the cytologic vs histologic diagnoses.[24] These studies show that the overall accuracy of SCLC vs NSCLC is 0.98, with individual study results ranging from 0.94 to 1.0. Indeed, the chance that a preoperative diagnosis of NSCLC is in error (the tumor is actually SCLC) is 0.02 (range, 0.01 to 0.07). On the other hand, the error rate of a diagnosis of SCLC (the tumor is actually NSCLC) is on average 0.09, with individual studies ranging from 0 to 0.33. As such, if the diagnosis of SCLC is made from a cytologic specimen but the radiographic and clinical findings do not support the diagnosis of SCLC, a biopsy specimen should be obtained if possible in order to perform a histologic evaluation.

Recommendations

11. In patients suspected of having lung cancer, the diagnosis of NSCLC made on cytology results (*eg*, sputum, TTNA, or bronchoscopic specimens) is highly reliable and can be accepted with a high degree of certainty. Grade of recommendation, 1B

12. The possibility of an erroneous diagnosis of SCLC on a cytology specimen must be kept in mind if the clinical presentation or clinical course is not consistent with that of SCLC. In such a case, it is recommended that further testing (biopsy for histologic evaluation) be performed to establish a definitive cell type. Grade of recommendation, 1B

Conclusion

A variety of techniques is available to assist the clinician in achieving a definitive diagnosis of lung cancer. Selection of the most appropriate test is best done in a multidisciplinary fashion with input from a pulmonologist, chest radiologist, and thoracic surgeon. Furthermore, the most appropriate test is usually determined by the type of lung cancer (SCLC or NSCLC), the size and location of the tumor, and the presumed stage of the cancer.

A diagnosis should be obtained by whatever method is easiest in patients who are presumed to have SCLC or who have very clear evidence of advanced NSCLC (*eg*, a large pleural effusion or metastatic disease). Sputum cytology is a reasonable first step in patients with central lesions with or without evidence of metastatic disease in whom a semi-invasive procedure might pose a higher risk; however, diagnostic accuracy depends on the rigorous acquisition, handling, and interpretation of samples. FB is the most useful test for central lesions, whereas in the case of peripheral lesions, the sensitivity of TTNA is higher than that of bronchoscopy.

Summary of Recommendations

1. In patients suspected of having SCLC based on the radiographic and clinical findings, it is recommended that the diagnosis be confirmed by the easiest method (*eg*, sputum cytology, thoracentesis, FNA, and bronchoscopy including TBNA, EBUS-NA,

and EUS-NA), as dictated by the patient's presentation. Grade of recommendation, 1C

2. In patients suspected of having lung cancer who have an accessible pleural effusion, thoracentesis is recommended to diagnose the cause of the pleural effusion. Grade of recommendation, 1C

3. In patients suspected of having lung cancer who have an accessible pleural effusion, if the pleural fluid cytology finding is negative (after at least two thoracenteses), thoracoscopy is recommended as the next step if establishing the cause of the pleural effusion is thought to be clinically important. Grade of recommendation, 1C

4. In patients suspected of having lung cancer who have a solitary extrathoracic site that is suspicious of a metastasis, it is recommended that tissue confirmation of the metastatic site be obtained if an FNA or biopsy of the site is feasible. Grade of recommendation, 1C

5. In patients suspected of having lung cancer, who have lesions in multiple distant sites that are suspected of metastases but in whom the biopsy of a metastatic site would be technically difficult, it is recommended that diagnosis of the primary lung lesion be obtained by the easiest method (eg, sputum cytology, bronchoscopy with TBNA or EBUS-NA, EUS-NA, or TTNA). Grade of recommendation, 1C

6. In patients suspected of having lung cancer, who have extensive infiltration of the mediastinum based on radiographic studies, it is recommended that the diagnosis of lung cancer be established by the easiest and safest method (*eg*, bronchoscopy with TBNA, EBUS-NA, EUS-NA, TTNA, or mediastinoscopy). Grade of recommendation, 1C

7. In patients suspected of having lung cancer, who present with a central lesion with or without radiographic evidence of metastatic disease, in whom a semi-invasive procedure such as bronchoscopy or TTNA might pose a higher risk, sputum cytology is recommended as an acceptable method of establishing the diagnosis. However, the sensitivity of sputum cytology varies by the location of the lung cancer. It is recommended that further testing be performed

Table 7—*Accuracy of Cytology for Distinguishing Between SCLC and NSCLC (Histology "Gold Standard")*

Study /Year	Patients, No.	Technique	Accuracy	FP Rate	FN Rate	Prevalence
Pilotti et al[46]/1982	252	Brush	0.96	0.00	0.04	0.15
Matsuda et al[176]/1986	443	Brush	0.94	0.11	0.04	0.24
Oswald et al[50]/1971	476	Sputum	0.97	0.21	0.01	0.08
Payne et al[177]/1981	656	Sputum	0.99	0.08	0.01	0.07
Clee et al[178]/1982	140	Sputum	0.98	0.00	0.02	0.15
Pilotti et al[179]/1982	400	Sputum	0.97	0.12	0.02	0.12
Risse et al[29]/1985	143	Sputum	0.97	0.03	0.03	0.24
Payne et al[177]/1981	126	TBNA	0.98	0.00	0.03	0.08
Wagner et al[44]/1989	18	TBNA	0.94	0.00	0.10	0.50
Clee et al[178]/1982	33	TBNA/brush	1.00	0.00	0.00	0.12
Clee et al[178]/1982	50	TBNA/brush	0.98	0.00	0.02	0.18
Pavy et al[162]/1974	17	TTNA	0.94	0.00	0.07	0.24
Flower and Verney[157]/1979	77	TTNA	0.97	0.50	0.00	0.03
Taft et al[154]/1980	33	TTNA	1.00	0.00	0.00	0.06
Payne et al[177]/1981	65	TTNA	0.98	0.33	0.00	0.03
Johnson et al[148]/1983	200	TTNA	0.98	0.00	0.03	0.15
Johnston[180]/1984	1,015	TTNA	0.98	0.12	0.01	0.09
Zaman et al[181]/1986	1,209	TTNA	0.98	0.09	0.01	0.10
Young et al[182]/1987	72	TTNA	0.99	0.00	0.01	0.03
Stanley et al[139]/1987	323	TTNA	0.99	0.04	0.00	0.10
Lovett et al[135]/1988	61	TTNA	1.00	0.00	0.00	0.07
Grode et al[131]/1993	224	TTNA	1.00	0.00	0.00	0.10
Knudsen et al[127]/1996	80	TTNA	0.99	0.25	0.00	0.04
Westcott et al[122]/1997	62	TTNA	1.00	0.00	0.00	0.06
Larscheid et al[120]/1998	130	TTNA	1.00	0.00	0.00	0.25
Mean			0.97			0.18
Total	6,305		0.98	0.09	0.02	0.12

dology finding if suspicion of lung cancer remains. Grade of recommendation, 1C

8. In patients suspected of having lung cancer who have a central lesion, bronchoscopy is recommended to confirm the diagnosis. However, it is recommended that further testing be performed if bronchoscopy results are nondiagnostic and suspicion of lung cancer remains. Grade of recommendation, 1C

9. In expert hands, use of radial probe US device can increase the diagnostic yield of FB while dealing with peripheral lesions of < 20 mm in size. Its use can be considered prior to referring the patient for TTNA. Grade of recommendation, 2B

10. In patients suspected of having lung cancer who have a small (< 2 cm) peripheral lesion, and who require tissue diagnosis before further management can be planned, TTNA is recommended. However, it is recommended that further testing be performed if TTNA results are nondiagnostic and suspicion of lung cancer remains. Grade of recommendation, 1B

11. In a patient suspected of having lung cancer, the diagnosis of NSCLC made on cytology findings (*eg*, sputum, TTNA, or bronchoscopic specimens) is highly reliable and can be accepted with a high degree of certainty. Grade of recommendation, 1B

12. The possibility of an erroneous diagnosis of SCLC in a cytology specimen must be kept in mind if the clinical presentation or clinical course is not consistent with that of SCLC. In such a case, it is recommended that further testing (*ie*, biopsy for histologic evaluation) be performed to establish a definitive cell type. Grade of recommendation, 1B

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Initial Evaluation of the Patient With Lung Cancer: Symptoms, Signs, Laboratory Tests, and Paraneoplastic Syndromes*

ACCP Evidenced-Based Clinical Practice Guidelines (2nd Edition)

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Background: **This chapter of the guidelines is intended to provide an evidence-based assessment of the initial evaluation of patients recognized as having lung cancer and the recognition of paraneoplastic syndromes.**
Methods: **The current medical literature that is applicable to this issue was identified by a computerized search and was evaluated using standardized methods. Recommendations were framed using the approach described by the Health and Science Policy Committee of the American College of Chest Physicians.**
Results: **Patients with lung cancer usually present with multiple symptoms, both respiratory related and constitutional. There is usually a time delay between symptom recognition by the patient and the ultimate diagnosis of lung cancer by the physician. Whether this time delay impacts prognosis is unclear, but delivering timely and efficient care is an important component in its own right. Lung cancer may be accompanied by a variety of paraneoplastic syndromes. These syndromes may not necessarily preclude treatment with a curative intent.**
Conclusions: **The initial evaluation of the patient with known or suspected lung cancer should include an assessment of symptoms, signs, and laboratory test results in a standardized manner as a screen for identifying those patients with paraneoplastic syndromes and a higher likelihood of metastatic disease.** ***(CHEST 2007; 132:149S–160S)***

Key words: evaluation; laboratory tests; paraneoplastic syndrome; signs; symptoms

Abbreviations: ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; HOA = hypertrophic osteoarthropathy; LEMS = Lambert-Eaton myasthenic syndrome; PTH = parathyroid hormone; PTH-rP = parathyroid hormone-related peptide; SIADH = syndrome of inappropriate antidiuretic hormone; SVCO = superior vena cava obstruction; VEGF = vascular endothelial growth factor

Lung cancer, unfortunately, is usually recognized late in its natural history. In large part, this reflects the peculiarities of pulmonary anatomy. A pulmonary nodule could grow for a considerable period of time, and potentially spread outside the lung, before it would cause symptoms. Consequently, at the initial presentation most patients with lung cancer have advanced disease. In general, of 100 newly presenting patients with lung cancer, 80 will be inoperable at presentation and only approximately 20 will proceed to attempted resection.[1] These observations explain why the 5-year mortality rates for lung cancer remain at approximately 85 to 90%. An understanding of how patients with lung cancer initially present will possibly allow the earlier identification of this increasingly common disease.

Materials and Methods

To update previous recommendations on the initial evaluation of the patient with lung cancer, guidelines on lung cancer diagnosis and management published between 2002 and May

2005 were identified by a systematic review of the literature (see "Methodology for Lung Cancer Evidence Review and Guidelines Development" section). Those guidelines including recommendations that are specific to the initial evaluation of the lung cancer patient were identified for possible inclusion in this section. Supplemental material appropriate to this topic was obtained by a literature search of a computerized database (MEDLINE). Recommendations were developed by the writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guidelines Development" section), and reviewed by all members of the lung cancer panel and the Thoracic Oncology Network prior to approval by the Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.

Presenting Symptoms of Lung Cancer

Initial presenting symptoms in patients with lung cancer may be respiratory related, but are often constitutional and attributable to metastatic disease (Table 1).[2–7] Cough is reported to be the most common presenting symptom of lung cancer; other respiratory symptoms include dyspnea, chest pain, and hemoptysis.[8–10] Patients with lung cancer usually present with multiple symptoms, including both respiratory and constitutional.[8,9] In a series of 678 consecutive lung cancer patients, at presentation 183 patients (27%) had symptoms related to the primary tumor; 232 patients (34%) had nonspecific systemic symptoms suggestive of metastases, including anorexia, weight loss and fatigue; and 219 patients (32%) had symptoms specific to a metastatic site.[11] The percentage of patients found to have lung cancer incidentally through chest radiographs has been consistently low. In the series reported in 1970 by Carbone et al[11] of 678 consecutive newly diagnosed lung cancer patients in the United States, only 44 patients (6%) were asymptomatic. In a community-based survey of lung cancer patients in Sweden who had received new diagnoses between 1997 and 1999, only 24 of 364 patients (7%) were asymptomatic.[12] Buccheri and Ferrigno[8] described the initial presentation of 1,277 consecutive lung cancer patients who received diagnoses at a single center in Italy from 1989 to 2002. Only 154 of these patients (13%) were asymptomatic at diagnosis. Prognosis in lung cancer has been clearly related to the type of presenting symptoms.[11] There was a better 5-year survival rate reported for asymptomatic patients (18%) than for those patients with symptoms related to the primary tumor (12%). Those patients with nonspecific symptoms had a 6% 5-year survival rate, and those patients with symptoms indicating metastatic disease fared the worst, with none alive at 5 years.

Table 1—*Range of Frequencies of Initial Symptoms and Signs of Lung Cancer

Symptoms and Signs	Range of Frequency, %
Cough	8–75
Weight loss	0–68
Dyspnea	3–60
Chest pain	20–49
Hemoptysis	6–35
Bone pain	6–25
Clubbing	0–20
Fever	0–20
Weakness	0–10
Superior vena cava obstruction	0–4
Dysphagia	0–2
Wheezing and stridor	0–2

*Modified from references 2 to 7.

In addition to the time delay between the development of the lung cancer and initial symptoms, there are usually a series of other delays before treatment is eventually initiated. Patients with lung cancer may notice a new symptom or a change in their usual respiratory symptoms but delay in reporting this to their general practitioner. Corner and colleagues[9] interviewed 22 patients with newly diagnosed lung cancer in the United Kingdom. Patients in this study had noted many different symptoms prior to presentation to their general practitioner, with cough and breathing changes being the most common. Of note was that patients described the onset of these symptoms between 4 months and 2 years (median time, 12 months) before they presented to their general practitioner. Koyi et al[13] reviewed the clinical course of 134 patients with lung cancer in whom cancer was newly diagnosed in 1997 and 1998 in Graevleborg, Sweden. The mean delay between symptom onset and first visit to their general practitioner was 43 days (range, 0 to 256 days). The one specific symptom that has been described as prompting more rapid presentation was hemoptysis.[9]

Even when patients present to the general practitioner with a symptom compatible with lung cancer, the general practitioner may not consider lung cancer a possibility. In the review by Koyi et al,[13] the

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mean time from initial patient presentation to the general practitioner and the general practitioner obtaining a chest radiograph was 56 days (range, 0 to 477 days). This delay may be understandable. Although lung cancer is a huge public health problem, on average the general practitioner does not see lung cancer patients often and usually has little personal experience with the disease. It has been estimated that a general practitioner in the United Kingdom might encounter a new lung cancer patient only once in every 8 months of regular practice.[14] In addition, the presenting symptoms of lung cancer are nonspecific, common, and more usually attributable to benign causes. Okkes et al[15] reviewed detailed records of patient encounters for 54 general practitioners in the Netherlands from 1985 to 1995. For patients who presented with cough (11,092 separate patient encounters), lung cancer was not listed as a separate entity among the 20 most common eventual diagnoses. The 19th most common listing was "other diseases of the respiratory tract." This listing presumably included lung cancer but only accounted for 3% of all eventual explanations for cough as a presenting symptom. Hamilton and colleagues[10] performed a retrospective review of detailed general practitioner records for 247 patients who presented with lung cancer and compared the presenting symptoms in these patients with matched control subjects taken from the same general practitioners' practices. They found that the most common presenting symptoms for lung cancer patients were poor predictors of the eventual diagnosis. Even hemoptysis was more frequently explained by benign conditions than by lung cancer.

Delays in the eventual diagnosis of lung cancer may also occur after referral of the patient to a specialist consultant. In the study by Koyi et al,[13] on average it took the consultant 33 days to establish the diagnosis of lung cancer, but in 10% of all patients it took > 60 days to reach the diagnosis. This delay is sometimes related to evaluating changes in either the chest radiograph or chest CT scan over time, at least in lung cancer patients who present with a solitary nodule and in whom a wait-and-watch approach is sometimes adopted (see the chapter in these guidelines on "Management of Patients With Pulmonary Nodules").

Overall, the time from recognition of the first symptom related to lung cancer by the patient to diagnosis of the disease and an eventual treatment decision may be lengthy. For instance, in the careful assessment of 134 patients in whom lung cancer had been newly diagnosed in Sweden, on average it took 203 days from symptom onset to treatment decision.[13] How these delays might affect overall prognosis for lung cancer, though, is not clear. In a small study from California, a group of 84 patients who underwent surgical resection of a stage I or II non-small cell lung cancer was divided into those who had an interval of < 90 days between the initial presentation and undergoing the actual operation (n = 46) and those with an interval of > 90 days (n = 38).[16] The mean time from presentation to operation for the entire group was 126 days (range, 1 to 641 days). No difference in 5-year survival was found between those whose delay was < 90 days and those with a delay of > 90 days. A larger study[17] of 1,082 patients with stage I and II lung cancer reported from Spain found that delays between the date of pathologic diagnosis and operation (mean interval, 35 days; range, 1 to 154 days) did not affect long-term survival. However, a study from Sweden[18] of 466 patients who had received treatment for non-small cell lung cancer showed that patients with more advanced disease had shorter time intervals between the first symptoms and treatment (median time delay from symptom to treatment for stage IV disease: patients with advanced disease, 3.4 months; patients with stage I-II disease, 5.5 months). Paradoxically, patients with short treatment delays had a worse prognosis, although the authors were unable to fully control for the obvious selection biases that confound observational studies of the relationship between the timeliness of care and survival.[18]

The relationship between the time from symptom onset to lung cancer diagnosis and prognosis is not clear. Confounding factors include tumor biology, as well as issues relating to the health system and access to care. Important considerations with delays in treatment, besides potentially missing the opportunity for cure or effective palliation, are the emotional distress of patients and their family members. Although further work is clearly needed to better facilitate the process from identification of disease to treatment decision for the lung cancer patient, timely care for these patients should be expected. The British Thoracic Society[19] recommended that all patients with suspected lung cancer should be evaluated by a respiratory specialist within 7 days and that the results of diagnostic tests should be communicated to the patient within 2 weeks. The RAND Corporation, in a quality indicator published for lung cancer care,[20] specified that a diagnosis of lung cancer should be established within 2 months of presentation and that treatment should begin within 6 weeks of diagnosis.

Recommendation

1. It is recommended that patients with known or suspected lung cancer receive timely and efficient care. Grade of recommendation, 1C

Presenting Radiographic Features of Lung Cancer

The chest radiograph plays a pivotal role in the recognition of lung cancer. Certainly, in the asymptomatic patient an abnormality on the chest radiograph would be the first clue to the presence of lung cancer. In patients with symptoms related to the primary tumor, the chest radiograph may often strongly support a suspicion of carcinoma of the lung. For patients presenting with either nonspecific systemic complaints or symptoms suggestive of metastatic disease, the chest radiograph will be helpful in focusing attention quickly on the lung as the most likely primary site. The radiographic appearance of lung cancer at initial presentation may be quite variable. In general, lung cancers present slightly more often on the right side than the left, and in the upper lobes rather than in the lower lobes.[21–23] Lung cancers may be seen centrally or peripherally, with a predominance of central locations at presentation. It has been estimated that up to 40% of the radiographic findings associated with lung cancer are related to central tumors causing airway obstruction with secondary atelectasis and lung parenchyma consolidation.[24,25] Peripheral tumors are classically thought to present as solitary pulmonary nodules (see chapter in these guidelines on "Management of Patients With Pulmonary Nodules"), but could also present radiographically as lung masses, ground-glass opacities or complex abnormalities.

Clues from the chest radiograph may suggest the diagnosis of lung cancer, but may not be helpful in identifying a histologic subtype. Adenocarcinoma is the most common type of lung cancer, accounting for 30 to 35% of all cases.[26] Although adenocarcinomas are traditionally thought to occur more frequently peripherally, they may develop centrally as well. Squamous cell carcinoma may account for about 30% of all lung cancers. They have typically been thought to arise in the central bronchi and extend into the hilum and mediastinum, but may also develop in the lung parenchyma where they may cavitate[27,28]; they may be slower growing and metastasize late.[27] Large cell carcinoma comprises 10 to 20% of all lung cancers and is also seen more commonly peripherally. Small cell lung carcinoma comprises 15 to 25% of all lung cancers, and, like squamous cell carcinoma, also usually develops in the proximal airways and involves the hilum and mediastinum. Unlike squamous cell carcinoma, evidence of regional and/or distant metastatic disease at the time patients present with small cell lung carcinoma is the norm.

Symptoms Related to the Primary Tumor

Of the presenting symptoms in patients with lung cancer, cough, dyspnea, chest pain, and hemoptysis may be related to the primary tumor (Table 1). Cough is the most common presenting symptom in patients with lung cancer. Many lung cancers occur in the central airways and may lead to postobstructive pneumonia or may cause lymph node enlargement, which may lead to cough. The failure of acute exacerbations of COPD to clear should raise suspicion of the presence of a neoplasm. Dyspnea develops commonly and is usually associated with increasing cough and amounts of sputum. If the tumor is occluding a main airway, it can cause breathlessness, which may be associated with a unilateral wheeze. Chest discomfort is also commonly reported by lung cancer patients at diagnosis. This is often of an ill-defined nature, intermittent and aching in quality. Definite pleuritic pain may occur as a result direct spread of the tumor to the pleural surface.

Hemoptysis is a common presenting symptom in patients with lung cancer. It is rarely severe and usually consists only of blood streaking of the sputum. The most common description is that of coughing up blood for several days in succession. The chest radiograph finding is usually abnormal in patients with hemoptysis from lung cancer. However, it has been estimated that up to 5% of patients with hemoptysis and either a normal chest radiograph finding or a chest radiograph finding with no localizing abnormalities will have lung cancer.[29] Lung cancers in these cases may be within the endobronchial tree, an area in which even CT scanning may fail to detect the cancer.[30] Consequently, in patients presenting with hemoptysis who are >40 years of age and have COPD and a history of smoking, even though the chest radiograph findings may be unremarkable, there should still be a high index of suspicion for lung cancer. Besides careful observation, the clinician may consider further diagnostic tests, such as chest CT scan or bronchoscopy. Sputum cytology may be a useful screening tool in these patients.[29]

Symptoms and Signs of Intrathoracic Spread

The intrathoracic spread of lung cancer, either by direct extension or lymphatic spread, produces a variety of symptoms and signs. These may be caused by the involvement of nerves (*eg*, recurrent laryngeal nerve, phrenic nerve, brachial plexus, and sympathetic nerve trunks), chest wall and pleura, vascular structures (*eg*, superior vena cava, pericardium, and heart), and visceral structures (*eg*, the esophagus).

Recurrent laryngeal nerve palsy, which causes hoarseness, has been reported in 2 to 18% of lung cancer patients. It is more common in left-sided tumors because of the circuitous route of the left recurrent laryngeal nerve around the aortic arch. It is associated with poor expectoration with coughing and an increased risk of aspiration. Phrenic nerve dysfunction may be noted on the chest radiograph by the presence of an elevated hemidiaphragm, or it can present with breathlessness in patients already compromised by lung disease. The superior sulcus or Pancoast tumor arises posteriorly in the apex of an upper lobe near the brachial plexus, commonly infiltrating the eighth cervical nerve root and the first and second thoracic nerve roots. This causes pain, cutaneous temperature change, and muscle wasting along the relevant nerve root. Symptoms and signs may be misleading initially, often resulting in a delay of many months before the true diagnosis is revealed. Horner syndrome occurs because of the involvement of the sympathetic chain and stellate ganglion, and is recognized by the typical triad of small pupil with ipsilateral ptosis and lack of facial sweating.

Chest wall and pleural invasion by the primary tumor, causing localized chest pain, is a common presenting symptom. More than 50% of patients with lung cancer complain of chest pain during the course of their disease. The pain is usually dull, tends to be persistent, poorly localized, and unrelated to breathing or coughing. Retrosternal pain may be due to hilar and mediastinal nodal involvement. When chest pain is particularly severe, persistent, and localized, it is usually related to either direct invasion of the pleura or chest wall by the primary tumor, or to a rib metastasis. Tenderness may be elicited at the site of rib involvement, and, rarely, a soft tissue mass can be palpated. Pleural involvement occurs in 8 to 15% of patients with lung cancer. Pleuritic chest pain can occur with the early phase of neoplastic pleural invasion but may disappear with the onset of a pleural effusion. Pleural effusion, which may result in dyspnea, is generally caused by direct pleural extension but may also be secondary to mediastinal node involvement and lymphatic obstruction.

Lung cancer accounts for 46 to 75% of all cases of superior vena cava obstruction (SVCO). The most common histologic subtype associated with SVCO is small cell carcinoma.[4,31,32] Direct invasion by the primary tumor into the mediastinum or lymphatic spread with enlarged right paratracheal metastatic lymph nodes causes the SVCO. The patient will complain of swelling of the face, including the neck and eyelids, upper torso, neck, and arms. Dilated veins will be visible over the upper torso, shoulders and arms. Other symptoms related to SVCO include headache, dizziness (particularly on bending forwards), drowsiness, blurring of vision, cough, and dysphagia.[31,33] Metastases to other vascular structures in the mediastinum, such as the heart and pericardium, usually occur by direct lymphatic spread. At autopsy, cardiac involvement occurs in about 15% of patients, and a small number of patients will have tamponade.[34] In patients with primary lung cancer, the pericardium is the most common site of cardiac involvement, causing an effusion or supraventricular arrhythmias.[35]

Metastatic disease causing enlargement of the subcarinal lymph nodes can cause dysphagia by compressing the middle third of the esophagus. Very occasionally, tracheal primary tumors may grow into the esophagus, also causing dysphagia.

Symptoms, Signs, and Laboratory Tests Indicating Extrathoracic Metastases

About one third of patients present with symptoms as a result of distant metastases. The most common sites of distant metastasis from lung cancer are the bones; liver; adrenal glands and intraabdominal lymph nodes; brain and spinal cord; and lymph nodes and skin. Lung cancer can metastasize to virtually any bone, although the axial skeleton and proximal long bones are most commonly involved. The primary symptom resulting from bone involvement is pain, which may have a pleuritic component when the ribs are involved. Bone pain is present in up to 25% of all patients at presentation.

Liver metastases occur commonly with lung cancer. However, liver function test results are seldom abnormal until the metastases are numerous and large, or they block the hepatic ducts, which is when jaundice will occur. Hepatic metastases most commonly produce symptoms of weakness and weight loss. When present, hepatic metastases carry a very poor prognosis. Adrenal lesions and paraaortic lymph node metastases may occur and are most commonly seen with small-cell lung cancers; in the latter cell type, they are often discovered during staging. Clinical evidence of adrenal insufficiency is rarely seen.

Intracranial metastases occur in 10% of lung cancer patients at presentation. Spinal cord metastases are less common and tend to occur in patients with cerebral metastases. Brain metastasis may produce headache, nausea and vomiting, focal neurologic symptoms or signs, seizures, confusion, and personality changes. The lung is the primary site of approximately 70% of cancers that initially present with symptomatic brain metastases.[36]

The most common site of palpable lymphadenopathy is the supraclavicular fossa, which can be in-

volved in 15 to 20% of cases during the course of the disease. Identifying an enlarged lymph node or subcutaneous nodule due to metastatic lung cancer is extremely helpful in facilitating both diagnosis and staging. Fine-needle aspiration can be performed quickly at the bedside or as an outpatient with little morbidity and with a high sensitivity.[37]

Standardized Evaluation for Systemic Metastases

Carbone et al[11] and Feinstein and colleagues[38–42] have explored the relationship between symptoms at presentation and prognosis in a large cohort of consecutive lung cancer patients. Patients with the best prognosis were either asymptomatic or had symptoms referable only to the primary tumor. In patients either with systemic symptoms of anorexia, weight loss, and fatigue or with symptoms attributable to metastatic disease, prognosis was especially poor. The relationship between systemic symptoms and prognosis was conserved with standard staging of lung cancer. Within any individual tumor stage, there was a gradient of worsening prognosis in patients who presented with anorexia, weight loss, and fatigue. The biological association between systemic symptoms and worse prognosis was not entirely clear, although, intuitively, patients with systemic symptoms would be clinically suspected of having extensive disease.

Hooper and colleagues[43,44] used a cluster of clinical factors, including symptoms, signs, and standard laboratory tests, to screen patients for metastatic disease. Included within these clinical factors were weight loss and anemia. They found that abnormalities in these factors were associated with radiographic evidence of metastatic disease. The more abnormalities noted in the clinical assessment, the more likely that metastases would be detected. They also found that patients with no abnormalities in these clinical factors were extremely unlikely to have evidence of metastatic disease found on a CT scan. Silvestri et al[45] adapted the criteria of Hooper et al[43,44] (Table 2) and retrospectively asked whether they would be a useful screen for detecting adrenal metastases. As with the work by Hooper et al,[43,44] if no clinical abnormalities were noted, adrenal metastases were not found by CT scan; the more clinical abnormalities that were found, the more likely it was that adrenal metastases would be found. Both the work by Silvestri et al[45] and a study by Quinn and coworkers[46] pointed out that abnormalities in the clinical assessment would often not be helpful in identifying the site of metastases. However, the recognition of abnormalities in the clinical screen strongly suggested the presence of metastases.

Silvestri et al[45] also considered whether clinical evaluation would be useful in identifying which patients with lung cancer would have extrathoracic metastases detected by CT scanning of the brain or abdomen or by radionuclide bone scans.[47] They performed a metaanalysis[47] of all studies in lung cancer patients that provided data on both radiographic studies and the clinical factors adapted from the criteria of Hooper et al.[43,44] Consistent with earlier work, this metaanalysis showed that patients with clinical abnormalities were often found to have metastatic disease. However, if no abnormalities were noted in the clinical assessment, patients were very unlikely to have evidence of metastatic disease on CT scans of the brain or abdomen or on radionuclide bone scans. These authors concluded that performing an assessment of various clinical factors through a thorough history and physical examination, and standard laboratory tests would be a useful screen for identifying patients with a higher likelihood of metastatic disease.

Recommendation

2. It is recommended that all patients with known or suspected lung cancer give a thorough history and undergo a thorough physical examination and standard laboratory tests as a screen for metastatic disease. Grade of recommendation, 1B

Paraneoplastic Syndromes

Paraneoplastic syndromes are a group of clinical disorders that are associated with malignant diseases

Table 2—*Features of a Standardized Evaluation for Systemic Metastases

Symptoms	Signs	Laboratory Tests
Constitutional: weight loss > 10 lb	Lymphadenopathy (> 1 cm)	Hematocrit < 40% in men
Musculoskeletal: focal skeletal pain	Hoarseness, superior vena cava syndrome	Hematocrit < 35% in women
Neurologic: headaches, syncope, seizures, extremity weakness, or recent change in mental status	Bone tenderness, hepatomegaly (> 13-cm span), focal neurologic signs, papilledema, and soft tissue mass	Elevated alkaline phosphatase, γ-glutamyltransferase, or serum glutamicoxaloacetic transaminase level

*Modified from references 42 and 44.

that are not directly related to the physical effects of primary or metastatic tumors.[48,49] Paraneoplastic syndromes may occur in 10% of patients with bronchogenic carcinoma.[2,3] The extent of paraneoplastic symptoms is unrelated to the size of the primary tumor, and in some cases can precede the diagnosis of malignant disease. At other times they may occur late in the illness, or herald the first sign of recurrence. The exact mechanism by which paraneoplastic syndromes occur is not fully understood in all cases, but in many cases it appears to be related to either the production of biologically active substances by the tumor itself (*eg*, polypeptide hormones or cytokines) or in response to the tumor (*eg*, antibodies). Although a wide variety of paraneoplastic syndromes have been associated with lung cancer (Table 3), the most commonly recognized include endocrine, joint, and neurologic abnormalities.

Table 3—*Paraneoplastic Syndromes Associated With Lung Cancer

Endocrine syndromes
SIADH production
Nonmetastatic hypercalcemia
Cushing syndrome
Gynecomastia
Hypercalcitonemia
Elevated levels of LSH and FSH
Hypoglycemia
Hyperthyroidism
Carcinoid syndrome
Neurologic syndromes
Subacute sensory neuropathy
Mononeuritis multiplex
Intestinal pseudo-obstruction
LEMS
Encephalomyelitis
Necrotizing myelopathy
Cancer associated retinopathy
Skeletal syndromes
Hypertrophic osteoarthropathy
Clubbing
Renal syndromes
Glomerulonephritis
Nephrotic syndrome
Metabolic syndromes
Lactic acidosis
Hypouricemia
Systemic syndromes
Anorexia and cachexia
Fever
Collagen-vascular syndromes
Dermatomyositis
Polymyositis
Vasculitis
Systemic lupus erythematosus
Cutaneous
Acquired hypertrichosis languinosa
Erythema gyratum repens
Erythema multiforme
Tylosis
Erythroderma
Exfoliative dermatitis
Acanthosis nigricans
Sweet syndrome
Pruritus and urticaria
Hematologic
Anemia
Leucocytosis and eosinophilia
Leukemoid reactions
Thrombocytosis
Thrombocytopenic purpura
Coagulopathies
Thrombophlebitis
Disseminated intravascular coagulation

*LSH = lutein-stimulating hormone; FSH = follicle-stimulating hormone. Modified from references 1 and 11.

Common Endocrine Paraneoplastic Syndromes Associated With Lung Cancer

Hypercalcemia: The incidence of hypercalcemia in patients with lung cancer ranges from 2 to 6% at presentation to 8 to 12% throughout the course of the disease. Symptoms include nausea, vomiting, abdominal pain, constipation, polyuria, thirst, dehydration, confusion, and irritability. Squamous cell carcinoma is most frequently associated with hypercalcemia. Although bone metastases may be found in patients with lung cancer and hypercalcemia, most commonly humoral mechanisms account for the hypercalcemia.[50,51] Bioassays have suggested that there are increased levels of parathyroid hormone (PTH)-like activity in lung cancer patients with hypercalcemia.[52] Increased levels of urinary cyclic adenosine monophosphate have been reported in lung cancer patients, which is consistent with an increased PTH effect.[53] However, serum immunoreactive PTH levels are low to undetectable in patients with lung cancer and hypercalcemia.[54] A protein with PTH-like activity has been purified from lung cancer cell lines.[55,56] Increased bone resorption as the explanation for hypercalcemia has been attributed to this PTH-related protein (PTH-rP) released from lung cancer cells.[50] Serum levels of PTH-rP may be a valuable indicator of survival in lung cancer patients. Hiraki et al[57] found in a small group of patients with lung cancer and hypercalcemia that elevated circulating levels of PTH-rP were associated with shorter survival times. Increased serum PTH-rP levels were also associated with a higher likelihood of bony metastases. The authors speculated that PTH-rP, besides increasing bone resorption, might also play a role in facilitating bone metastases.

Syndrome of Inappropriate Antidiuretic Hormone Production: Hyponatremia, the most obvious sign of syndrome of inappropriate antidiuretic hormone

(SIADH) production, has been reported to occur in a wide incidence of lung cancer patients. Elevated antidiuretic hormone (ADH) levels and impaired water handling are found in possibly 30 to 70% of patients with lung cancer,[50] but the production of excess ADH does not always produce symptoms.[58–60] Only 1 to 5% of lung cancer patients have symptoms that are attributable to the SIADH production. Manifestations of SIADH production include confusion, unexplained seizures, decreased level of consciousness, and coma. Biochemically, the SIADH production is defined as low serum sodium and a dilute plasma osmolality along with a higher, or "inappropriate," urine osmolality, in the presence of continued urinary sodium excretion. The SIADH production is mainly associated with small cell lung cancer, although other malignant tumors of the lung may rarely be associated with this syndrome.[58,61,62] Although a variety of hormones, including atrial natriuretic peptide, have been implicated as possibly contributing to the hyponatremia found in lung cancer patients, hormone assays performed under controlled settings have shown that elevated plasma ADH levels are consistently found in these patients and seem to explain the impaired ability to excrete a water load.[63] The excess levels of ADH have been reported to originate from either ectopic production by lung cancer cells[59] or inappropriate peripheral baroreceptor stimulation of ADH release from the hypothalamus.[63] The syndrome resolves promptly (within 3 weeks) with the initiation of combination cytotoxic chemotherapy in 80% of patients with small cell lung cancer, but commonly recurs with tumor progression.[64]

Cushing Syndrome: Ectopic production of adrenocorticotropic hormone (ACTH) by small cell lung cancer cells is the most common explanation for Cushing syndrome.[50] ACTH is the most commonly produced ectopic hormone in lung cancer patients. It is not unusual to find increased serum levels of ACTH in patients with lung cancer; it may be detectable in up to 50% of patients with lung cancer.[65] However, some patients with Cushing syndrome may have normal basal ACTH levels.[66] In these patients, precursors of ACTH, such as proopiomelanocortin, may be elevated, suggesting that Cushing syndrome could develop due either to ectopic production or to aberrant processing of ACTH by small cell lung cancer cells.[50] Clinical manifestations of Cushing syndrome, which include weakness, muscle wasting, drowsiness, confusion, possible psychosis, dependent edema, moon facies, hypokalemic alkalosis, and hyperglycemia, are found in only a very small proportion of lung cancer patients. Cushing syndrome has been described in 1 to 5% of patients with small cell carcinoma,[67,68] but this may be an overestimate. In a 2005 report[66] of the National Institutes of Health experience with Cushing syndrome, only 3 of the 90 cases were attributed to small cell lung cancer. Most commonly, Cushing syndrome occurred in patients with pulmonary carcinoid (35 of 90 patients). Resection of the primary tumor, if possible, will effectively treat Cushing syndrome. Most patients with Cushing syndrome due to small cell lung cancer present with extensive stage disease and have a poor response to chemotherapy.[50]

Digital Clubbing and Hypertrophic Osteoarthropathy

Digital clubbing is an enlargement of the terminal segments of the fingers and/or toes due to proliferation of connective tissue beneath the nail matrix. Quantitative indexes of the nail profile angle, hyponychial angle and phalangeal depth ratio can be determined to assist in identifying clubbing.[69] Hypertrophic osteoarthropathy (HOA) is a systemic disorder, which involves both a painful symmetrical arthropathy, usually of the ankles, wrists, and knees, and periosteal new bone formation in the distal long bones of the limbs. Histologic features of HOA include vascular hyperplasia, edema, and excessive fibroblast and osteoblast proliferation.[70]

Clubbing and HOA may be associated with any cell type of lung cancer, although they are associated most frequently with squamous cell carcinoma and adenocarcinoma, and least frequently with small cell lung carcinoma. The exact mechanism responsible for the development of clubbing and HOA is unknown. In the past, explanations included neurogenic, hormonal, and vascular mechanisms.[71] More recently, the overexpression of vascular endothelial growth factor (VEGF) has been implicated as contributing to the pathogenesis of clubbing and HOA. In the case of a young woman with lung cancer and HOA, serum VEGF levels were initially elevated; after resection of the cancer, the serum VEGF levels fell and HOA remitted. Histochemical studies of the resected tumor showed increased VEGF messenger RNA expression, suggesting ectopic production by the lung cancer cells.[70]

Clubbing is much more common than HOA. In one study[72] of 111 consecutive patients with pathologically proven lung cancer, clubbing was present in 32 patients (29%). The phenomenon was significantly more common among women than men (40% vs 19%, respectively), and in patients with non-small cell lung cancer than in those with small cell lung cancer (35% vs 4%, respectively).[72] HOA is seen in $< 5\%$ of patients with non-small cell lung cancer.[73]

Small cell lung cancer is a rarer cause of HOA; in one series,[74] it accounted for only 1% of the patients with HOA. Anecdotal observations indicate that clubbing and HOA may resolve with successful treatment of the primary tumor, particularly surgical resection of a non-small cell lung cancer.

Neurologic Syndromes

A variety of poorly understood neurologic syndromes may occur in patients with lung cancer.[46] The diagnosis of a neurologic paraneoplastic syndrome is made once other causes, such as electrolyte imbalance, metastatic disease, cerebral and spinal vascular disease, infections, and treatment toxicity, are excluded. The neurologic syndromes include the Lambert-Eaton myasthenic syndrome (LEMS), limbic encephalopathy, polyneuropathy, cerebellar degeneration, retinopathy, opsoclonus-myoclonus, and autonomic neuropathy.[75,76] In LEMS, which is the most widely recognized of these disorders, patients present with the gradual onset of proximal lower extremity weakness; proximal upper extremity weakness is usually less noticeable. The syndrome may be worse in the morning and improve during the day. Although extraocular muscle involvement is uncommon, ptosis is often found.[77] Paraneoplastic neurologic syndromes have been associated almost exclusively with small cell lung cancer. These syndromes have been reported to affect 4 to 5% of lung cancer patients,[75] but the incidence is probably lower. In 1991, Elrington et al[78] reported that in a prospective survey of 150 consecutive cases of small cell lung cancer only two patients (1%) had LEMS and one patient (< 1%) had a polyneuropathy. A 2005 study[76] of 432 consecutive patients with small cell lung cancer showed similar results. LEMS was found in seven patients (1.6%), polyneuropathy in two patients (< 1%), subacute cerebellar degeneration in one patient (< 1%), and limbic encephalitis in three patients (< 1%).[76] The severity of the neurologic symptoms is unrelated to tumor bulk; in fact, the syndromes seem to be found more often in patients with limited disease, and in some patients a primary malignant lesion may be undetected before death despite disabling symptoms.[76,78–80]

The neurologic syndromes associated with lung cancer seem to develop through autoimmune mechanisms. Nearly all of the paraneoplastic neurologic syndromes are associated with the presence of type 1 antineuronal nuclear antibodies (also known as *anti-Hu antibodies*).[81] The Hu antigen is normally found in neurons, but, because the developing CNS is sequestered from the immune system by the blood-brain barrier, healthy adults do not have anti-Hu antibodies. Small cell lung cancers express Hu antigen, and up to 20% of patients with small cell lung cancer have detectable circulating levels of anti-Hu antibodies, although paraneoplastic neurologic syndromes will not develop in all of these patients.[76,82] In patients with LEMS, IgG antibodies directed against the P/Q voltage-gated presynaptic calcium channel interfere with Ca++-dependent neurotransmitter release.[83,84] At autopsy, lymphocytic inflammatory infiltrates in patients with paraneoplastic neurologic syndromes are found in areas of the nervous system that correspond to the neurologic deficits, supporting the concept that the autoantibodies play a key role in the pathogenesis of the neurologic syndromes. Lymphocytic infiltrates have also been found around the primary tumor, suggesting that the immune response may actually limit progression of the underlying small cell lung cancer.[85]

The response of the neurologic paraneoplastic syndrome to effective chemotherapy in patients with small cell lung cancer is variable.[86,87] Sustained improvements in the neurologic symptoms have been reported, although this is less commonly seen in patients with motor or sensory neuropathies.[88] In a small series[89] of patients with small cell lung cancer, the overall prognosis was more favorable in those patients with LEMS than in those without it.

Recommendation

3. It is recommended that patients with lung cancer and a paraneoplastic syndrome not be precluded from potentially curative therapy on the basis of these symptoms alone. Grade of recommendation, 2C

Summary

Most patients with lung cancer will be symptomatic at presentation. A minority of patients presents with symptoms related to the primary tumor, but most patients present with either nonspecific systemic symptoms, including anorexia, weight loss, and fatigue, or specific symptoms indicating metastatic disease. Asymptomatic patients and patients with symptoms related to the primary tumor have better 5-year survival rates than those patients with systemic symptoms or symptoms indicating metastatic disease. The initial evaluation of the patient with known or suspected lung cancer should include an assessment of symptoms, signs, and laboratory test results in a standardized manner as a screen for identifying those patients with a higher likelihood of metastatic disease.

Paraneoplastic syndromes, which occur in up to 10% of patients with lung cancer, are a group of clinical disorders that are associated with malignant diseases not directly related to the physical effects of primary or metastatic tumors. These syndromes may be due to the production of biologically active substances, such as polypeptide hormones, antibodies, or cytokines. Paraneoplastic symptoms are unrelated to the size of the primary tumor, in some cases can precede the diagnosis of malignant disease, and at other times may occur late in the illness or may herald the first sign of recurrence.

Summary of Recommendations

1. It is recommended that patients with known or suspected lung cancer receive timely and efficient care. Grade of recommendation, 1B

2. It is recommended that all patients with known or suspected lung cancer give a thorough history, and undergo a thorough physical examination and standard laboratory tests as a screen for metastatic disease. Grade of recommendation, 1C

3. It is recommended that patients with lung cancer and a paraneoplastic syndrome not be precluded from potentially curative therapy on the basis of these symptoms alone. Grade of recommendation, 2C

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Physiologic Evaluation of the Patient With Lung Cancer Being Considered for Resectional Surgery*

ACCP Evidenced-Based Clinical Practice Guidelines (2nd Edition)

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Background: **This section of the guidelines is intended to provide an evidence-based approach to the preoperative physiologic assessment of a patient being considered for surgical resection of lung cancer.**

Methods: **Current guidelines and medical literature applicable to this issue were identified by computerized search and evaluated using standardized methods. Recommendations were framed using the approach described by the Health and Science Policy Committee.**

Results: **The preoperative physiologic assessment should begin with a cardiovascular evaluation and spirometry to measure the FEV_1. If diffuse parenchymal lung disease is evident on radiographic studies or if there is dyspnea on exertion that is clinically out of proportion to the FEV_1, the diffusing capacity of the lung for carbon monoxide (DLCO) should also be measured. In patients with either an FEV_1 or DLCO < 80% predicted, the likely postoperative pulmonary reserve should be estimated by either the perfusion scan method for pneumonectomy or the anatomic method, based on counting the number of segments to be removed, for lobectomy. An estimated postoperative FEV_1 or DLCO < 40% predicted indicates an increased risk for perioperative complications, including death, from a standard lung cancer resection (lobectomy or greater removal of lung tissue). Cardiopulmonary exercise testing (CPET) to measure maximal oxygen consumption ($\dot{V}O_2max$) should be performed to further define the perioperative risk of surgery; a $\dot{V}O_2max$ of < 15 mL/kg/min indicates an increased risk of perioperative complications. Alternative types of exercise testing, such as stair climbing, the shuttle walk, and the 6-min walk, should be considered if CPET is not available. Although often not performed in a standardized manner, patients who cannot climb one flight of stairs are expected to have a $\dot{V}O_2max$ of < 10 mL/kg/min. Data on the shuttle walk and 6-min walk are limited, but patients who cannot complete 25 shuttles on two occasions will likely have a $\dot{V}O_2max$ of < 10 mL/kg/min. Desaturation during an exercise test has not clearly been associated with an increased risk for perioperative complications. Lung volume reduction surgery (LVRS) improves survival in selected patients with severe emphysema. Accumulating experience suggests that patients with extremely poor lung function who are deemed inoperable by conventional criteria might tolerate combined LVRS and curative-intent resection of lung cancer with an acceptable mortality rate and good postoperative outcomes. Combining LVRS and lung cancer resection should be considered in patients with a cancer in an area of upper lobe emphysema, an FEV_1 of > 20% predicted, and a DLCO of > 20% predicted.**

Conclusions: **A careful preoperative physiologic assessment will be useful to identify those patients who are at increased risk with standard lung cancer resection and to enable an informed decision by the patient about the appropriate therapeutic approach to treating their lung cancer. This preoperative risk assessment must be placed in the context that surgery for early-stage lung cancer is the most effective currently available treatment for this disease.** ***(CHEST 2007; 132:161S–177S)***

Key words: cardiopulmonary exercise testing; diffusing capacity of the lung for carbon monoxide; lung cancer; lung resection surgery; predicted postoperative lung function; preoperative assessment; spirometry

Abbreviations: CPET = cardiopulmonary exercise test; DLCO = diffusing capacity of the lung for carbon monoxide; LVRS = lung volume reduction surgery; PPO = predicted postoperative; %PPO = percent predicted postoperative; $\dot{V}O_2max$ = maximal oxygen consumption

Surgery is the best option for achieving a cure in patients with lung cancer, but many potentially resectable tumors occur in individuals with abnormal pulmonary function that is usually due to cigarette smoking. These patients may be at increased risk for both immediate perioperative complications and long-term disability following curative-intent surgical resection of their lung cancer. Cigarette smoking will also predispose these patients to other comorbid conditions, specifically atherosclerotic cardiovascular disease, which will further increase perioperative risk. Consequently, in considering whether a patient should undergo curative-intent surgical resection of lung cancer, the immediate perioperative risk from comorbid cardiopulmonary disease and the long-term risk of pulmonary disability must be balanced against the risk of reduced survival due to suboptimally treated (with radiation therapy rather than surgery) lung cancer.

The task of the preoperative physiologic assessment is to identify patients who are at increased risk for both perioperative complications and long-term disability from surgical resection of lung cancer using the least invasive tests possible. The purpose of this preoperative physiologic assessment is to enable adequate counseling of the patient on treatment options and risks so that they can make a truly informed decision. In the future, hopefully, the preoperative physiologic assessment will serve as the basis for interventions to possibly reduce the risk of perioperative complications and long-term pulmonary disability from curative-intent surgical resection of lung cancer.

To update previous recommendations on the preoperative physiologic evaluation of patients with lung cancer who are being considered for curative-intent surgery,[1] guidelines on lung cancer diagnosis and management published between 2002 and May 2005 were identified by a systematic review of the literature (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter). Those guidelines including recommendations specific to the preoperative physiologic evaluation were identified for inclusion in this section. Supplemental material appropriate to this topic was obtained by literature search of a computerized database (MEDLINE) and a review of the reference lists of relevant articles. Recommendations were developed by the writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), and reviewed by all members of the lung cancer panel and the Thoracic Oncology Network prior to approval by the Health and Science Policy Committee and the Board of Regents of the American College of Chest Physicians.

Current Guidelines

Although numerous reviews[2–7] have been published on the preoperative risk assessment of patients with lung cancer being considered for curative-intent surgical resection, most available guidelines[8–15] on the management of non-small cell lung cancer (NSCLC) do not address the preoperative evaluation process. The British Thoracic Society[16] and the American College of Chest Physicians[1] have provided guidelines with specific recommendations on the steps needed to evaluate the preoperative risk. The recommendations of these two guidelines follow a similar approach, relying on physiologic testing to estimate perioperative risk and the effect of resection on postoperative lung function.

General Issues Regarding Risk

Multidisciplinary Team

Patients with lung cancer who are seen by a physician with expertise in the management of this disease are more likely to have histologic confirmation of lung cancer and referral for potentially curative treatment.[17–19] Evaluation by a multidisciplinary team, which includes a thoracic surgeon specializing in lung cancer, a medical oncologist, a radiation oncologist, and a pulmonologist, is essential in the risk assessment of patients being evaluated for curative-intent surgery. Multidisciplinary input will be especially useful in patients who are marginal surgical candidates as a basis for discussing the proposed surgical procedure and treatment options with the patient and appropriate family or surrogates.

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Risk Thresholds

In presenting the option of curative-intent surgical therapy to a patient with lung cancer, it is important to recognize that risk assessment is a complex process. Risks related to standard surgical resection for lung cancer (*ie*, lobectomy or greater removal of lung tissue) include perioperative morbidity and mortality and long-term functional disability. Individual patient circumstances increase or decrease the risks from standard surgical resection. In this guideline, the effect on average mortality risk with standard surgical lung cancer resection for various physiologic abnormalities will be extrapolated from published data. This risk will be compared to the risk for patients with adequate cardiopulmonary reserve as a basis for estimating relative risk. However, patient preference as to what would be the maximal acceptable surgical risk (*eg*, the threshold mortality rate above which the patient would not accept the procedure) should also be explored. Mathematical approaches, based on decision analysis techniques, have been useful for conceptually describing the interplay between risk and patient preference but are not routinely used for individual patient care.[20] In addition to a discussion of the balance between risks and benefits for standard surgical resection of lung cancer, the responsible physician and patient should also discuss nonstandard treatment options, such as minimally invasive lobectomy, sublobar resections, conventional radiotherapy, stereotactic radiotherapy, and radiofrequency ablation.

Age

Age had been considered to be a factor that might increase perioperative risks, but age alone should not be a reason to deny patients with lung cancer access to curative-intent surgical resection.[21] As the population ages, the number of patients ≥ 70 years of age will rise; it is estimated that $\geq 40\%$ of patients with lung cancer in 2005 were ≥ 75 years of age.[18] For patients > 70 years of age, the reported mortality rate is between 4% and 7% for lobectomy and around 14% for pneumonectomy.[16,22,23] These reported rates are higher than those for patients < 70 years of age (lobectomy, 1 to 4%; pneumonectomy, 5 to 9%); the difference may be more a function of comorbidity than age alone. In a 2003 series[24] of 126 consecutive patients > 70 years of age who were undergoing curative-intent surgical resection, the overall 30-day mortality rate was 3.2%, with comorbid disease being the most important influence on mortality.

Limited information suggests that carefully selected patients who are > 80 years of age can tolerate lung cancer resection. A retrospective analysis[25] from Johns Hopkins Hospital reported that 17% of the octogenarians in whom lung cancer was diagnosed between 1980 and 2002 underwent surgical resection. In this series[25] of 68 patients in their 80s who were undergoing curative-intent surgery for NSCLC, the 30-day mortality rate was 8.8%. Port et al[26] described outcomes for 61 octogenarians who underwent various types of curative-intent surgical resections of lung cancer, including 4 patients who underwent pneumonectomy. The 30-day mortality rate in this series was 1.6%. A comprehensive geriatric assessment might be useful preoperatively in elderly patients. Fukuse and colleagues[27] found that dependence for performing activities of daily living and impaired cognition were important predictors of complications following pulmonary surgery.

Cardiovascular Risk

As with any planned major operation, especially in a population that is predisposed to atherosclerotic cardiovascular disease due to cigarette smoking, a preoperative cardiovascular risk assessment should be performed. The generally recommended approach to this risk assessment (Table 1) has been described in the American College of Cardiology and American Heart Association guidelines for perioperative cardiovascular evaluation for noncardiac surgery.[28] Patients with major factors for increased perioperative cardiovascular risk should undergo a preoperative cardiologic evaluation.

Surgical Experience

It has been recommended that the surgical mortality risk for lobectomy should be expected to be $< 4\%$, and for a pneumonectomy $< 9\%$.[16] Accumulating information indicates that when curative-intent surgical resection is performed by a general surgeon rather than a trained thoracic surgeon[29,30] and in a hospital in which these operations are performed infrequently[30–34] the surgical mortality rates may exceed these threshold values. Also to be considered within the realm of the surgical experience is the efficiency with which the preoperative evaluation takes place. A large retrospective study from Spain[35] has reported a median delay of 35 days between the date of pathologic diagnosis and the date of surgery. A smaller study[36] from the United States documented a median preoperative interval of 82 days. Although postoperative survival times did not seem to be influenced in either study by the preoperative delay, in general, the interval between diagnosis and curative-intent surgery should be minimized. These observations indicate that the experience of both the surgeon performing the procedure

Table 1—*Clinical Predictors of Increased Perioperative Cardiovascular Risk, Including Myocardial Infarction, Heart Failure, and Death

Clinical Predictors	Description
Major	
Unstable coronary syndromes	Acute (within 7 d) or recent (from 7 to 30 d) myocardial infarction with evidence of important ischemic risk by clinical symptoms or non-invasive study; and Unstable or severe angina (Canadian class III or IV)
Decompensated heart failure	
Significant arrhythmias	High-grade atrioventricular block; Symptomatic ventricular arrhythmias in the presence of underlying heart disease; and Supraventricular arrhythmias with uncontrolled ventricular rate
Severe valvular disease	
Intermediate	
Mild angina pectoris (Canadian class I or II)	
Prior myocardial infarction by history or pathologic Q waves	
Compensated or prior heart failure	
Diabetes mellitus (particularly insulin dependent)	
Renal insufficiency	
Minor	
Advanced age	
Abnormal ECG (left ventricular hypertrophy, left bundle branch block, and ST-T abnormalities)	
Rhythm other than sinus rhythm (*eg*, atrial fibrillation)	
Low functional capacity (*eg*, inability to climb one flight of stairs with a bag of groceries)	
History of stroke	
Uncontrolled systemic hypertension	

*Adapted from Eagle et al.[28]

and the hospital at which surgery occurs should be considered in planning curative-intent surgical resection of lung cancer.

Previous Chemotherapy

Induction chemotherapy may be used prior to curative-intent surgery, but chemotherapy may affect preoperative lung function. Leo and colleagues[37] found in 30 patients with NSCLC who underwent chemotherapy that FEV_1 increased but DLCO decreased prior to surgery. Decreases in postchemotherapy DLCO were significantly associated with postoperative respiratory complications. Matsubara et al[38] observed significantly lower DLCO levels and greater postoperative morbidity and mortality in 92 patients receiving induction chemotherapy compared to 666 patients who underwent surgery without induction chemotherapy.

Recommendations

1. It is recommended that patients with lung cancer be assessed for curative surgical resection by a multidisciplinary team, which includes a thoracic surgeon specializing in lung cancer, a medical oncologist, a radiation oncologist, and a pulmonologist. Grade of recommendation, 1C

2. It is recommended that patients with lung cancer not be denied lung resection surgery on the grounds of age alone. Grade of recommendation, 1B

3. It is recommended that patients with lung cancer being evaluated for surgery who have major factors for increased perioperative cardiovascular risk have a preoperative cardiologic evaluation. Grade of recommendation, 1C

Risk of Suboptimal Treatment of Lung Cancer

Little information is available on the long-term survival of patients who were deemed to be inoperable because of physiologic limitations, especially when compared to a group of patients with similar physiologic limitations who underwent surgical resection. In a study[39] reporting on outcomes for a group of 66 high-risk lung cancer patients, 5 patients who were at very high risk for poor outcome underwent curative-intent surgical resection. One patient died in the perioperative period, but the long-term survival curve for the whole group of 5 high-risk

patients undergoing surgery, including surgical death, was no different than that for 39 similar patients who were deemed to be inoperable.[39]

Recent studies from Japan[40] and the United States[41] have provided information on prognosis for patients with early-stage lung cancer who did not undergo curative-intent surgery. From 1982 to 1991, 4,947 patients with clinical stage I lung cancer were identified in the National Chest Hospital Study Group for Lung Cancer in Japan.[40] Of these 4,947 patients, 4,127 (83%) were treated surgically. The 799 patients (16%) who were treated nonoperatively had a 5-year survival rate of 16.6%. Many of these patients were treated with some combination of radiation therapy, chemotherapy, and immunotherapy, but no significant effect of these treatment modalities on survival was seen. Interestingly, 49 of the patients (6%) treated nonoperatively survived for >5 years. The reasons why surgery was not performed were not provided but probably were related to comorbid disease and patient refusal.

Between 1994 and 1999, stage I or IIa lung cancer was diagnosed in 128 patients at a single US hospital.[41] Of these 128 patients, 49 (38%) did not receive any treatment, and their median ($\pm$ SD) survival time was 14.2 $\pm$ 2.4 months. This was significantly worse than the median survival time of 46.2 $\pm$ 3.2 months for the 43 patients (34%) who underwent lobectomy. Another 36 patients (28%) underwent radiation therapy, and their median survival time was 19.9 $\pm$ 5.6 months. This survival time was significantly greater than that for the no-treatment group, but the radiation therapy was often for palliative purposes, not curative purposes. The survival results for this single-center study are similar to the data collected on outcomes of patients with stage I lung cancer from 1988 to 2001 that was reported in the Surveillance, Epidemiology, and End Results registry.[42] The median survival time for untreated patients was 14 months; it was 21 months for patients treated with radiation therapy.[42]

The survival benefits of conventional radiation therapy for early-stage NSCLC are small, and a cure should not be expected.[42] Qiao and colleagues[43] evaluated the results of radiation therapy, usually provided to medically inoperable patients, in the treatment of stage I NSCLC from 18 studies. They found that the median survival time from these studies ranged from 18 to 33 months, and that the mean 5-year survival rate was 21 $\pm$ 8%. Local control of the cancer and survival seemed to be higher in patients receiving $>$ 60 to 65 Gy of radiation. Newer techniques for administering radiation therapy may improve overall survival with a reduced risk for lung toxicity.[44,45] Three-dimensional conformal radiotherapy may allow the tolerable administration of up to 84 Gy of radiation with potentially improved survival.[46]

These data provide useful background information on the prognosis for patients with stage I and II lung cancer who do not undergo curative-intent surgical resection. Overall survival is poor with no therapy; radiation therapy provides a survival benefit compared to no therapy, but a suboptimal outcome compared to surgery (see "Treatment of Non-small Cell Lung Cancer Stage I and II" chapter). Guidelines for the management of NSCLC strongly advise the use of radiation therapy with or without chemotherapy in patients who choose to not undergo operative resection.[10,12,47,48] However, it should be recognized that the risks of reduced long-term survival due to suboptimal (nonoperative) treatment of early-stage lung cancer are substantial.

Risk of Perioperative Morbidity and Mortality

Morbidity and mortality rates following lung resection have decreased over time.[22] Postoperative cardiopulmonary complications that have historically been noted to be of the greatest concern after lung resection (*eg*, acute hypercapnea, mechanical ventilation lasting $>$ 48 h, arrhythmias, pneumonia, pulmonary emboli, myocardial infarction, and lobar atelectasis requiring bronchoscopy[49]) now may be more effectively managed. For instance, atrial fibrillation occurs in up to 19% of patients following lung cancer resection.[50] The risk of postoperative atrial fibrillation is greater in men $>$ 55 years of age and with a resting heart rate $>$ 72 beats/min.[51] Prophylactic use of either calcium channel blockers or β-blockers will significantly reduce the risk of atrial tachyarrhythmias after thoracic surgery.[52] Newer surgical techniques, such as the use of an intercostal muscle flap to protect the intercostal nerve[53] or video-assisted thoracoscopy,[54] may minimize the postoperative risks of reductions in lung function. However, even with modern anesthetic, surgical, and postoperative care techniques, the risk of perioperative morbidity and mortality following either lobectomy or pneumonectomy are still appreciable. The approach to estimating these risks from underlying pulmonary disease is based on a preoperative physiologic assessment (Fig 1).

Spirometry and Diffusing Capacity

The FEV_1 obtained by spirometry is the most commonly used test to assess the suitability of patients with lung cancer for surgery. Spirometry should be performed according to established methods when the patient is clinically stable and receiving

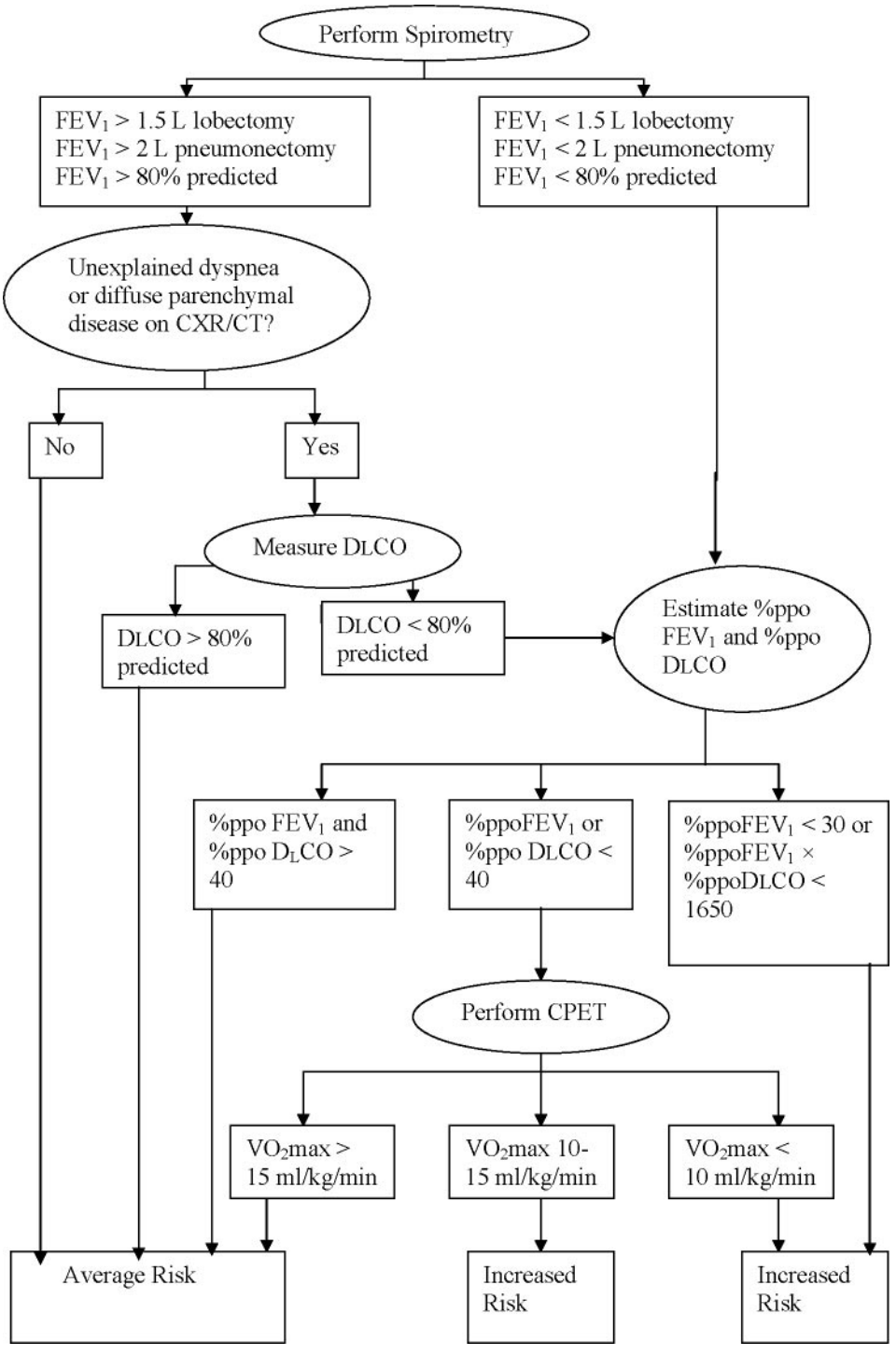

FIGURE 1. Preoperative physiologic assessment of perioperative risk. CXR = chest radiograph.

maximal bronchodilator therapy. The FEV_1 can be expressed in either absolute values or converted into percent predicted values using standard equations. Data from > 2,000 patients in three large series from the 1970s have shown that a mortality rate of < 5% can be achieved if the preoperative FEV_1 is > 1.5 L in patients before undergoing a lobectomy, and > 2 L in patients undergoing a pneumonectomy.[16] Smaller studies[55–57] also agree with these minimal thresholds. Relying on absolute values of FEV_1, though, might create bias against older patients, people of small stature, and women who might tolerate lower levels of

lung function. Although it is not possible to recalculate percent predicted values from published data on absolute values, an FEV_1 of $> 80\%$ predicted has been accepted as indicating that the patient should be considered suitable to undergo pneumonectomy without further evaluation.[58]

Interest in the diffusing capacity of the lung for carbon monoxide (DLCO) as a useful marker of operative risk was stimulated by Ferguson et al[59] who related preoperative DLCO to postresection morbidity and mortality in 237 patients. Patients were selected for surgery on the basis of clinical evaluation and spirometry, but not the DLCO, which was also measured. They found the preoperative DLCO expressed as percent predicted to have a higher correlation with postoperative deaths than the FEV_1 expressed as percent predicted, or any other factor tested. In this study, a DLCO of $< 60\%$ predicted was associated with increased mortality. Also, the risk of pulmonary complications increased twofold to threefold with a DLCO of $< 80\%$ predicted.

Spirometry and DLCO measurements should, consequently, be viewed as complementary physiologic tests. If there is evidence of diffuse parenchymal lung disease on radiographic studies or dyspnea on exertion that is thought to be out of proportion clinically to the FEV_1, DLCO should be measured using established methods. In a prospective study of 137 patients with an operable lung cancer, those with an FEV_1 of $> 80\%$ predicted, a DLCO of $> 80\%$ predicted, and no significant cardiac history were deemed to be suitable to undergo pneumonectomy and survived the operation.[58] In this study, patients with either an FEV_1 or a DLCO of $< 80\%$ predicted underwent additional physiologic testing. Further recommended physiologic tests for risk assessment aim to predict remaining lung function following the proposed curative-intent surgical resection.

Recommendations

4. In patients being considered for lung cancer resection, spirometry is recommended. If the FEV_1 is > 80% predicted or > 2 L and there is no evidence of either undue dyspnea on exertion or interstitial lung disease, the patient is suitable for resection including pneumonectomy without further physiologic evaluation. If the FEV_1 is > 1.5 L and there is no evidence of either undue dyspnea on exertion or interstitial lung disease, the patient is suitable for a lobectomy without further physiologic evaluation. Grade of recommendation, 1C

5. In patients being considered for lung cancer resection, if there is evidence of either undue dyspnea on exertion or interstitial lung disease, even though the FEV_1 might be adequate, measuring DLCO is recommended. Grade of recommendation, 1C

6. In patients being considered for lung cancer resection, if either the FEV_1 or DLCO are < 80% predicted, it is recommended that postoperative lung function be predicted through additional testing or calculation. Grade of recommendation, 1C

Predicted Postoperative Lung Function

In patients with a preoperative FEV_1 or DLCO of $< 80\%$ predicted, predicted postoperative (PPO) lung function may be calculated by estimating the amount of functioning lung tissue that would be lost with the surgical resection. The methods used for this purpose, including ventilation scans,[56,60–63] perfusion scans,[56,60–66] quantitative CT scans,[67,68] and anatomic estimation, based on counting the number of segments to be removed,[65,69] seem to provide similar quantitative estimates of PPO lung function. The radionuclide perfusion scan method is preferred to estimate the PPO FEV_1 and DLCO after pneumonectomy because the anatomic method tends to underestimate actual postoperative FEV_1 values.[70] The anatomic method is recommended to estimate lung function after a lobectomy.[1,16] However, there are potential advantages to using quantitative CT scan methods. Because this imaging procedure is routinely used for staging purposes, estimating the amount of lung tissue to be lost at surgery from these images may eliminate the need for additional testing (*eg*, perfusion scans) to predict postoperative lung function.[68,71] Quantitative CT scans may also prove to be a more sensitive indicator of diffuse parenchymal lung disease, either emphysema or interstitial lung disease, than the combination of FEV_1 and DLCO.[72] Other techniques in development, such as oxygen-enhanced MRI,[73] may prove to be especially useful in predicting postoperative lung function.

Olsen et al[74] suggested a threshold PPO FEV_1 of 0.8 L as the lower limit for allowing patients to undergo surgical resection. However, Pate and colleagues[75] found that 12 patients with a mean PPO FEV_1 of 0.7 L tolerated thoracotomy for lung cancer resection. This experience might have reflected the resection of less lung tissue than anticipated. However, it demonstrates an important objection to using an absolute value of PPO FEV_1 as a threshold for operability. Using absolute values for PPO lung function suffers from the same objection to their use with preoperative FEV_1. This approach might pre-

vent older patients, people of small stature, and women, all of whom might tolerate a lower absolute FEV_1, from undergoing a potentially curative lung cancer resection. Consequently, the percent PPO (%PPO) values for FEV_1 and DLCO are routinely used instead of absolute values for establishing risk assessment thresholds.

The %PPO FEV_1 after pneumonectomy is calculated using the perfusion method with the following formula:

$$\text{PPO } FEV_1 \text{ postpneumonectomy} = \text{preoperative } FEV_1 \times (1 - \text{fraction of total perfusion for the resected lung})$$

The preoperative FEV_1 is taken as the best measured postbronchodilator value. A quantitative radionuclide perfusion scan is performed to measure the fraction of total perfusion for the resected lung. The PPO FEV_1 can be converted into the %PPO FEV_1 using standard equations. The PPO and %PPO DLCO postpneumonectomy can be determined using the same formula. Although several studies[56,61,76] have demonstrated good correlation between the actual postoperative FEV_1 and the PPO FEV_1, the %PPO values estimated by the perfusion method may be up to 10% less than the actual measured values 3 months after the patient has undergone resection. This measurement approach, therefore, errs on the side of safety.[65,66,77]

The %PPO FEV_1 after lobectomy is calculated using the anatomic method with the following formula:

$$\text{PPO } FEV_1 \text{ postlobectomy} = \text{preoperative } FEV_1 \times (1 - y/z)$$

where the preoperative FEV_1 is taken as the best measured postbronchodilator value, y is the number of functional or unobstructed lung segments to be removed, and z is the total number of functional segments.[71] The PPO FEV_1 can be converted into %PPO FEV_1 using standard equations. The PPO and %PPO DLCO after lobectomy can be calculated using the same formula. The %PPO FEV_1 calculated after lobectomy using the anatomic method is strongly correlated with the actual postoperative FEV_1.[56,69] The anatomic method can also be applied to segmentectomies because lobectomy does not cause a significantly greater loss of function when compared to segmentectomy.[78]

Risk Related to %PPO Lung Function

The perioperative risk increases when the FEV_1 is $< 40\%$PPO.[60,65,66,79,80] Markos et al[60] and Holden et al[79] reported 50% mortality rates (3 of 6 patients and 5 of 10 patients, respectively) when the FEV_1 was $< 40\%$PPO. Wahi et al[80] found a perioperative mortality rate of 16% in patients with an FEV_1 of $< 41\%$PPO vs 3%PPO in those patients with better predicted lung function. Pierce and colleagues[65] found that 5 of 13 patients with an FEV_1 of $< 40\%$PPO died soon after undergoing the operation, and Bolliger et al[66] reported that 2 of 4 patients with similar lung function died of respiratory failure perioperatively. However, others have reported better results in very small numbers of patients with lung function this poor. Olsen et al[81] and Morice and colleagues[82] reported on two and three patients, respectively, who had a preoperative $FEV_1 < 40\%$ predicted and survived curative-intent surgery. Beccaria et al[83] described no deaths among seven patients undergoing surgery with an FEV_1 of $< 40\%$PPO, although two patients had prolonged postoperative courses. Nakahara and colleagues[84,85] found, though, an especially high postoperative mortality rate (60% [6 of 10 patients]) when the FEV_1 was $< 30\%$PPO.

Ferguson et al[59] noted that the DLCO, expressed as the %PPO, was a strong predictor of mortality. Others[60,65] have also found that perioperative risk increases substantially with a DLCO of $< 40\%$PPO. Pierce et al[65] suggested that a product of %PPO FEV_1 and %PPO DLCO of $< 1{,}650\%$PPO might serve as a more discriminating threshold for perioperative risk assessment. Others[86] have made a similar observation.

Although an FEV_1 or DLCO of $< 40\%$PPO indicates an increased risk for perioperative complications, including death, from curative-intent surgery, these patients can successfully undergo lung cancer resection. Ribas et al[86] described a selected group of 65 patients who met these physiologic criteria but still underwent curative-intent lobectomy/wedge resection (n = 44) or pneumonectomy (n = 21). There were only four postoperative deaths (mortality rate, 6.2%) and cardiopulmonary complications in 31 patients (47.7%). Others have also reported[87,88] successful surgical resections of lung cancers in patients with severely reduced FEV_1 and/or DLCO values. Although these studies indicate that lung cancer resection can be performed with an acceptable perioperative risk even in patients with poor lung function reserve, it is prudent to more thoroughly evaluate these patients prior to pulmonary resection.

RECOMMENDATIONS

7. In patients with lung cancer who are being considered for surgery, either an FEV_1 of $< 40\%$PPO or a DLCO of $< 40\%$PPO indicates

an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients undergo exercise testing preoperatively. Grade of recommendation, 1C

8. In patients with lung cancer being considered for surgery, either a product of %PPO FEV_1 and %PPO DLCO of < 1,650%PPO or an FEV_1 of < 30%PPO indicates an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients should be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

Cardiopulmonary Exercise Testing

Formal cardiopulmonary exercise testing (CPET) is a sophisticated physiologic testing technique, which includes recording the exercise ECG, the heart rate response to exercise, minute ventilation, and oxygen uptake per minute. Maximal oxygen consumption ($\dot{V}O_2$max) is measured from this type of exercise test. Previous guidelines[1,16] have recommended the use of CPET as the next step in the preoperative risk assessment process in those patients with either FEV_1 or DLCO below 40%PPO.

The risk for perioperative complications has generally, but not always,[86] been reported to be higher in patients with a lower measured $\dot{V}O_2$max. The risk for postoperative mortality can generally be stratified by $\dot{V}O_2$max. Patients with a preoperative $\dot{V}O_2$max of 15 to 20 mL/kg/min can undergo curative-intent lung cancer surgery with an acceptably low mortality rate.[39,49,82,89–92] In several case series,[60,79,81,89] patients with a $\dot{V}O_2$max of < 10 mL/kg/min had a very high risk for postoperative death (Table 2). Bechard and Wetstein[89] reported that 2 of 7 patients with a $\dot{V}O_2$max of < 10 mL/kg/min died in the postoperative period, Olsen et al[81] described deaths in 3 of 11 patients, and Holden and colleagues[79] noted deaths in 2 of 4 patients; however, in another small series[60] there were no deaths among the 5 patients with this very low $\dot{V}O_2$max. A $\dot{V}O_2$max of 10 to 15 mL/kg/min indicates an increased risk of perioperative death[39,60,81,89,90,92–94] (Table 2).

In patients with borderline lung function, $\dot{V}O_2$max may be helpful in further evaluating the risk for perioperative complications. Morice et al[82] reported that eight patients with an FEV_1 of < 33%PPO and a $\dot{V}O_2$max of > 15 mL/kg/min underwent lobectomy with no fatal complications. In patients with both an FEV_1 and a DLCO of < 40%PPO, a $\dot{V}O_2$max of < 15 mL/kg/min indicates a very high surgical risk.[90]

Table 2—*Preoperative Exercise Testing for $\dot{V}O_2$max and Perioperative Mortality*

Study	Deaths/Total (%)
$\dot{V}O_2$max 10–15 mL/kg/min	
Smith et al[93]	1/6 (33)
Bechard and Wetstein[89]	0/15 (0)
Olsen et al[81]	1/14 (7.1)
Walsh et al[39]	1/5 (20)
Bolliger et al[90]	2/17 (11.7)
Markos et al[60]	1/11 (9.1)
Wang et al[94]	0/12 (0)
Win et al[92]	2/16 (12.5)
Total	8/96 (8.3)
$\dot{V}O_2$max < 10 mL/kg/min	
Bechard and Wetstein[89]	2/7 (29)
Olsen et al[81]	3/11 (27)
Holden et al[79]	2/4 (50)
Markos et al[60]	0/5 (0)
Total	7/27 (26)

Pulmonary Artery Pressures and Diffusing Capacity

Measurements of pulmonary arterial pressure during exercise have not proven to be helpful in predicting the patients in whom perioperative complications will develop.[81,86,95] Measuring the DLCO during exercise might be a better predictor of perioperative risk than $\dot{V}O_2$max, but is a technically demanding technique and not readily available.[96]

Stair Climbing and Walking Tests

If CPET were unavailable, then another type of exercise test should be considered. Stair climbing has historically been used as a surrogate CPET. If a patient were able to climb three flights of stairs, they were considered to be a suitable candidate for lobectomy. Pneumonectomy candidates were expected to be able to climb five flights of stairs. This approach was found to correlate with lung function; climbing three flights indicates an FEV_1 of > 1.7 L and climbing five flights of stairs indicates an FEV_1 of > 2 L.[97] Several groups have shown that the ability to climb > 12 to 14 m of stairs, which is approximately three flights of stairs, effectively identifies patients who are at low risk for postoperative complications following usually lobectomy, even though these patients might have had an FEV_1 or DLCO of < 40%PPO.[98,99] However, there are limitations to the usefulness of stair climbing. It has not been performed in a standardized manner. The duration of stair climbing, the speed of ascent, the

number of steps per flight, the height of each step, and the criteria for stopping the test have varied from study to study. Patients with, for example, comorbid conditions, such as musculoskeletal disease, neurologic abnormalities, and peripheral vascular insufficiency may be unable to perform the test. In general terms, though, patients who can climb five flights of stairs will have a $\dot{V}O_2$max of $>$ 20 mL/kg/min, and patients who cannot climb one flight of stairs will have a $\dot{V}O_2$max of $<$ 10 mL/kg/min.[100] Brunelli and colleagues[101,102] have found that patients who are unable to perform stair climbing because of comorbid conditions were at an increased risk for perioperative death after lung cancer resection.

Other surrogate tests for CPET are the shuttle walk and the 6-min walk test, but the data on the value of these tests in predicting $\dot{V}O_2$max are limited.[103] The shuttle walk requires that patients walk back and forth between two markers set 10 m apart. The walking speed is paced by an audio signal, and the walking speed is increased each minute in a graded fashion. The end of the test occurs when the patient is too breathless to maintain the required speed. In one study,[104] an inability to complete 25 shuttles on two occasions suggested a $\dot{V}O_2$max of $<$ 10 mL/kg/min. For the 6-min walk test, patients are instructed to walk as far as possible in the time allotted. Rest during the test is permissible. Interpretation of the distance walked in 6 min is currently not well standardized.[105]

Desaturation

The shuttle walk and 6-min walk tests may be more effective in identifying patients who desaturate during exercise than is the CPET.[106] The value of this observation, though, is unclear. Greater than 4% desaturation during exercise had been reported[16,60,65,107] to indicate an increased risk for perioperative complications. However, a study[108] from the United Kingdom has reported similar perioperative complication rates for patients who desaturated $>$ 4% during a shuttle walk and those who did not.

Composite Scores

Investigators have proposed using composite scores to predict perioperative complications. Epstein et al[109] developed the multifactorial cardiopulmonary risk index, an empirically derived score based on points awarded for cardiac and pulmonary risk. There was a strong association between this score and postoperative complications in a group of 42 patients. Birim et al[110] found that patients with more comorbid conditions, identified by the Charlson comorbidity index, were also more likely to have major complications following lung cancer resection. Melendez and Barrera[111] used regression analysis to develop the predictive respiratory complication quotient, which is based on %PPO FEV_1, %PPO DLCO, and oxygenation. This score also was effective in identifying patients who are at increased risk for perioperative complications. Brunelli et al[112] adapted the physiologic and operative severity score for the enumeration of mortality and morbidity, a score originally used for general surgery issues, to evaluation of post-lung resection problems. They suggested that this score might be a useful method for comparing the complication rates among different institutions. More recently, Ferguson and Durkin[113] developed a simple score based on the FEV_1, DLCO and age of the patient which seems to compare favorably with other scoring systems[109,112] and is easy to administer. Future work is needed to determine whether these scores might replace the current recommended approach based on exercise testing.

RECOMMENDATIONS

9. In patients with lung cancer who are being considered for surgery, a $\dot{V}O_2$max of < 10 mL/kg/min indicates an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. These patients should be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

10. Patients with lung cancer who are being considered for surgery who have a $\dot{V}O_2$max of < 15 mL/kg/min and both an FEV_1 and a DLCO of < 40%PPO are at increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

11. Patients with lung cancer who are being considered for surgery and walk < 25 shuttles on two shuttle walks or less than one flight of stairs are at increased risk for perioperative death and cardiopulmonary complications with standard lung resection. These patients should be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

Arterial Blood Gas Tensions

Historically, hypercapnea ($PaCO_2$, $>$ 45 mm Hg) has been quoted as an exclusion criterion for lung

resection.[16,114,115] This recommendation was made on the basis of the association of hypercapnea with poor ventilatory function.[116] The few studies that have addressed this issue, however, have suggest that preoperative hypercapnea is not an independent risk factor for increased perioperative complications. Stein et al[117] showed that hypercapnea was associated with serious postoperative respiratory difficulties in five patients, but there were no deaths. Morice et al[82] reported on three patients with preoperative hypercapnea who survived curative-intent lung cancer surgery. In two series[118,119] of lung cancer patients undergoing surgery, perioperative complications were not higher in patients with preoperative hypercapnea. Preoperative hypoxemia, defined as an arterial oxygen saturation (Sa_{O_2}) of $< 90\%$, has been associated with an increased risk of postoperative complications.[106]

Recommendations

12. In patients with lung cancer who are being considered for surgery, a Pa_{CO_2} of > 45 mm Hg is not an independent risk factor for increased perioperative complications. However, it is recommended that these patients undergo further physiologic testing. Grade of recommendation, 1C

13. In patients with lung cancer who are being considered for surgery, an Sa_{O_2} of < 90% indicates an increased risk for perioperative complications with standard lung resection. It is recommended that these patients undergo further physiologic testing. Grade of recommendation, 1C

Risk of Long-term Pulmonary Disability

Following lung resection, lung function should be expected to decrease. Serial studies have shown that FEV_1 decreases within the first several months following lung cancer resection, but tends to recover to a small extent by 6 months after surgery.[77,120,121] Although the preoperative physiologic evaluation is usually fairly accurate in predicting the PPO FEV_1, some investigators[118,122] have found that the PPO FEV_1 will actually underestimate the eventual postoperative FEV_1. Exercise capacity will also decrease following lung resection. Nezu et al[120] found that, similar to the observations with postoperative changes in FEV_1, the effects on $\dot{V}O_2$max were most evident at 3 months and improved somewhat by 6 months after surgery. Decreases of up to 13% in $\dot{V}O_2$max and work capacity have been described following a lobectomy, and between 20% and 28% after a pneumonectomy.[77,120,123] Surprisingly, the most common limiting symptom in postoperative exercise studies[77,120,123] has been leg discomfort, rather than dyspnea. Bolliger et al[77] found that exercise was limited by leg muscle fatigue in 53% of patients preoperatively. This was not altered after lobectomy, but there was a switch to dyspnea as the limiting factor after pneumonectomy (3 months after resection, 61% of patients; 6 months after resection, 50% of patients).

Early investigators in this field suggested that a postoperative FEV_1 of < 0.8 L would result in an unacceptable incidence of hypercapnea and pulmonary disability.[74] Unfortunately, there are few data available describing changes in quality of life following curative-intent lung resection. A cross-sectional survey[124] examined respiratory symptoms and quality of life in 142 long-term survivors of NSCLC. Most of these patients (74%) had undergone a lobectomy, with 12% having had a pneumonectomy and 11% a wedge resection. The most commonly reported postoperative respiratory symptom was dyspnea, but cough and wheeze were also frequently described. The majority of these patients (63%) described dyspnea when they hurried, 32% had to stop to catch their breath when walking, and 11% were so breathless that they could not leave their house. Dyspnea occurred significantly more often in patients with restrictive and/or obstructive ventilatory abnormalities, but the use of bronchodilators to control dyspnea was not well described. Dyspnea had a significant impact on multiple dimensions of quality of life, such as physical functioning, physical role limits, and social functioning. The findings in this study point out the need for more information on the interplay between changes in lung function (including both FEV_1 and D_{LCO}) and respiratory symptoms, and quality of life following curative-intent surgical resection.

Methods To Reduce Perioperative Risks and Long-term Pulmonary Disability

Lung Volume Reduction Surgery

Lung volume reduction surgery (LVRS) for patients with severe emphysema has been shown in a large prospective, randomized, controlled trial[125] to provide a survival advantage in selected patients with predominantly upper lobe emphysema and low exercise capacity. Patients with an FEV_1 of $< 20\%$ predicted and either homogeneous emphysema or a D_{LCO} of $< 20\%$ predicted do poorly with LVRS.[126] Anecdotal experience has shown that the lung resected during LVRS occasionally contained unsus-

pected lung cancers.[127,128] Multiple case series[129–139] have suggested that patients with extremely poor lung function can tolerate combined LVRS and resection of the lung cancer with an acceptable mortality rate and surprisingly good postoperative outcomes.

McKenna et al[129] reported 11 cases of lung cancer (3%) in their group of 325 patients who were referred for LVRS. These 11 patients had an average preoperative FEV_1 of 0.65 L (FEV_1 range, 12 to 29% predicted). None of these patients would have been acceptable candidates to undergo lung cancer resection based on the traditional criteria, but all underwent combined LVRS and resection of stage I lung cancers by either lobectomy or wedge resection. There were no deaths or major complications; lung function and exercise capability were improved postoperatively. Pompeo et al[137] described the outcomes of 16 patients who had undergone both LVRS and curative-intent surgical resection of NSCLC. Postoperatively there were significant improvements in FEV_1 and quality of life. Encouraging long-term survival results were also noted.

Although indications for combined LVRS and lung cancer resection are still evolving, the most promising candidates would be patients who have a cancer in the upper lobe that is also affected by emphysema and who have a DLCO and FEV_1 of $> 20\%$ predicted. However, Mentzer and Swanson[140] have suggested a more aggressive approach. They consider LVRS for patients with severe dyspnea, hypoxia and hypercapnea, and poor lung function (including patients with an FEV_1 of $< 20\%$ predicted), provided there was heterogeneous emphysema and some potential for the recruitment of relatively preserved lung tissue.

Smoking Cessation

A retrospective analysis[141] of 300 patients undergoing lung cancer surgical resection found that postoperative pulmonary complication rates for patients who had quit smoking > 2 months prior to undergoing the operation were similar to those who had quit within 2 months of the surgery (19% vs 23%, respectively; $p > 0.05$). Another retrospective study[142] of 288 consecutive patients undergoing pulmonary surgery suggested that smoking abstinence of at least 4 weeks may be associated with reduced perioperative respiratory complications. Prospective, controlled trials are needed to more clearly define the effect that smoking cessation preoperatively might have on reducing perioperative problems. However, smoking cessation should be strongly encouraged at the time of diagnosis of lung cancer because it might reduce the development of metachronous tumors (see the chapter on "Follow-up and Surveillance").

Pulmonary Rehabilitation

As yet, there are no robust data to recommend the routine use of preoperative pulmonary rehabilitation for patients with lung cancer. However, there is some information suggesting that pulmonary rehabilitation might be helpful in preparing patients for LVRS.[143] In the National Emphysema Treatment Trial,[143] all patients underwent pulmonary rehabilitation prior to randomization to either receive medical treatment or undergo LVRS. Pulmonary rehabilitation provided important benefits in dyspnea, quality of life, and exercise ability. Although there was no comparison group for the pulmonary rehabilitation portion of the study, overall, rehabilitation was thought to play an important role in preparing patients for LVRS. The effects of pulmonary rehabilitation should be evaluated in future studies of patients being prepared for both lung cancer resection and LVRS.

Recommendations

14. In patients with very poor lung function and a lung cancer in an area of upper lobe emphysema, it is recommended that combined LVRS and lung cancer resection be considered if both the FEV_1 and the DLCO are $> 20\%$ predicted. Grade of recommendation, 1C

15. It is recommended that all patients with lung cancer be counseled regarding smoking cessation. Grade of recommendation, 1C

Summary

Patients with lung cancer often have concomitant diffuse parenchymal and/or obstructive airway disease and atherosclerotic cardiovascular disease as a consequence of their smoking habit. These diseases may place these patients at increased risk for perioperative complications, including death, and long-term pulmonary disability after lung cancer resection. A careful preoperative physiologic assessment will be useful to identify those patients who are at increased risk with standard lung cancer resection and to enable an informed decision by the patient about the appropriate therapeutic approach to treating their lung cancer. This preoperative risk assessment must be placed in the context that surgery for early-stage lung cancer is the most effective currently available treatment for this disease.

Summary of Recommendations

1. It is recommended that patients with lung cancer be assessed for curative surgical resection by a multidisciplinary team, which includes a thoracic surgeon specializing in lung cancer, a medical oncologist, a radiation oncologist, and a pulmonologist. Grade of recommendation, 1C

2. It is recommended that patients with lung cancer not be denied lung resection surgery on the grounds of age alone. Grade of recommendation, 1B

3. It is recommended that patients with lung cancer who are being evaluated for surgery and have major factors for increased perioperative cardiovascular risk have a preoperative cardiologic evaluation. Grade of recommendation, 1C

4. In patients being considered for lung cancer resection, spirometry is recommended. If the FEV_1 is > 80% predicted or > 2 L and there is no evidence of either undue dyspnea on exertion or interstitial lung disease, the patient is suitable for resection including pneumonectomy without a further physiologic evaluation. If the FEV_1 is > 1.5 L and there is no evidence of either undue dyspnea on exertion or interstitial lung disease, the patient is suitable for a lobectomy without further physiologic evaluation. Grade of recommendation, 1C

5. In patients being considered for lung cancer resection, if there is evidence of either undue dyspnea on exertion or interstitial lung disease, even though the FEV_1 might be adequate, measuring Dlco is recommended. Grade of recommendation, 1C

6. In patients being considered for lung cancer resection, if either the FEV_1 or Dlco are < 80% predicted, it is recommended that postoperative lung function be predicted through additional testing. Grade of recommendation, 1C

7. In patients with lung cancer who are being considered for surgery, either an FEV_1 of < 40%PPO or a Dlco of < 40%PPO indicates an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients undergo exercise testing preoperatively. Grade of recommendation, 1C

8. In patients with lung cancer who are being considered for surgery, either a product of %PPO FEV_1 and %PPO Dlco of < 1,650%PPO or an FEV_1 of < 30%PPO indicates an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients should be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

9. In patients with lung cancer being considered for surgery, a $\dot{V}o_2max$ of < 10 mL/kg/min indicates an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. These patients should be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

10. Patients with lung cancer being considered for surgery who have a $\dot{V}o_2max$ of < 15 mL/kg/min and both an FEV_1 and a Dlco of < 40%PPO are at an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

11. Patients with lung cancer being considered for surgery who walk < 25 shuttles on two shuttle walks or less than one flight of stairs are at increased risk for perioperative death and cardiopulmonary complications with standard lung resection. Thesepatients should be counseled aboutnonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

12. In patients with lung cancer who are being considered for surgery, a $Paco_2$ of > 45 mm Hg is not an independent risk factor for increased perioperative complications. However, it is recommended that these patients undergo further physiologic testing. Grade of recommendation, 1C

13. In patients with lung cancer who are being considered for surgery, an Sao_2 of < 90% indicates an increased risk for perioperative complications with standard lung resection. It is recommended that these patients undergo further physiologic testing. Grade of recommendation, 1C

14. In patients with very poor lung function and a lung cancer in an area of upper lobe emphysema, it is recommended that combined LVRS and lung cancer resection be considered if both the FEV_1 and the DLCO are > 20% predicted. Grade of recommendation, 1C

15. It is recommended that all patients with lung cancer be counseled regarding smoking cessation. Grade of recommendation, 1C

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Noninvasive Staging of Non-small Cell Lung Cancer*

ACCP Evidenced-Based Clinical Practice Guidelines (2nd Edition)

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Background: **Correctly staging lung cancer is important because the treatment options and the prognosis differ significantly by stage. Several noninvasive imaging studies including chest CT scanning and positron emission tomography (PET) scanning are available. Understanding the test characteristics of these noninvasive staging studies is critical to decision making.**

Methods: **Test characteristics for the noninvasive staging studies were updated from the first iteration of the lung cancer guidelines using systematic searches of the MEDLINE, HealthStar, and Cochrane Library databases up to May 2006, including selected metaanalyses, practice guidelines, and reviews. Study designs and results are summarized in evidence tables.**

Results: **The pooled sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis were 51% (95% confidence interval [CI], 47 to 54%) and 85% (95% CI, 84 to 88%), respectively, confirming that CT scanning has limited ability either to rule in or exclude mediastinal metastasis. For PET scanning, the pooled estimates of sensitivity and specificity for identifying mediastinal metastasis were 74% (95% CI, 69 to 79%) and 85% (95% CI, 82 to 88%), respectively. These findings demonstrate that PET scanning is more accurate than CT scanning. If the clinical evaluation in search of metastatic disease is negative, the likelihood of finding metastasis is low.**

Conclusions: **CT scanning of the chest is useful in providing anatomic detail, but the accuracy of chest CT scanning in differentiating benign from malignant lymph nodes in the mediastinum is poor. PET scanning has much better sensitivity and specificity than chest CT scanning for staging lung cancer in the mediastinum, and distant metastatic disease can be detected by PET scanning. With either test, abnormal findings must be confirmed by tissue biopsy to ensure accurate staging.** ***(CHEST 2007; 132:178S–201S)***

Key words: CT scan; lung cancer; mediastinum; metastases; noninvasive; positron emission tomography; staging

Abbreviations: CI = confidence interval; FDG = fluoro-2-deoxy-D-glucose; NPV = negative predictive value; NSCLC = non-small cell lung cancer; PET = positron emission tomography; PPV = positive predictive value; ROC = receiver operating characteristic; SCLC = small cell lung cancer

After a tissue diagnosis of lung cancer has been established or in patients in whom the clinical suspicion is high and surgery is the recommended next step, consideration must turn toward the determination of the extent of disease, or stage, because this will impact directly on management and prognosis. The most significant dividing line is between those patients who are candidates for surgical resection and those who are inoperable but will benefit from chemotherapy, radiation therapy, or both. Staging with regard to a patient's potential for surgical resection is most applicable to non-small cell lung cancer (NSCLC); whereas, for small cell lung cancer (SCLC) a more simplified staging classification of limited and extensive disease is employed. Except in rare cases of

surgically operable limited stage small cell cancer, the implication of staging on the management of SCLC is between chemotherapy and radiation for limited disease vs chemotherapy alone for extensive disease.[1]

The basis for staging NSCLC is the TNM system[2,3] (see Table 1 for TNM descriptors and Figure 1 for stage grouping). From a practical standpoint, the involvement of disease in the mediastinum, reflected in the N designator in the system, most often determines appropriateness for surgical resection.

Patients with sage IA, IB, IIA, and IIB disease can benefit from surgical resection. Patients with stage IIIA, IIIB, and IV disease almost never meet the criteria for surgery. The current role of chemotherapy followed by surgery for selected patients with stage IIIA disease remains controversial.

Staging can be used to predict survival and to guide the patient toward the most appropriate treatment regimen or clinical trial. Even with clinical stage I, surgically resectable, potentially curable disease, the 5-year survival rate after surgery is only 50%. Approximately 60% of cancer recurrences are presumably from extrathoracic micrometastatic involvement at presentation, which is not currently detectable with existing diagnostic modalities. Patients with clinical stage II disease (T1N1M0 or T2N1M0) have a 5-year survival rate after surgery of 30%. At clinical stage IIIA, the 5-year survival rate is 17%, and at stage IIIB it is only 5%.[3] These patients are generally treated with combined chemotherapy and radiotherapy. The 5-year survival rate for patients with stage IV disease is virtually nil, and this disease is treated either with chemotherapy and supportive care or with supportive care alone. Thus, one can see that it is critical to stage patients accurately as the treatment modalities and subsequent patient outcomes vary widely based on stage designation.

For this edition of the lung cancer guidelines, investigators from the Duke University Evidence-Based Practice Center and the authors of this guideline updated a systematic review of the diagnostic accuracy of noninvasive tests for staging in patients

Table 1—*TNM Descriptors*

Tumors	Description
Primary tumor (T)	
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor < 3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)
T2	Tumor with any of the following features of size or extent: > 3 cm in greatest dimension; involves main bronchus; > 2 cm distal to the carina; invades the visceral pleura; and is associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3	Tumor of any size that directly invades any of the following chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium, or tumor in the main bronchus < 2 cm distal to the carina but without involvement of the carina or associated atelectasis or obstructive pneumonitis of the entire lung
T4	Tumor of any size that invades any of the following: mediastinum; heart; great vessels; trachea; esophagus; vertebral body; and carina or tumor with a malignant pleural or pericardial effusion or with satellite tumor nodule(s) within the primary tumor lobe of the lung
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes involved by direct extension of the primary tumor
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis to contralateral mediastinal, contralateral, hilar ipsilateral or contralateral scalene or supraclavicular lymph node(s)
Distant metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

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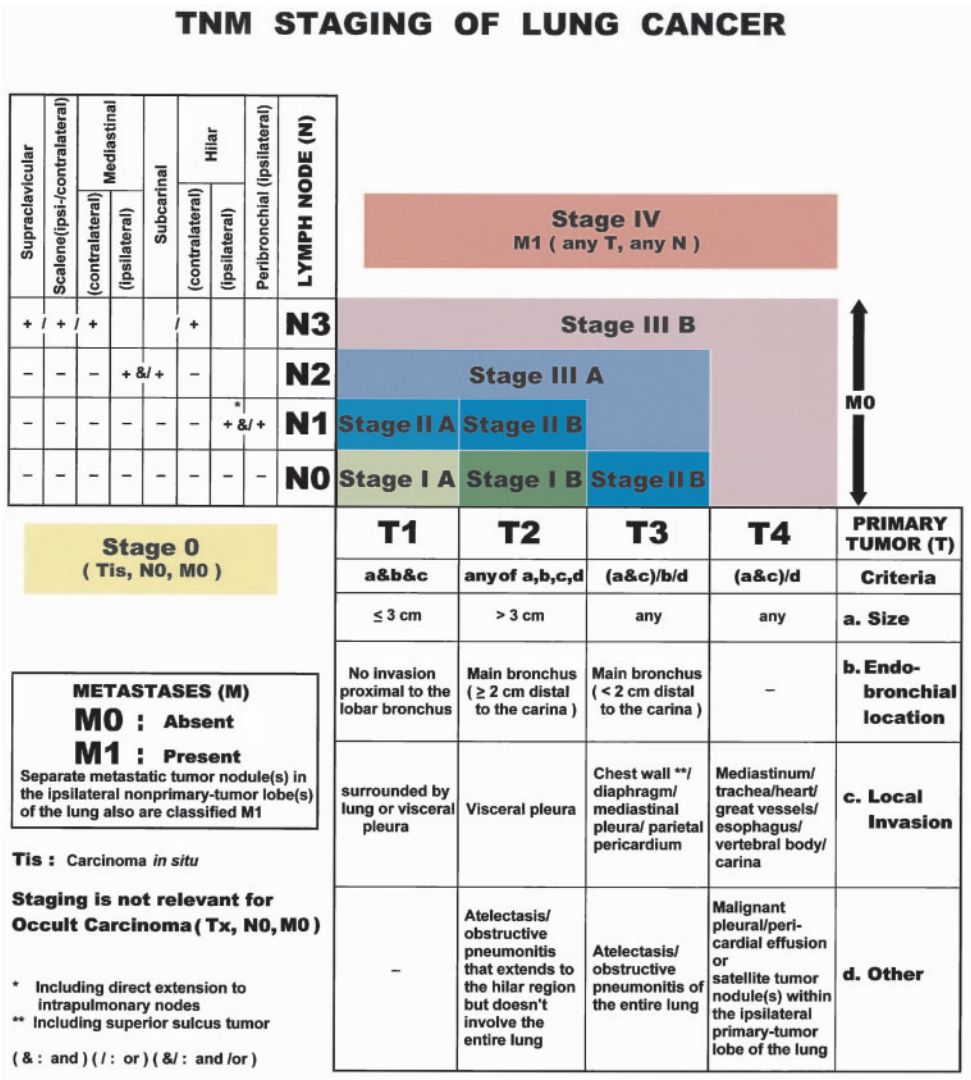

FIGURE 1. TNM staging of lung cancer.

with NSCLC. The methods and results of the initial review have been published previously and a more complete description of the methodology can be found there.[4] Briefly, the search strategy used computerized searches of the MEDLINE bibliographic database (January 1991 to May 2006), HealthStar, and the Cochrane Library. In addition, we searched the reference lists of included studies, selected textbooks, practice guidelines, systematic reviews, and metaanalyses in order to ensure that all relevant studies were identified. Only articles that had been published in English were considered.

SELECTION CRITERIA

Titles and abstracts, and the full text of all articles passing the title-and-abstract screen were evaluated independently by at least two of the authors for inclusion or exclusion based on the following five criteria: (1) publication in a peer-reviewed journal; (2) study size of 20 patients (except for studies involving CT scan evaluation of the mediastinum, for which 50 patients were required); (3) patient group not included in a subsequent update of the study; (4) histologic or cytologic confirmation of mediastinal nodes or extrathoracic sites in addition to the primary tumor; and (5) availability of the raw data needed to calculate independently the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of CT scanning, positron emission (PET) scanning, MRI, or endoscopic ultrasonography, or the raw data needed to calculate the NPV of the clinical evaluation.[4]

Grading Recommendations

Recommendations were developed by the writing committee, graded by a standardized method (see the "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), and reviewed by all members of the lung cancer panel prior to approval by the Thoracic Oncology Network, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.

Noninvasive Staging of the Mediastinum

Staging is a critical part of the evaluation of every patient with lung cancer. Defining malignant involvement of the mediastinal lymph nodes is particularly important, as the status of these nodes will in many cases determine whether there is surgically resectable disease. the clinical staging of lung cancer is usually directed by noninvasive imaging modalities. On the basis of such tests, clinicians will determine the likelihood of the presence or absence of tumor involvement in regional lymph nodes.

In general, patients with lung cancer can be separated into four groups with respect to intrathoracic radiographic characteristics (including both the primary tumor and the mediastinum), as shown in Figure 2. Distinguishing these groups is particularly useful in defining the need for and selection of invasive staging tests. The first group (radiographic group A) involves patients with mediastinal infiltration that encircles the vessels and airways, so that discrete lymph nodes can no longer be discerned or measured. In these situations, the presence of mediastinal involvement (stage III disease) is generally accepted based on imaging studies alone, and the major issue is to obtain tissue by whatever approach is easiest in order to distinguish between SCLC and NSCLC. The second group (radiographic group B) involves patients with mediastinal node enlargement in whom the size of discrete nodes can be measured. In these patients, mediastinal nodal involvement is suspected but must be confirmed. The last two groups involve patients with normal mediastinal nodes. In radiographic group C, the presence of a central tumor or suspected N1 disease makes the chance of N2,3 nodal involvement relatively high (20 to 25%) despite normal-sized nodes, and further confirmation is needed.[5–8] In the final group (*ie*, those patients with a peripheral clinical stage I tumor), the chance of mediastinal involvement is quite low, and generally further confirmation of this is not needed (radiographic group D).[6–8]

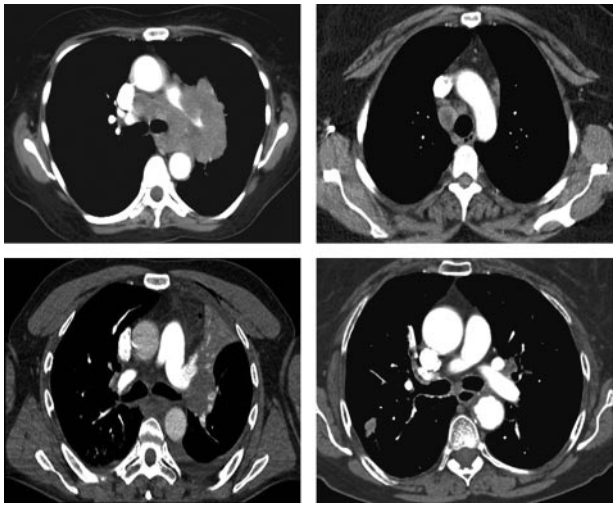

Figure 2. *Top left*: mediastinal infiltration by tumor. *Top right*: enlarged discrete N2,3 nodes. *Bottom left*: a central tumor or a tumor with enlarged N1 nodes, but a normal mediastinum. *Bottom right*: a peripheral small tumor (seen in lower left corner of image) with normal-sized lymph nodes.

A widely accepted definition of normal-sized mediastinal lymph nodes is a short-axis diameter of ≤ 1 cm on a transverse CT scan image. The term *discrete nodal enlargement* implies that discrete nodes are seen on the CT scan and are defined well enough to be able to measure their size (and are > 1 cm in size). Mediastinal infiltration is present when there is abnormal tissue in the mediastinum that does not have the appearance and shape of distinct lymph nodes, but instead has an irregular, amorphous shape. In this case, it is difficult to distinguish discrete nodes and impossible to come up with a measurement of the size of nodes. This occurs when multiple nodes are matted together to the point where the boundary between them is obscured, and can be assumed to involve extensive extranodal spread of the tumor. It may progress to the point where mediastinal vessels and other structures are partially or completely encircled. Finally, the distinction between a central tumor vs a peripheral tumor has also not been codified, but most authors consider any tumor in the outer two thirds of the hemithorax to be peripheral. Assessing the radiographic characteristics of the mediastinum will generally require that the clinician look at the images. This is because there is no standard format for how radiographic findings are reported (*eg*, the term *lymphadenopathy* is often used when there is a suspected malignancy, even though the mediastinal nodes are well below 1 cm in size).

The four radiographic groups are defined by anatomic characteristics seen on a CT scan (*ie*, size, location, and extent), and not by metabolic characteristics (*ie*, by PET scan) for many reasons. First, a CT scan is relatively inexpensive and essentially is

always performed as a preliminary step in order to define the nature of a pulmonary abnormality and to arrive at a clinical diagnosis of suspected lung cancer. Second, the information gained from the clinical history, physical examination, and chest CT can define whether other tests such as a PET scan are indicated. Finally, the technical considerations and performance characteristics of invasive staging procedures are likely to be driven primarily by anatomic characteristics rather than by metabolic ones. In other words, the location and size of a lymph node are important in determining how feasible and reliable an invasive test is, and these issues are unaffected by whether the node in question is metabolically active on PET scanning or not. Further discussion of the best approach to confirming a diagnosis of mediastinal tumor involvement by tissue acquisition can be found in chapter 13 of this supplement on invasive staging.

Chest Radiograph

The majority of lung cancers are initially detected on a plain chest radiograph. In some situations, the plain radiograph may be sufficient to detect spread of the tumor to the mediastinum. For example, the presence of bulky lymphadenopathy in the superior or contralateral mediastinal areas may be considered adequate evidence of metastatic disease, precluding a further imaging evaluation of the chest. This may be particularly true if the patient is too ill or is unwilling to undergo treatment of any kind. However, it is recommended that tissue confirmation be obtained if possible by the least invasive method available. It is widely accepted that the chest radiograph is in general an insensitive measure of mediastinal lymph node involvement with lung cancer; thus, further noninvasive and/or invasive assessment is usually necessary.

CT Scan of the Chest

CT scanning of the chest is the most widely available and commonly used noninvasive modality for evaluation of the mediastinum in lung cancer. The vast majority of reports evaluating accuracy of CT scanning for mediastinal lymph node staging have employed the administration of IV contrast material. IV contrast is not absolutely necessary in performing chest CT scanning for this indication, but may be useful in helping to distinguish vascular structures from lymph nodes as well as in delineating mediastinal invasion by centrally located tumors. A CT scan of the chest should be performed in all cases of lung cancer unless the patient is so debilitated that no treatment is planned or they are unwilling to undergo further evaluation.

Various CT scan criteria have been used to define the malignant involvement of mediastinal lymph nodes. Notwithstanding the radiographic descriptions of mediastinal nodal involvement, the most widely used criterion is a short-axis lymph node diameter of $\geq$ 1 cm on a transverse CT scan. However, numerous other criteria have also been used including the following: (1) a long-axis diameter of $\geq$ 1 cm; (2) a short-axis diameter of $\geq$ 1.5 cm; (3) a short-axis diameter $\geq$ 1 cm plus evidence of central necrosis or disruption of the capsule; and (4) a short-axis diameter of $\geq$ 2 cm regardless of nodal morphology. The reported sensitivity and specificity for identifying malignant involvement will vary depending on which criteria are used in the assessment of individual nodal stations.[9,10] The majority of studies evaluating CT scan accuracy have used a short-axis diameter of $\geq$ 1 cm as the threshold for abnormal nodes. In doing so, a conscious effort has been made to strike an appropriate balance between sensitivity and specificity in an understandable effort to minimize the number of false-positive evaluations without producing an unacceptable number of false-negative evaluations.

For the purposes of these guidelines, investigators from the Duke University Evidence-based Practice Center and the authors of this section of the supplement conducted a systematic review of the medical literature relating to the accuracy of CT scanning for noninvasive staging of the mediastinum in patients with lung cancer.[4] Thirty-five studies published from 1991 through June 2006 evaluating the performance characteristics of CT scanning for this purpose were identified based on their fulfillment of the following criteria: (1) publication in a peer-reviewed journal; (2) a study size of $>$ 50 patients; (3) patient group not included in a subsequent update of the study; (4) histologic or cytologic confirmation of mediastinal nodes or extrathoracic site as well as the primary tumor; and (5) availability of the raw data needed to calculate independently sensitivity, specificity, PPV, and NPV. These 43 studies[6,11–44,52,87,121,122,178–181] are outlined in Table 2. The combined studies yielded 5,111 evaluable patients.[6,11–44,52,87,121,122,178–181] The median prevalence of mediastinal metastasis was 28% (range, 18 to 56%). Almost all studies specified that CT scanning was performed following the administration of IV contrast material and that a positive test result was defined as the presence of one or more lymph nodes that measured $>$ 1 cm on the short-axis diameter. Individual study estimates of sensitivity and specificity are shown in Figure 3, which also displays the summary receiver operator characteristic (ROC) curve for mediastinal staging

Table 2—*Accuracy of CT Scanning for Staging the Mediastinum in Lung Cancer Patients**

Study/Year	Patients, No.	CT Scan Technique	Sensitivity	Specificity	PPV	NPV	Prevalence
Analysis by nodal station							
Gupta et al[52]/2000	54	Contrast	0.68	0.31	0.31	0.68	0.32
Berlangieri et al[178]/1999	50	Contrast	0.65	0.9	0.41	0.96	0.1
Graeber et al[121]/1999	96	Contrast	0.63	0.6	0.51	0.71	0.4
Gupta et al[122]/1999	103	Contrast	0.64	0.61	0.52	0.72	0.4
Kernstine et al[87]/1999	64	Contrast	0.65	0.79	0.37	0.92	0.16
Vansteenkiste et al[24]/1998	68	Contrast	0.96	0.45	0.96	0.47	0.93
Vansteenkiste et al[25]/1998	56	Contrast	0.95	0.64	0.95	0.63	0.88
Kobayashi and Kitamura[179]/1995	76	Contrast	0.76	0.76	0.78		
Primack et al[18]/1994	159	Contrast	0.58	0.86	0.71	0.77	0.38
Seely et al[180]/1993	104	Contrast	0.48	0.94	0.4	0.96	0.07
Izbicki et al[181]/1992	108	Contrast	0.24	0.93	0.44	0.84	0.18
Summary	938		0.86	0.79	0.82	0.84	0.52
Analysis by patient							
Takamochi et al[12]/2005	71	Contrast	0.20	0.89	0.33	0.81	0.21
Pozo-Rodriguez et al[6]/2005	132	Contrast	0.86	0.67	0.49	0.93	0.27
Nomori et al[11]/2004	80	NR	0.5	0.95	0.70	0.90	0.18
Kelly et al[44]/2004	69	Contrast	0.46	0.86	0.43	0.87	0.19
Kimura et al[43]/2003	203	Contrast	0.63	0.97	0.88	0.89	0.24
Reed et al[42]/2003	302	Contrast	0.37	0.91	0.58	0.81	0.25
Schillaci et al[41]/2003	83	Contrast	0.69	0.75	0.67	0.77	0.42
Eggeling et al[40]/2002	73	Contrast	0.82	0.50	0.79	0.55	0.70
Kiernan et al[39]/2002	92	Contrast	0.64	0.94	0.80	0.88	0.27
Nosotti et al[38]/2002	87	Contrast	0.64	0.88	0.64	0.88	0.25
von Haag et al[37]/2002	52	Contrast	0.50	0.65	0.16	0.91	0.12
Laudanski et al[36]/2001	92	Contrast	0.60	0.73	0.51	0.79	0.33
Poncelet et al[35]/2001	62	Contrast	0.56	0.68	0.23	0.90	0.15
Wallace et al[34]/2001	121	Contrast	0.87	0.35	0.75	0.54	0.69
Dunagan et al[33]/2001	72	Contrast	0.50	0.87	0.56	0.84	0.25
Kamiyoshihara et al[32]/2001	546	Contrast	0.33	0.90	0.46	0.84	0.20
Osada et al[31]/2001	335	Contrast	0.56	0.93	0.77	0.83	0.30
Pieterman et al[30]/2000	102	Contrast	0.75	0.66	0.50	0.85	0.31
Takamochi et al[29]/2000	401	Contrast	0.30	0.82	0.30	0.83	0.20
Marom et al[28]/1999	79	Contrast	0.59	0.86	0.84	0.63	0.56
Saunders et al[27]/1999	84	NR	0.20	0.90	0.30	0.84	0.18
Suzuki et al[26]/1999	440	Contrast	0.33	0.92	0.56	0.82	0.23
Vansteenkiste et al[25]/1998	68	Contrast	0.75	0.63	0.58	0.78	0.41
Vansteenkiste et al[24]/1998	56	Contrast	0.86	0.79	0.80	0.85	0.50
Bury et al[20]/1997	64	Contrast	0.79	0.84	0.58	0.93	0.22
Gdeedo et al[23]/1997	100	Contrast	0.63	0.57	0.41	0.76	0.32
Buccheri et al[21]/1996	80	Contrast	0.64	0.74	0.48	0.84	0.28
Bury et al[22]/1996	53	Contrast	0.71	0.81	0.63	0.85	0.32
Aaby et al[19]/1995	57	NR	0.72	0.91	0.86	0.81	0.44
Primack et al[18]/1994	159	Contrast	0.63	0.86	0.73	0.79	0.38
Yokoi et al[17]/1994	113	Contrast	0.62	0.80	0.61	0.81	0.33
McLoud et al[16]/1992	143	Contrast	0.64	0.62	0.44	0.79	0.31
Jolly et al[15]/1991	336	Contrast	0.71	0.86	0.69	0.87	0.30
Cole et al[14]/1993	150	NR	0.26	0.81	0.26	0.81	0.21
Webb et al[13]/1991	154	Contrast	0.52	0.69	0.31	0.84	0.21
Summary	5,111		0.51 (0.47–0.54)	0.86 (0.84–0.88)			0.28

*NR = not reported.

with CT scanning. ROC curves illustrate the tradeoff between sensitivity and specificity as the threshold that defines a positive test result varies from most to least stringent. The summary ROC method rests on the assumption that individual study estimates of sensitivity and specificity represent unique points on a common ROC curve. A summary ROC curve that lies closer to the upper left-hand corner of the diagram indicates better overall diagnostic accuracy. The pooled sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis were 51% (95% confidence interval [CI], 47 to 54%) and 86% (95% CI, 84 to 88%), respectively. The corresponding positive and negative likelihood ratios were 3.4 and 0.6, respectively, confirming that CT scanning has a limited ability either to rule in or

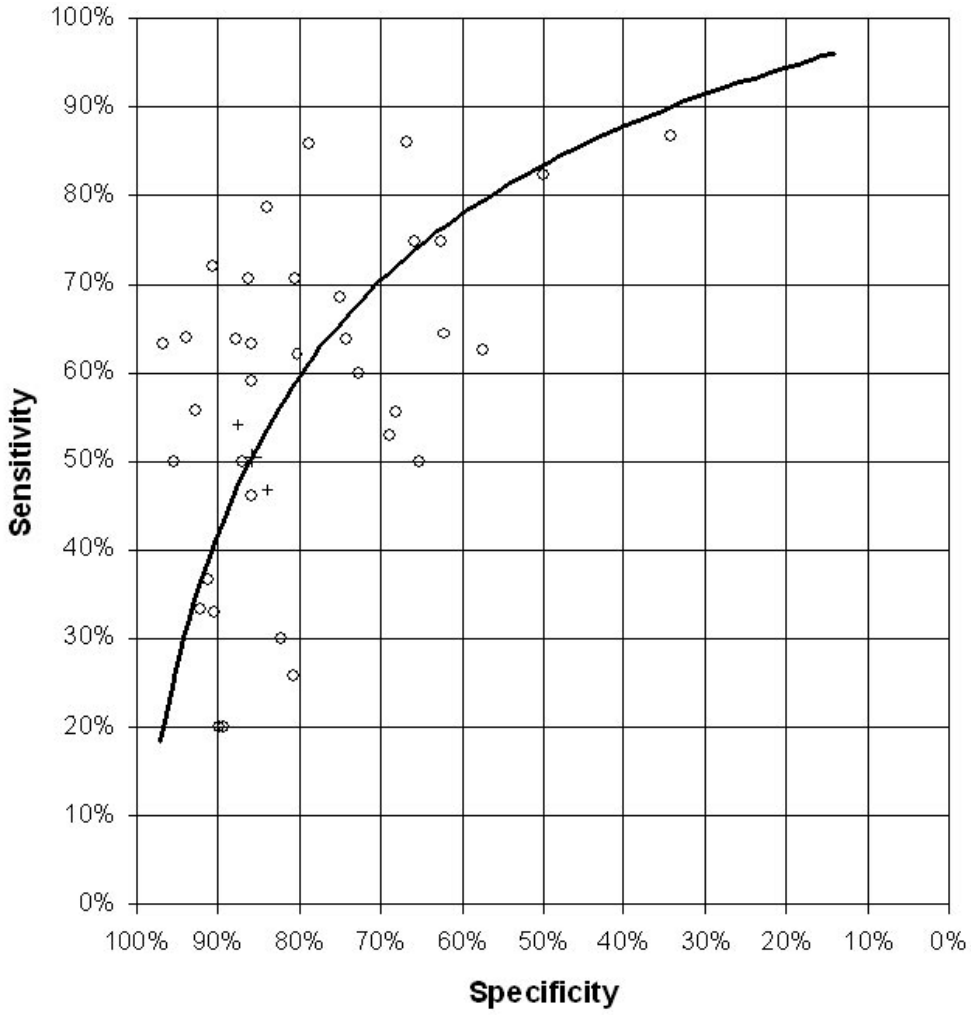

FIGURE 3. Summary ROC curve for imaging mediastinal lymph nodes > 1 cm in diameter with a standard CT scan. Open circles = individual study estimates of sensitivity and specificity (a study showing the highest accuracy will appear in the top left corner of the graph); dark line = summary ROC curve; large "+" = sensitivity and specificity at the mean threshold point on the summary ROC curve; smaller "+" = 95% CIs about the mean threshold summary sensitivity and specificity estimates.

exclude mediastinal metastasis. The combined estimates should be interpreted with caution as the studies were statistically heterogeneous. Still, these findings mirror those of other analyses addressing the accuracy of CT scanning for staging the mediastinum in NSCLC. A large metaanalysis by Gould and colleagues[45] reported the median sensitivity and specificity of CT scanning for identifying malignant mediastinal nodes as 61% and 79%, respectively, while an earlier metaanalysis by Dwamena and colleagues[46] reported average sensitivity and specificity of 64% and 74%, respectively.

CT scanning is clearly an imperfect means of staging the mediastinum, but it remains the best overall anatomic study available for the thorax. A CT scan usually guides the choice of nodes for selective node biopsy by invasive techniques, and thus continues to be an important tool for diagnosing lung cancer. The choice of individual nodes for sampling as well as the choice of the most appropriate invasive technique (including transbronchial, transthoracic, or transesophageal needle aspiration, mediastinoscopy, or more extensive surgery) will typically be directed by the findings of the CT scan. However, the limitation of CT scan-based mediastinal lymph node evaluation is evident in the fact that 5 to 15% of patients with clinical T1N0 (clinical stage I) tumors will be found to have positive lymph node involvement by surgical lymph node sampling.[47]

Based on the currently available data relating to the performance characteristics of CT scanning for the evaluation of the mediastinum in patients with NSCLC, two important messages emerge. First, approximately 40% of all nodes that are deemed to

be malignant by CT scan criteria are actually benign. Patient characteristics are a large factor, as specificity can be affected by clinical factors such as the presence of postobstructive pneumonitis.[16] Second, approximately 20% of all nodes that are deemed to be benign by CT scan criteria are actually malignant. CT scanning can thus both overstage and understage the mediastinal nodes. In sum, there is no node size that can reliably determine tumor stage and operability. In cases in which the CT scan criteria for the identification of a metastatic node are met, the clinician must still prove beyond a reasonable doubt by biopsy or resection that the node is indeed malignant. Given the limitations of its imperfect sensitivity and specificity, it is usually inappropriate to rely solely on the CT scan to determine mediastinal lymph node status in patients with NSCLC. Nonetheless, CT scanning continues to play an important and necessary role in the evaluation of these patients. This conclusion is supported by the most recent American Thoracic Society/European Respiratory Society statement[47] on the pretreatment evaluation of NSCLC and British Thoracic Society guidelines[48] on the selection of patients with lung cancer for surgery, both of which recommend CT scanning for the evaluation of mediastinal lymph nodes in all patients with suspected NSCLC. In the mediastinum, a CT scan can provide a road map that guides the location and modality to be used for subsequent biopsy procedures. In addition, patients with a very low pretest probability of metastasis (*eg*, those with small, peripheral T1 primary tumors) and no evidence of lymph node enlargement on a CT scan arguably might not require invasive staging prior to definitive thoracotomy. For example, when the clinical pretest probability is 10%, the posttest probability is approximately 6% when CT scan results are negative in the mediastinum.

Recommendations

1. For patients with either a known or suspected lung cancer who are eligible for treatment, a CT scan of the chest with contrast including the upper abdomen (liver and adrenal glands) should be performed. Grade of recommendation, 1B

2. In patients with enlarged discrete mediastinal lymph nodes on CT scans (> 1 cm on the short axis) and no evidence of metastatic disease, further evaluation of the mediastinum should be performed prior to definitive treatment of the primary tumor. Grade of recommendation, 1B

PET Scanning

PET scanning is an imaging modality based on the biological activity of neoplastic cells. Lung cancer cells demonstrate increased cellular uptake of glucose and a higher rate of glycolysis when compared to normal cells.[49] The radiolabeled glucose analog ^{18}F-fluoro-2-deoxy-D-glucose (FDG) undergoes the same cellular uptake as glucose and is phosphorylated by hexokinase, generating ^{18}F-FDG-6-phosphate. The combination of increased uptake of ^{18}F-FDG and a decreased rate of dephosphorylation by glucose-6-phosphatase in malignant cells results in an accumulation of ^{18}F-FDG-6-phosphate in these cells.[50,51] The concentrated isotope can then be identified using a PET camera. FDG-PET (subsequently referred to as PET) is thus a metabolic imaging technique that is based on the function of a tissue rather than its anatomy. Standardized quantitative criteria for an abnormal PET scan finding in the mediastinum are unfortunately lacking. A qualitative assessment is usually based on a comparison of uptake in the lesion or structure in question compared to the background activity of the lung or liver. A standard uptake value of < 2.5 is sometimes used as a threshold level for normalcy, but this measurement may vary with the new generation of scanners. Despite the lack of standardized criteria defining positive findings, PET scanning has proved useful in differentiating neoplastic from normal tissues. However, the technique is not infallible as nonneoplastic processes including granulomatous and other inflammatory diseases as well as infections may also demonstrate positive PET imaging findings. Further, size limitations are an issue, with the lower limit of spatial resolution of the current generation of PET scanners being approximately 7 to 10 mm. However, smaller lesions may be detected, depending on the intensity of uptake of the isotope in abnormal cells.[30,52] Additionally, certain well-differentiated low-grade malignancies, particularly bronchioloalveolar cell carcinoma and typical carcinoid tumors, are known to have higher false-negative finding rates.[53–57]

A burgeoning number of studies in the last several years have reported on the utility of PET scanning in the assessment of the mediastinum in patients with lung cancer. The increasing availability of the technology now allows PET scanning to be used widely as a diagnostic tool. It should be noted that PET scanning is primarily a metabolic examination and has limited anatomic resolution. It is usually possible by PET scanning to identify lymph node stations, but not individual lymph nodes. CT scanning provides much more anatomic detail but lacks the functional information provided by PET scanning. Newer generation inte-

grated PET-CT imagers may combine the advantages of both studies, but there are as yet few studies addressing the accuracy of this modality.[58]

As was done for CT scanning, investigators from the Duke University Evidence-based Practice Center performed a systematic review[4] of the medical literature relating to the accuracy of PET scanning for noninvasive staging of the mediastinum in patients with lung cancer. Studies evaluating the performance characteristics of PET scanning for this purpose were identified based on their fulfillment of the following criteria: (1) publication in a peer-reviewed journal; (2) study size of > 20 patients; (3) patient group not included in a subsequent update of the study; (4) histologic or cytologic confirmation of mediastinal nodes or extrathoracic site as well as the primary tumor; and (5) availability of the raw data needed to calculate independently sensitivity, specificity, PPV, and NPV. All studies were interpreted in conjunction with patients' CT scan findings so that the PET scan findings were correlated with the anatomic location of the lesion seen on the CT scan. In all studies, ^{18}F-FDG was the radiopharmaceutical used for imaging. Forty-four studies [6,8,11,12,20,22,24,25,27,28,30,33,35,37,39,42,44,52,59–78,87,121,122,178,182,183] published between 1994 and June 2006 were identified, yielding 2,865 evaluable patients. These studies are displayed in Table 3. The median prevalence of mediastinal metastasis was 29% (range, 5 to 64%). Figure 4 shows individual study estimates of sensitivity and specificity and the summary ROC curve for the PET scans. Pooled estimates of sensitivity and specificity for identifying mediastinal metastasis were 74% (95% CI, 69 to 79%) and 85% (95% CI, 82 to 88%), respectively. Corresponding positive and negative likelihood ratios for mediastinal staging with PET scanning were 4.9 and 0.3, respectively. These findings demonstrate that PET scanning is more accurate than CT scanning for staging of the mediastinum in patients with lung cancer, though it is far from perfect.

PET scanning may provide an additional benefit in that it is a whole-body study. The usual extrathoracic staging of lung cancer will typically include a combination of bone scintigraphy, brain imaging by CT scanning or MRI and abdominal CT scanning or the inclusion of the upper abdomen in a chest CT scan. PET scanning is able to provide information about the primary site in the chest as well as intrathoracic and extrathoracic metastases with a single study. The exception to this is the definition of metastases in the brain, as the brain will normally avidly take up ^{18}F-FDG. Several studies[30,42,79] have reported on the ability of PET scanning to identify extrathoracic metastases in patients whose tumors had been deemed resectable by conventional imaging. The rate of detection of unanticipated M1 disease by PET scanning has been reported as 1 to 8% in patients with clinical stage I disease and 7 to 18% in patients with clinical stage II disease.[42,79] The identification of unanticipated distant metastases by PET scanning in such patients should result in the avoidance of unwarranted thoracotomies, but all positive findings in surgical candidates should be confirmed by biopsy unless there is overwhelming evidence of distant metastasis.[80]

To summarize, PET scanning has both higher sensitivity and higher specificity than CT scanning for the evaluation of mediastinal lymph nodes, and can provide important information regarding the presence of metastatic disease outside the thorax. In the mediastinum, PET scanning is more accurate than CT scanning in identifying abnormal nodes that can be sampled by directed biopsy. Accordingly, PET scanning has assumed an increasingly important role in the evaluation of patients with lung cancer. However, broader experience with PET scanning has not yet allowed a precise definition of its role in the staging evaluation of lung cancer. PET scanning is not infallible. False-positive PET scan findings may result in missed opportunities for a cure by surgical resection. Conversely, false-negative PET scan findings may lead to fruitless thoracotomies in patients with unresectable disease. The potential consequences of both false-positive and false-negative PET scan findings in an environment in which PET scanning is increasingly relied on for staging must be considered when PET scanning is included in the evaluation of NSCLC.

Some studies[45,81–83] have pointed out that the accuracy of PET imaging in the mediastinum is dependent on the size of the nodes identified by CT scanning. PET scanning is more sensitive (but less specific) when CT scanning identifies enlarged nodes.[45,81] In a metaanalysis evaluating the conditional test performance of PET and CT scanning, Gould and colleagues[45] reported median sensitivity and specificity of PET scans of 100% and 78%, respectively, in patients with enlarged lymph nodes. PET scanning is thus very accurate in identifying malignant nodal involvement when nodes are enlarged. However, PET scanning will falsely identify malignancy in approximately one-fourth of patients with nodes that are enlarged for other reasons, usually inflammation, or infection. Positive PET findings in this situation should be confirmed by directed biopsy. Failure to do so could result in patients with surgically resectable disease being denied curative surgery. An argument could also be made that a patient in whom the clinical assessment of pretest probability of malignant node involvement is high should proceed directly to biopsy without PET, as a negative

Table 3—*Accuracy of PET Scanning for Staging the Mediastinum in Lung Cancer Patients*

Study/Year	Patients, No.	Sensitivity	Specificity	PPV	NPV	Prevalence
Analysis by nodal station						
Gupta et al[52]/2000	54	0.96	0.93	0.86	0.98	0.32
Yasukawa et al[182]/2000	41	0.86	0.91	0.79	0.94	0.29
Berlangieri et al[178]/1999	50	0.8	0.97	0.73	0.98	0.1
Graeber et al[121]/1999	96	0.98	0.94	0.91		
Gupta et al[122]/1999	103	0.92	0.95	0.92	0.95	0.4
Kernstine et al[87]/1999	64	0.7	0.86	0.48	0.94	0.16
Vansteenkiste et al[24]/1998	68	0.99	0.86	0.99	0.89	0.93
Vansteenkiste et al[25]/1998	56	0.93	0.47	0.92	0.5	0.87
Steinert et al[63]/1997	47	0.89	0.99	0.96	0.97	0.25
Sasaki et al[183]/1996	29	0.76	0.98	0.93	0.93	0.24
Summary	608	0.95	0.9	0.94	0.92	0.61
Analysis by patient						
Takamochi et al[12]/2005	71	0.40	0.88	0.46	0.84	0.21
Pozo-Rodriguez et al[6]/2005	132	0.81	0.76	0.56	0.91	0.27
Halpern et al[78]/2005*	36	0.5	0.77	0.45	0.80	0.28
Verhagen et al[8]/2004	56	0.58	0.90	0.83	0.71	0.46
Nomori et al[11]/2004	80	0.86	0.97	0.86	0.97	0.18
Kelly et al[44]/2004	69	0.62	0.98	0.89	0.92	0.19
Demura et al[77]/2003	50	0.87	0.63	0.50	0.92	0.30
Fritscher-Ravens et al[76]/2003	33	0.75	0.88	0.86	0.79	0.48
Gonzalez-Stawinski et al[75]/2003	202	0.66	0.78	0.48	0.88	0.23
Konishi et al[74]/2003	54	0.80	0.92	0.50	0.98	0.09
Reed et al[42]/2003	302	0.61	0.84	0.56	0.87	0.25
Zimny et al[73]/2003	33	0.83	0.81	0.71	0.89	0.36
Kernstine et al[72]/2002	237	0.82	0.82	0.51	0.95	0.19
Kiernan et al[39]/2002	88	0.88	0.86	0.71	0.95	0.28
Vesselle et al[71]/2002	118	0.81	0.96	0.92	0.90	0.36
von Haag[37]/2002	52	0.67	0.91	0.50	0.95	0.12
Changlai et al[70]/2001	127	0.88	0.83	0.90	0.79	0.64
Poncelet et al[35]/2001	61	0.67	0.85	0.43	0.94	0.15
Tatsumi et al[69]/2000	21	0.80	0.82	0.80	0.82	0.48
Dunagan et al[33]/2001	81	0.52	0.88	0.61	0.84	0.26
Farrell et al[68]/2000	84	1.00	0.93	0.40	1.00	0.05
Liewald et al[67]/2000	76	0.93	0.78	0.69	0.95	0.35
Pieterman et al[30]/2000	102	0.91	0.86	0.74	0.95	0.31
Roberts et al[66]/2000	100	0.88	0.91	0.75	0.96	0.24
Magnani et al[65]/1999	28	0.67	0.84	0.67	0.84	0.32
Marom et al[28]/1999	79	0.73	0.94	0.85	0.88	0.56
Saunders et al[27]/1999	84	0.71	0.97	0.86	0.93	0.20
Vansteenkiste et al[24]/1998	68	0.93	0.95	0.93	0.95	0.41
Vansteenkiste et al[25]/1998	56	0.86	0.43	0.60	0.75	0.50
Bury et al[20]/1997	64	0.86	1.0	1.0	0.96	0.22
Guhlmann et al[64]/1997	32	0.87	1.0	1.0	0.89	0.47
Steinert et al[63]/1997	47	0.92	0.97	0.92	0.97	0.28
Bury et al[22]/1996	30	0.88	0.86	0.88	0.86	0.53
Sazon et al[62]/1996	32	1.00	1.00	1.00	1.00	0.50
Scott et al[61]/1996	27	1.00	1.00	1.00	1.00	0.33
Chin et al[60]/1995	30	0.78	0.81	0.64	0.89	0.30
Wahl et al[59]/1994	23	0.82	0.75	0.75	0.82	0.48
Summary	2,865	0.74 (0.69–0.79)	0.85 (0.82–0.88)			0.29

*Calculations are based on the data reported in Table 2. The results of this study should be interpreted with caution as there is a minor inconsistency between the results in the text and those in Table 3.

PET result would not negate a strong clinical suspicion for tumor. In this situation, negative PET findings would be unlikely to change the clinical suspicion for malignancy enough to defer histologic confirmation. As a counter-argument, PET scanning might still impact the decision process if unexpected extra-thoracic sites of abnormal activity are found, and patients with clinical stage III disease are at highest risk for occult distant metastasis. Identification of such foci might affect the choice of biopsy site and have a significant impact on the clinical stage and the

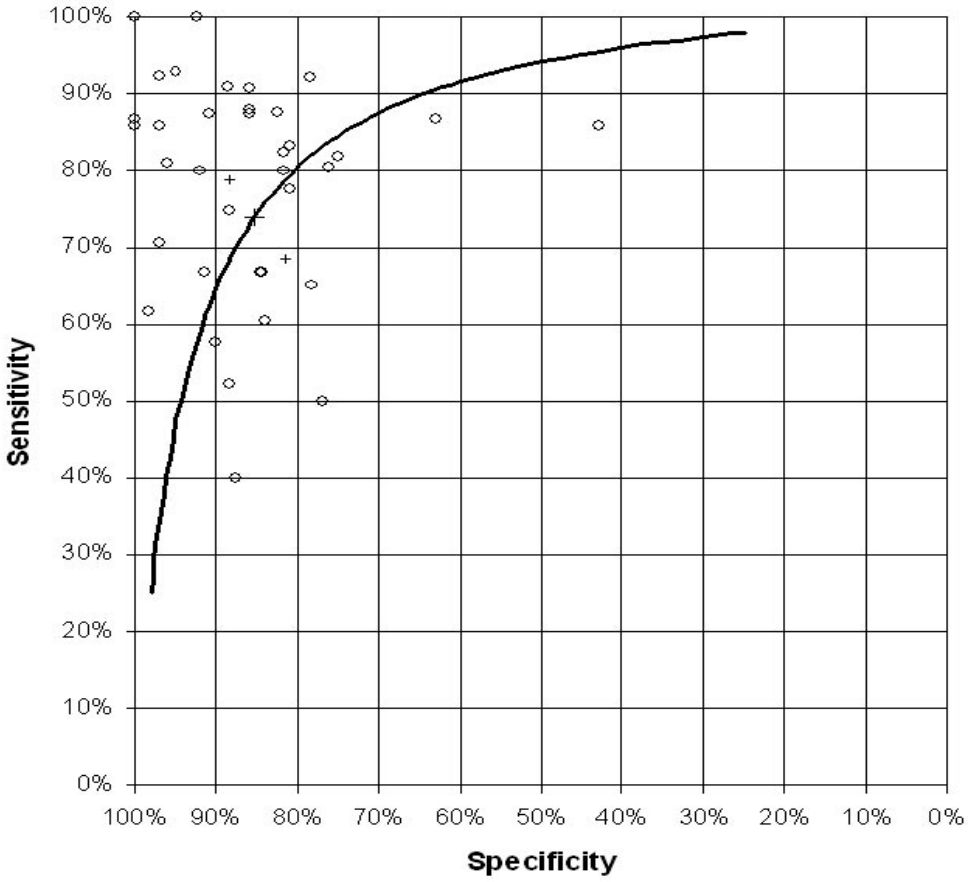

FIGURE 4. Summary ROC curve for imaging mediastinal lymph nodes > 1 cm diameter with FDG-PET scanning. Open circles = individual study estimates of sensitivity and specificity (a study showing the highest accuracy will appear in the top left corner of the graph); dark line = summary ROC curve; larger "+" = sensitivity and specificity at the mean threshold point on the summary ROC curve; smaller "+" = 95% CIs about the mean threshold summary sensitivity and specificity estimates.

decision of whether a patient should undergo surgical resection. Whether this is adequate reason to pursue PET scanning in patients with enlarged mediastinal nodes by CT scanning in whom the clinical suspicion for malignant involvement is high is unanswered.

Conversely, PET scanning is less sensitive (but more specific) in patients with normal-sized mediastinal nodes seen by CT scanning. Based on the data presented in Table 2, CT scanning of the mediastinum is falsely negative in approximately 20% of patients with normal-sized nodes and malignant nodal involvement. In the metaanalysis reported by Gould and colleagues,[45] the median sensitivity and specificity of PET scanning in this group of patients were 82% and 93%, respectively. These data indicate that nearly 20% of patients with normal-sized nodes but with malignant involvement had falsely negative PET scan findings. Corresponding positive and negative likelihood ratios were approximately 12.0 and 0.2, respectively. In this study, when both CT and PET scan results were negative and the pretest probability of mediastinal lymph node metastasis was estimated at 35% (which corresponds to the median prevalence of mediastinal metastasis in studies of PET scanning), the posttest probability of mediastinal metastasis was approximately 9% (95% CI, 4 to 14%). This addresses the controversial question of whether a negative PET scan finding in patients with normal-sized lymph nodes by CT scanning can obviate the need to perform further invasive mediastinal evaluation prior to thoracotomy. In this situation, we believe that the appropriate invasive staging procedure would be mediastinoscopy, as there are no enlarged nodes to directly biopsy by other techniques. While PET scanning samples all mediastinal nodal groups, it is clearly less sensitive for nodes with a diameter of < 7 to 10 mm. While mediastinoscopy cannot sample all mediastinal nodal groups, it can detect microscopic disease even in small nodes. Ultimately, the decision as

to whether a negative PET scan finding can be used to obviate mediastinoscopy will require clinical judgment that incorporates multiple factors, including the clinical pretest probability of mediastinal metastasis, patient preferences, and local availability and expertise in both mediastinoscopy and PET imaging (see the "Invasive Mediastinal Staging of Lung Cancer" chapter for further recommendations).

The utility of PET scanning in patients with stage 1A disease is less clear as the prevalence of mediastinal and distant metastatic disease is low and the evidence for utilizing PET scanning is poor. Further study in this specific patient population is warranted prior to making a recommendation that has a higher level of evidence.

In summary, PET scanning is the most accurate noninvasive imaging modality available to evaluate the mediastinum in patients with lung cancer. Abnormal findings on PET scans may be important in identifying mediastinal nodes for directed biopsy. PET scanning is also a whole-body study and offers additional information relating to extrathoracic sites of possible disease involvement (see "The Search for Metastatic Disease" section). However, wider experience with PET scanning has increased the awareness of the potential for and consequences of both false-positive and false-negative findings.

Recommendations

3. PET scanning to evaluate for mediastinal and extrathoracic staging should be considered in patients with clinical 1A lung cancer being treated with curative intent. Grade of recommendation, 2C

4. Patients with clinical 1B-IIIB lung cancer being treated with curative intent, should undergo PET scanning (where available) for mediastinal and extrathoracic staging. Grade of recommendation, 1B

5. In patients with an abnormal result on FDG-PET scans, further evaluation of the mediastinum with sampling of the abnormal lymph node should be performed prior to surgical resection of the primary tumor. Grade of recommendation, 1B

Integrated PET and CT Scanning

An important shortcoming of dedicated PET imaging is its limited spatial resolution, which results in poor definition of anatomic structures. As a result, it may be difficult for PET scanning to distinguish between mediastinal and hilar lymph nodes, or to differentiate between a central primary tumor and a lymph node metastasis, even when the results of PET and CT scans are visually correlated. This limitation has been addressed by the development of "dual-modality" or "integrated" PET/CT scanning systems, in which a CT scanner and a PET scanner are combined in a single gantry. Some studies[24,25,58,84,85] have begun to examine the accuracy of integrated PET/CT scanners for lung cancer staging. The total number of patients evaluated by this hybrid technique is still relatively small. Estimates of accuracy for identifying mediastinal metastasis are limited, though early studies have indicated[24,25,85] that the sensitivity and specificity are at least as good as those with PET scanning alone.

MRI for Staging the Mediastinum

Like CT scanning, MRI is an anatomic study. Data relating to the accuracy of the evaluation of the mediastinum with MRI in patients with NSCLC are limited, but available reports[13,86] suggest that the accuracy of MRI is as good as CT scanning. Two reports[86,87] also have suggested that the use of contrast enhancement may improve the accuracy of MRI in this situation. MRI may be superior to CT scanning for defining lung cancer spread in the thorax in specific situations. Because MRI can detect differences in intensity between tumor and normal tissues, including bone, soft tissues, fat, and vascular structures, it may be more accurate than CT scanning in delineating direct tumor invasion of the mediastinum, chest wall, diaphragm, or vertebral bodies.[13,88–91] This may be particularly useful in evaluating superior sulcus tumors or tumors abutting the mediastinum, structures of the chest wall, and diaphragm. However, most centers continue to rely on CT scanning as the noninvasive anatomic study of choice for evaluating potential mediastinal spread of lung cancer.

Recommendation

6. For patients with either a known or suspected lung cancer who are eligible for treatment, an MRI of the chest should not routinely be performed for staging the mediastinum. MRI may be useful in patients with NSCLC where there is concern for involvement of the superior sulcus or brachial plexus involvement. Grade of recommendation, 1B

The Search for Metastatic Disease

The purpose of extrathoracic scanning in patients with NSCLC is usually to detect metastatic disease,

especially at common metastatic sites such as the adrenal glands, liver, brain, and skeletal system, thereby sparing the patient fruitless radical treatment.[92] However, scans can only detect macroscopic metastatic deposits that have reached a size within the resolution capability of the imaging modality in question, and this can be considered a major shortcoming of all conventional tests currently used to detect distant metastases in patients with NSCLC. In more recent years, increasing attention has focused on the use of immunocytochemical techniques using monoclonal antibodies to detect occult micrometastases, which are sometimes associated with a worse prognosis, in the bone marrow of NSCLC patients.[93–98] Such techniques may add a new dimension to metastatic staging in the near future.

In the meantime, the preferred scans for staging patients with NSCLC in 2007 are CT scanning of the chest, CT scanning or MRI with contrast of the brain, and ^{99}Tc nuclear imaging of the skeletal system. The use of whole-body PET scans for extrathoracic staging is evolving, and PET scanning may ultimately play a significant role in the assessment of distant disease. The very limited extant data regarding whole-body single photon emission CT scanning for metastatic disease suggest that its performance is slightly inferior to that of PET scanning.[72,79]

It is clear that the use of extrathoracic scans must always be subordinate to a thoughtful overall clinical strategy for each individual patient. For example, a whole-body PET scan has little role in the diagnosis of a patient with clinically obvious, accessible advanced disease, such as skin metastases or massive hepatic replacement by metastatic tumor seen on CT scans.[53,54,99] In other circumstances, the need for tissue confirmation of metastatic disease can supercede the need for additional sophisticated scanning. For instance, in certain patients an adrenal biopsy, rather than a PET scan, may be required to clarify the nature of a unilateral adrenal mass seen on a CT scan.

It is well established that abnormal symptoms, physical examination findings, and routine blood tests in the initial clinical evaluation of patients with NSCLC are associated with a significant yield (approximately 50%) of abnormal scan findings.[92] Moreover, a rough semiquantitative relationship has been demonstrated in some studies[92,100] between the number of abnormal "clinical factors" and the frequency of abnormal scan findings. In the absence of all clinical factors, the scan yield is much lower, giving rise to the recommendation that scans be omitted in this setting,[31,48,100–104] though controversy persists on this point.[105] Other important variables focus on the primary lesion, since more scan abnormalities are associated with advanced thoracic lesions (T and N factors).[106,107] This is particularly true for patients with N2 disease, in whom asymptomatic metastases have been documented at a higher rate than would have been expected.[106,107] There has been some controversy with regard to cell type and the incidence of asymptomatic metastases. Several studies[108,109] have documented a higher incidence of brain metastases with adenocarcinomas as opposed to squamous cell cancers, but a large series[104] of patients with stage I and II lung cancer found no difference.

Several important caveats pertain to scanning for distant metastases in general. First is the issue of false-positive scan findings. Clinical entities that frequently give rise to false-positive scan findings include adrenal adenomas (present in 2 to 9% of the general population), hepatic cysts, degenerative joint disease, old fractures, and a variety of nonmetastatic space-taking brain lesions. When clinically indicated, additional imaging studies and/or biopsies are performed to establish the diagnosis, but complications and costs resulting from such subsequent investigations have received insufficient attention.[110,111] A second problem is that of false-negative scan findings (*ie*, metastases that are present but not picked up by current scanning techniques). This was demonstrated convincingly by Pagani,[112] who found metastatic NSCLC in 12% of radiologically normal adrenal glands by percutaneous biopsy; a more recent autopsy series[113] suggested that the sensitivity of CT scanning for adrenal metastases may be as low as 20%. A third difficulty is that most studies fail to carefully specify exactly which elements comprise the prescan clinical evaluation, or invoke differing clinical indicators to mandate scanning. Organ-specific findings such as headache and non-organ-specific complaints such as weight loss are both important.[100,114] The current preferred "expanded" clinical evaluation includes organ-specific and constitutional signs and symptoms, along with simple laboratory test results, as shown in Table 4.[92] Furthermore, Guyatt et al[115] have shown that careful delineation and quantification of historical features using a 5-point scale of severity can importantly affect the subsequent scan yield and ultimately the incidence of metastases after lung cancer surgery. A fourth issue is an ascertainment problem, since abnormal scan findings in many studies were not followed up with definitive biopsy proof of metastatic disease. This may relate to anatomic factors, overall debility, or refusal of the patient, or a variety of other cogent clinical concerns. Fifth, it must be noted that even biopsy proof of metastatic disease does not dictate a certain clinical management pathway. Carefully selected patients with localized lung cancers in

Table 4—*Clinical Findings Suggesting Metastatic Disease

Testing	Finding
Symptoms elicited in history	Constitutional: weight loss > 10 lb; and musculoskeletal: focal skeletal pain Neurological: headaches; syncope; seizures; extremity weakness; and recent changes in mental status
Signs found on physical examination	Lymphadenopathy (> 1 cm); hoarseness; superior vena cava syndrome; bone tenderness; hepatomegaly (> 13-cm span); focal neurologic signs, papilledema; and soft-tissue mass
Routine laboratory tests	Hematocrit: < 40% in men and 35% in women Elevated alkaline phosphatase, GGT, SGOT, and calcium levels

*GGT = γ-glutamyltransferase; SGOT = serum glutamic-oxaloacetic transaminase.

the thorax, accessible, solitary metastases to the brain or adrenal gland, and other favorable clinical features may obtain long-term survival with an aggressive treatment approach, including surgical extirpation of both the primary and metastatic site.[116,117] Finally, the lack of prospective randomized trials and outcome studies in the area of extrathoracic staging is striking. Two retrospective studies showed that scanning asymptomatic patients with early NSCLC did not help to predict recurrences postoperatively or to improve survival.[118,119] The only prospective randomized trial[120] showed no statistical difference in recurrence rates or survival in a group of patients who were randomized to undergo bone scintigraphy and CT scans of the head, liver, and adrenal glands, compared with the group assigned to undergo CT scans of the chest and mediastinoscopy, followed by thoracotomy when appropriate.

Utility of PET Scanning for Detecting Metastatic Disease

Since 1993, numerous studies have assessed the clinical utility of PET scans to assist in the search for metastatic disease in patients with NSCLC. In general, these tend to be relatively small, prospective, single-institution assessments in which whole-body PET scanning suggests the presence of unsuspected distant disease in 10 to 20% of cases.[20,27,121,122] The yield of unsuspected metastases depends on a number of factors, including whether PET scanning is gauged as an initial metastatic evaluation, or only after some metastases have already been detected via conventional scans.[42,123] The yield is higher in patients with clinical stage III disease,[79] and a relationship between thoracic nodal stage and PET scanning yield has been suggested.[124] When the area of interest is a single site (*eg*, adrenal glands or skeletal system), the performance characteristics (*ie*, sensitivity, specificity, PPV, NPV, and accuracy) of PET scanning are very favorable, often surpassing the performance of conventional imaging with CT scans or radionuclide bone imaging.[125,126] Furthermore, whole-body PET scanning enables the imaging of areas not covered in the traditional scanning algorithm, allowing the detection of occasional metastatic foci in, for example, skin, pelvis, skeletal muscle, soft tissue, kidney, and pancreas.[27] In most of these studies, abnormal PET scan findings are followed up with biopsy, serial conventional radiographs, and/or careful clinical assessment to confirm the veracity of the PET scan findings.

Nevertheless, several concerns pertain specifically to the emerging literature regarding PET scans as a test for distant disease. First, the exact criterion for a positive PET scan finding is usually based on an entirely subjective or semiquantitative comparison with background activity. Attempts to derive a reliable criterion based on standardized or differential uptake ratios have been generally unsuccessful to date. Second, several significant problems attend the use of PET scanning as an imaging modality for brain metastases. Not only does high baseline brain uptake pose a problem in detecting focal accumulations,[28] but many PET scanners include only the area from the base of the skull to the mid-thighs, thereby excluding much of the brain parenchyma from the images. Obtaining satisfactory brain PET scan images can require special equipment modifications and prolonged image-acquisition time.[20,127] Furthermore, the small size of most brain metastases may be problematic in terms of the limited resolution of conventional PET scans. Third, while there is some evidence that PET scanning can avert unnecessary thoracotomies,[80] improve clinical staging,[20,121,122,128] influence patient management decisions,[128] and alter radiotherapy planning,[79] there has been scant evidence to date linking PET scanning to an improvement in important patient outcomes such as recurrences of metastatic disease or mortality, and cost-effectiveness assessments are just beginning to emerge.[123,129,130] Fourth, a substantial ascertainment problem exists for negative PET scan findings, in that metastatic disease missed by PET scanning is generally unverifiable; thus, the false-negative rate is not truly knowable in most studies. But in one study,[131] 19% of patients who underwent a curative resection experienced a systemic relapse within a mean interval of 14 months despite a negative finding on a preoperative whole-body PET scan, suggesting that the false-negative problem may be significant. Finally, some of the larger, more recent

multiinstitutional studies[42] have shown substantially lower performance characteristics for PET scanning than those in the initial studies, with a PPV as low as 36% for metastatic disease.

To some extent, the very recent tempering of enthusiasm for PET scanning for distant disease likely reflects the usual trajectory of a new test, as greater experience accumulates in thousands of patients under a wide variety of clinical circumstances and interpretive expertise. In this sense, the experience with PET scanning echoes the experience with CT scanning of the mediastinum in patients with NSCLC, in which initial reports of sensitivity and specificity were in excess of 90%, before settling into the accepted values of 60 to 70% decades later. On the other hand, more recently introduced integrated PET/CT scanners offer the hope of combining metabolic imaging with precise anatomic resolution to further refine the search for metastatic disease.[58,84,132] In one highly publicized study,[58] integrated PET-CT scanning increased diagnostic certainty as to the precise location of metastasis in two of eight patients in whom conventional PET scanning detected unsuspected extrathoracic focal accumulations.

Thus, it is premature to definitively assess the role of whole-body PET scanning in the search for metastatic disease barely 10 years after its introduction into clinical practice. As of this writing, it appears that whole-body PET scanning is best suited to help resolve cases in which prior imaging of a possible metastatic deposit is equivocal, and to detect unsuspected distant metastasis in either the preoperative setting or in those patients who are at high risk for metastatic deposits even when they are clinically asymptomatic (clinical stage IIIA).[131]

Detection of Abdominal Metastases

Some PET scan studies can also be considered in the context of the scanning of individual organ systems in patients with NSCLC. Thirteen studies[105–107,109,133–141] evaluated the utility of clinical evaluation in detecting abdominal metastases in 1,291 patients using CT scanning as the reference standard (Table 5). Most of the studies limited study enrollment to patients with a negative clinical evaluation. In these nine studies,[107,109,133–137,139,140] the median prevalence of abdominal metastasis was 3% (range, 0 to 18%), and the median predictive value of a negative clinical evaluation was 97% (range, 82 to 100%). Four studies[105,106,138,141] enrolled patients with both positive and negative clinical evaluation findings. In these studies, the prevalence of abdominal metastasis ranged between 6% and 40%. Both sensitivity (range, 40 to 100%) and specificity (range, 27 to 65%) varied widely across studies. The use of CT scanning as an imperfect reference standard suggests that these estimates should be interpreted with caution.

It is relatively common to encounter adrenal masses on a routine CT scan, but many of these lesions are unrelated to the malignant process. A unilateral adrenal mass in a patient with NSCLC is more likely to be a metastasis than a benign lesion according to some studies,[92,142] but not others.[143,144] In the presence of clinical T1N0 NSCLC, adenomas predominate,[135,136] whereas adrenal metastases are

Table 5—*Utility of the Clinical Evaluation in Detecting Abdominal Metastases Using CT Scanning as the Reference Standard

Study/Year	Organ Scanned	Patients, No.	Routine Scan	Sensitivity	Specificity	PPV	NPV	Prevalence
Bilgin et al[105]/2002†	Liver	90	Yes	0.40	0.58	0.05	0.94	0.06
Miralles et al[141]/1993†	Liver	71	No	0.94	0.65	0.44	0.97	0.23
Silvestri et al[106]/1992	Adrenal	173	No	1.00	0.27	0.20	1.00	0.15
Ettinghausen et al[140]/1991	Adrenal	246	NR			‡	0.98	0.02
Salvatierra et al[109]/1990	Adrenal	146	Yes			‡	0.92	0.08
Grant et al[107]/1988	Liver, adrenal	114	Yes			‡	0.92	0.08
Whittlesey[139]/1988	Adrenal	180	Yes			‡	0.97	0.03
Mirvis et al[138]/1987	Liver, adrenal	72	Yes	0.90	0.58	0.59	0.89	0.40
Osada et al[137]/1987	Liver, adrenal	47	No			‡	1.00	0.00
Heavey et al[136]/1986	Adrenal	31	Yes, stage 1 disease			‡	0.97	0.03
Pearlberg et al[135]/1985	Liver, adrenal	23	Probably no			‡	1.00	0.00
Chapman et al[134]/1984	Adrenal	14	Yes			‡	0.86	0.14
Nielsen et al[133]/1982	Adrenal	84	Yes			‡	0.82	0.18
Summary		1,291		0.86 (0.62–0.96)	0.56 (0.25–0.93)	0.31	0.95	0.13

*See Table 2 for abbreviation not used in the text.

†Not included by Silvestri et al.[92]

‡PPV could not be estimated because the study evaluated with CT scanning only those patients in whom the clinical examination findings were negative.

frequently associated with large intrathoracic tumors or other extrathoracic metastases.[92,145] Many studies[140] have suggested that the size of a unilateral adrenal abnormality seen on a CT scan is an important predictor of metastatic spread, but this has not been a universal finding.

PET scans have performed exceptionally well in several studies specifically addressing the problem of adrenal metastases in NSCLC, with accuracy as high as 100% in two studies.[28,146] However, small lesions (< 15 mm) were underrepresented in these series, and other studies have noted rare false-positive findings in this site.[30,125,131]

Four possible approaches to distinguishing between malignant and benign adrenal masses have been proposed, as follows: evaluation by specific CT scanning or MRI criteria; evaluation with additional or serial imaging; evaluation by percutaneous biopsy; and evaluation by adrenalectomy. Well-defined, low-attenuation (fatty) lesions with a smooth rim on unenhanced CT scan are more likely to be benign adenomas,[147–149] but the CT scan appearance of many lesions is insufficiently distinctive.[147] Follow-up scanning with repeat CT, serial ultrasounds, MRI (especially with chemical shift and dynamic gadolinium-enhanced techniques[150]), 131-6-betaiodomethylnorcholesterol scanning,[151] or PET scanning can often help with the critical distinction between metastatic disease and adenoma. Percutaneous adrenal biopsy is a relatively safe and effective means of achieving a definitive diagnosis in doubtful cases, and is especially important when the histology of the adrenal mass will dictate subsequent management.[133,134] However, this procedure may be nondiagnostic or unfeasible due to anatomic constraints. When insufficient material results from a biopsy, repeat aspiration or even adrenalectomy should be considered.[140,147]

Most liver lesions are benign cysts or hemangiomas, but a contrast CT scan (or ultrasound) is often required to establish a likely diagnosis.[47] Percutaneous biopsy can be performed when diagnostic certainty is required. One metaanalysis[110] that specifically reviewed hepatic studies derived a pooled yield of 3% for liver metastases in asymptomatic patients with NSCLC. PET scanning can detect liver metastases with an accuracy of 92 to 100% and only rare false-positive findings, though data in patients with NSCLC are very limited at present.[20,28]

Detection of Brain Metastases

In most studies, the yield of CT scanning/MRI of the brain in NSCLC patients with negative clinical examination findings is 0 to 10%,[152–158] possibly ren-

Table 6—*Utility of the Clinical Evaluation in Detecting Brain Metastases Using Neuroimaging (CT Scanning/MRI/PET Scanning) as the Reference Standard*

Study/Year	Examination	Patients, No.	Routine Scan?	Sensitivity	Specificity	PPV	NPV	Prevalence
Bilgin et al[105]/2002*	Neurologic	90	No	0.50	0.56	0.15	0.88	0.13
Osada et al[31]/2001*	Neurologic	91	cT1-T2, < N2			†	0.98	0.02
Yokai et al[164]/1999*	Neurologic	155	Yes; CT scan			†	0.99	0.01
Cole et al[153]/1994*	Neurologic	42	No			†	1.00	0.00
Habets et al[163]/1992*	Neurologic	54	Yes	1.00	0.98	0.75	1.00	0.06
Kormas et al[158]/1992	Screening	157	N2 only			†	0.97	0.03
Salvatierra et al[109]/1990	Expanded	146	Adenocarcinoma and large cell cancer only	0.79	0.91	0.58	0.97	0.13
Grant et al[107]/1988	Screening	114	Yes			†	0.91	0.09
Osada et al[137]/1987	Screening	56	No			†	1.00	0.00
Crane et al[162]/1984	Neurologic	145	Yes	0.65	0.98	0.88	0.94	0.16
Hooper et al[100]/1984	Expanded	89	No	1.00	0.38	0.26	1.00	0.18
Levitan et al[161]/1984	Neurologic	55	Yes	0.73	1.00	1.00	0.91	0.27
Mintz et al[156]/1984	Neurologic	66	Yes	0.38	0.81	0.21	0.90	0.12
Tarver et al[108]/1984	Neurologic	323	Adenocarcinoma and SCLC only	0.83	0.78	0.64	0.91	0.32
Johnson et al[160]/1983	Neurologic	84	No	0.83	0.81	0.42	0.97	0.14
Jennings et al[159]/1980	Screening	102	NR			†	0.79	0.21
Butler et al[152]/1979	Screening	55	Yes			†	0.95	0.05
Jacobs et al[155]/1977	Screening	50	Yes			†	0.94	0.06
Summary		1,874		0.76 (0.61–0.87)	0.82 (0.69–0.91)	0.52	0.94	0.13

*Not included by Silvestri et al.[92]

†PPV could not be estimated because the study evaluated with neuroimaging only those patients in whom clinical examination findings were negative.

dering the test cost-ineffective.[154] Eighteen studies[31,100,105,107–109,137,152,153,155,156,158–164] evaluated the ability of clinical evaluation to detect brain metastases in comparison to CT in 1,830 patients (Table 6). Nine studies[31,107,137,152,153,155,158,159,164] limited enrollment to patients with a negative clinical evaluation. In these studies, the median prevalence of brain metastasis was 3% (range, 0 to 21%), and the median predictive value of a negative clinical evaluation finding was 97% (range, 79 to 100%). Nine other studies[100,105,108,109,156,160–163] enrolled patients with both positive and negative clinical evaluation findings. In these studies, the median prevalence of brain metastasis was higher (14%; range, 6 to 32%). The pooled sensitivity and specificity were 76% (95% CI, 61 to 87%) and 82% (95% CI, 69 to 91%), respectively.

An association among brain metastases, N2 disease in the chest, and adenocarcinoma histology has been described.[108,157,158] The rate of false-negative findings on CT scans wherein patients return with brain metastases within 12 months of the original scan is reported to be 3%.[158] False-positive scan results can be a problem in up to 11% of patients due to brain abscesses, gliomas, and other lesions[165]; therefore, biopsy may be essential in patients in whom management is critically dependent on the histology of the brain lesion.

MRI is more sensitive than CT scanning of the brain and picks up more lesions and smaller lesions,[166] but in some studies[164] this has not translated into a clinically meaningful difference in terms of survival. While studies show that MRI can identify additional lesions in patients with metastases, there are no studies that show that MRI is able to identify more patients with metastases from lung cancer compared to CT scanning. Therefore, CT scanning is an acceptable modality for evaluating patients for metastatic disease. If the primary lesion is more advanced than T1N0M0, MRI with contrast can identify asymptomatic, verifiable metastases to the brain in 22% of patients with NSCLC and surgically resectable thoracic disease.[167] However, the use of routine MRI in staging NSCLC patients with negative clinical evaluation findings has not been adequately studied to date; a role in patients with large cell carcinoma or stage III adenocarcinoma has been suggested.[168]

Many of the shortcomings of PET scans in imaging the brain have been alluded to. In addition, performance has been suboptimal, with sensitivity as low as 60%,[28] and occasional false-negative imaging findings of even sizable brain metastases.[169] One study[30] has suggested that PET scanning with ^{11}C-labeled choline may be far superior to the usual ^{18}F-FDG PET scanning for imaging brain metastases. In general, PET scanning is not considered to be reliable for detecting brain metastases.

Detection of Bone Metastases

The problem of false-positive scan abnormalities in radionuclide bone scintigraphy is particularly nettlesome, owing to the frequency of degenerative and traumatic skeletal damage and the difficulty in obtaining a definitive diagnosis via follow-up imaging or biopsy. False-positive bone imaging findings also occur with MRI, which may be no more accurate than nuclear bone imaging.[167] Eight studies examined the ability of the clinical evaluation to detect bone metastases in 723 patients using bone scanning as the reference standard (Table 7).[101–103,105,109,137,170,171] Two studies[102,137] limited enrollment to patients with negative clinical evaluation findings. In one study[102] that included patients with both SCLC and NSCLC, the prevalence and NPV were 16% and 84%, respectively. In a subsequent study[137] of patients with NSCLC, the prevalence and NPV were 30% and 70%, respectively. Six studies[101,103,105,109,170,171] enrolled patients with both positive and negative clin-

Table 7—*Utility of the Clinical Evaluation in Detecting Bone Metastases Using Radionuclide Bone Scanning as the Reference Standard*

Study/Year	Patients, No.	Histology	Routine Scan?	Sensitivity	Specificity	PPV	NPV	Prevalence
Bilgin et al[105]/2002	90	NSCLC	Yes	0.44	0.57	0.10	0.90	0.10
Michel et al[171]/1991	110	NSCLC	No	1.00	0.54	0.16	1.00	0.08
Tornyos et al[170]/1991	50	NSCLC	Yes	0.88	0.30	0.39	0.83	0.34
Salvatierra et al[109]/1990	146	NSCLC	No	0.79	0.88	0.50	0.97	0.13
Osada et al[137]/1987	66	NSCLC	Yes			*	0.70	0.30
Turner and Haggith[102]/1981	55	NSCLC/SCLC	No			*	0.84	0.16
Hooper et al[101]/1978	155	NSCLC/SCLC	No	0.90	0.40	0.36	0.92	0.27
Ramsdell et al[103]/1977	51	NSCLC	No	0.90	0.98	0.90	0.98	0.20
Summary	723			0.82 (0.57–0.94)	0.62 (0.32–0.85)	0.32	0.90	0.20

*PPV could not be estimated because the study evaluated with neuroimaging only those patients in whom the clinical examination findings were negative.

ical evaluation findings. In these studies, the median prevalence of bone metastasis was 16% (range, 8 to 27%), and the pooled sensitivity and specificity were 87% and 67%, respectively.

Using radionuclide bone scanning as the reference standard, the pooled negative predicted value of the clinical assessment was 90% (95% CI, 86 to 93%). The relatively high frequency of unsuspected positive scan findings has led some investigators[170] to recommend routine bone scanning in all preoperative patients. This concept is supported by the results of a study[172] in which 27% of asymptomatic patients were found to have skeletal metastases. False-negative findings on a bone scan can also be a problem, and in one series[171] skeletal metastases developed within 1 year in 6% of patients who had an initially negative bone scan result. PET scanning appears to have excellent performance characteristics in assessing bone metastases, with specificity, sensitivity, NPV, PPV, and accuracy all exceeding 90%,[28,126] though false-positive and false-negative findings are occasionally seen.[28,42,131] The accuracy of PET scanning surpassed that of radionuclide bone scanning in two direct comparative studies.[172,173]

Pleural/Lung Metastases

The limited data suggest that PET scanning can be useful in identifying lung metastases[28,174] and malignant pleural effusions[175,176] in NSCLC patients, though much of the data pertains to nonpulmonary malignancies. False-positive and false-negative findings have occasionally been noted.[30,175,177,178]

Recommendations

7. For patients with either a known or suspected lung cancer, a thorough clinical evaluation similar to that listed in Table 4 should be performed. Grade of recommendation, 1B

8. Patients with abnormal clinical evaluations should undergo imaging for extrathoracic metastases. Site-specific symptoms warrant a directed evaluation of that site with the most appropriate study (*eg*, head CT scanning/MRI plus either whole-body PET scanning or bone scanning plus abdominal CT scanning). Grade of recommendation, 1B

9. Routine imaging for extrathoracic metastases (*eg*, head CT scanning/MRI plus either whole-body PET scanning or bone scanning plus abdominal CT scanning) should be performed in patients with clinical stage IIIA and IIIB disease (even if they have negative clinical evaluation findings). Grade of recommendation, 2C

10. Patients with imaging study findings that are consistent with distant metastases should not be excluded from potentially curative treatment without tissue confirmation or overwhelming clinical and radiographic evidence of metastases. Grade of recommendation, 1B

Summary

CT scanning of the chest is useful in providing anatomic detail that better identifies the location of the tumor, its proximity to local structures, and whether or not lymph nodes in the mediastinum are enlarged. Unfortunately, the accuracy of chest CT scanning in differentiating benign from malignant lymph nodes in the mediastinum is unacceptably low. Whole-body PET scanning provides functional information on tissue activity, and has much better sensitivity and specificity than chest CT scanning for staging lung cancer in the mediastinum. In addition, distant metastatic disease can be detected by PET scanning. Still, positive findings on PET scans can occur as a result of nonmalignant etiologies (*eg*, infections), so tissue sampling to confirm suspected metastasis is usually required.

The clinical evaluation tool, that is, a thorough history and physical examination, remains the best predictor of distant metastatic disease. If the clinical evaluation finding is negative, then imaging studies such as CT scans of the head, bone scans, or abdominal CT scans are unnecessary and the search for metastatic disease is complete. If the signs, symptoms, or findings from the physical examination suggest malignancy, then sequential imaging, starting with the most appropriate study based on the clues obtained by the clinical evaluation, should be performed.

Abnormalities detected by any of the aforementioned imaging studies are not always cancer. Unless overwhelming evidence of metastatic disease is present on an imaging study, and where it will make a difference in treatment, all abnormal scan findings require tissue confirmation of malignancy so that patients are not denied the opportunity to have potentially curative treatment.

Summary of Recommendations

1. For patients with either a known or suspected lung cancer who are eligible for treatment, a CT scan of the chest with contrast including the upper abdomen (liver and adrenal glands) should be performed. Grade of recommendation, 1B

2. In patients with enlarged discrete mediastinal lymph nodes seen on CT scans (*ie*, > 1 cm on the short axis) and no evidence of metastatic disease, further evaluation of the mediastinum should be performed prior to definitive treatment of the primary tumor. Grade of recommendation, 1B

3. PET scanning to evaluate for mediastinal and extrathoracic staging should be considered in patients with clinical 1A lung cancer being treated with curative intent. Grade of recommendation, 2C

4. Patients with clinical 1B-IIIB lung cancer being treated with curative intent, should undergo PET scanning (where available) for mediastinal and extrathoracic staging. Grade of recommendation, IB

5. In patients with an abnormal result on FDG-PET scans, further evaluation of the mediastinum with sampling of the abnormal lymph node should be performed prior to surgical resection of the primary tumor. Grade of recommendation, 1B

6. For patients with either a known or suspected lung cancer who are eligible for treatment, an MRI of the chest should not be routinely performed for staging the mediastinum. MRI may be useful in patients with NSCLC in whom there is concern for involvement of the superior sulcus or brachial plexus. Grade of recommendation, 1B

7. For patients with either a known or suspected lung cancer, a thorough clinical evaluation similar to that listed in Table 4 should be performed. Grade of recommendation, 1B

8. Patients with abnormal clinical evaluation findings should undergo imaging for extrathoracic metastases. Site-specific symptoms warrant a directed evaluation of that site with the most appropriate study (*eg*, head CT scanning/MRI plus either whole-body PET scanning or bone scanning plus abdominal CT scanning). Grade of recommendation,1B

9. Routine imaging for extrathoracic metastases (*eg*, head CT scanning/MRI plus either whole-body PET scanning or bone scanning plus abdominal CT scanning) should be performed in patients with clinical stage IIIA and IIIB disease (even if they have a negative clinical evaluation finding). Grade of recommendation, 2C

10. Patients with imaging study findings that are consistent with distant metastases should not be excluded from potentially curative treatment without tissue confirmation or overwhelming clinical and radiographic evidence of metastases. Grade of recommendation, 1B

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Invasive Mediastinal Staging of Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **The treatment of non-small cell lung cancer (NSCLC) is determined by accurate definition of the stage. If there are no distant metastases, the status of the mediastinal lymph nodes is critical. Although imaging studies can provide some guidance, in many situations invasive staging is necessary. Many different complementary techniques are available.**
Methods: **The current guidelines and medical literature that are applicable to this issue were identified by computerized search and were evaluated using standardized methods. Recommendations were framed using the approach described by the Health and Science Policy Committee of the American College of Chest Physicians.**
Results: **Performance characteristics of invasive staging interventions are defined. However, a direct comparison of these results is not warranted because the patients selected for these procedures have been different. It is crucial to define patient groups, and to define the need for an invasive test and selection of the best test based on this.**
Conclusions: **In patients with extensive mediastinal infiltration, invasive staging is not needed. In patients with discrete node enlargement, staging by CT or positron emission tomography (PET) scanning is not sufficiently accurate. The sensitivity of various techniques is similar in this setting, although the false-negative (FN) rate of needle techniques is higher than that for mediastinoscopy. In patients with a stage II or a central tumor, invasive staging of the mediastinal nodes is necessary. Mediastinoscopy is generally preferable because of the higher FN rates of needle techniques in the setting of normal-sized lymph nodes. Patients with a peripheral clinical stage I NSCLC do not usually need invasive confirmation of mediastinal nodes unless a PET scan finding is positive in the nodes. The staging of patients with left upper lobe tumors should include an assessment of the aortopulmonary window lymph nodes.** ***(CHEST 2007; 132:202S–220S)***

Key words: anterior mediastinotomy; bronchoscopy; Chamberlain procedure; clinical staging; endobronchial ultrasound; esophageal ultrasound; mediastinal lymph nodes; mediastinoscopy; N2; N3; pathologic staging; staging; transbronchial needle aspiration; transthoracic needle aspiration; video-assisted thoracic surgery

Abbreviations: APW = aortopulmonary window; EBUS = endobronchial ultrasound; EUS = endoscopic ultrasound; FN = false negative; FP = false positive; LUL = left upper lobe; NA = needle aspiration; NSCLC = non-small cell lung cancer; PET = positron emission tomography; SCLC = small cell lung cancer; TBNA = transbronchial needle aspiration; TTNA = transthoracic needle aspiration; VATS = video-assisted thoracic surgery

This chapter addresses invasive procedures for confirmatory staging of the mediastinum in patients with lung cancer. The focus is on patients in whom there is a strong suspicion of lung cancer. Such a presumptive clinical diagnosis is generally possible by an experienced clinician after an assessment of risk factors, and a review of the clinical presentation and the radiographic appearance on a CT scan. If the presence of distant metastatic disease has been ruled out, the status of the mediastinum becomes the crucial factor in selecting the optimal treatment strategy. The initial clinical evaluation (*ie*, clinical presentation and CT scan findings) already yields a presumptive clinical stage with respect to the mediastinum, which may have been

Table 1—*Techniques of Invasive Mediastinal Staging*

Mediastinoscopy
EUS-NA
TBNA
EBUS-NA
TTNA
VATS staging
Chamberlain procedure
Extended cervical mediastinoscopy

supplemented by a positron emission tomography (PET) scan as well. However, noninvasive imaging tests can provide only a suspicion that involvement of the mediastinal nodes is present or absent, and in many clinical situations confirmation of the status of these nodes by an invasive test is necessary. The reliability of noninvasive tests is discussed in chapter 12 in this supplement. This chapter discusses the performance characteristics of the various invasive staging tests for the mediastinum, how to select a test, and how to interpret the results.

Several invasive tests are available to stage the mediastinum (Table 1). These include mediastinoscopy, the Chamberlain procedure (also known as an *anterior mediastinotomy*), transthoracic needle aspiration (TTNA) of the mediastinum, transbronchial needle aspiration (TBNA), endobronchial ultrasound (EBUS) with needle aspiration (NA), esophageal endoscopic ultrasound (EUS) with NA, and video-assisted thoracic surgery (VATS), which is also known as *thoracoscopy*. Invasive tests are also sometimes needed to confirm or exclude distant metastases, but these are not discussed in this chapter.

The invasive procedures listed in Table 1 are often needed to more accurately confirm the presumptive mediastinal stage, but they are also sometimes used simply to confirm the diagnosis of malignancy. This distinction is important because these are two entirely different situations, involving patients with very different tumor characteristics, with different test parameters that are of great importance, and therefore with differences in which test should be selected. For example, an invasive test in a patient with massive mediastinal infiltration by a malignancy is performed primarily for the purpose of diagnosis. In this case, the test to confirm the diagnosis is usually selected based on what can be accomplished more easily (both technically and for the patient), and the choice is driven primarily by patient-specific issues rather than the test-specific performance characteristics. On the other hand, in many patients invasive tests are needed to confirm the mediastinal stage. In this case, the choice of procedure is governed by how reliably the test will define the absence or presence of nodal involvement (*ie*, the test performance characteristics, and specifically the false-negative (FN) and false-positive (FP) rates for results of the test).

Obviously, in many situations an invasive test can provide both confirmation of the diagnosis and confirmation of the stage at the same time. This fact underlies the importance of not immediately pursuing a diagnostic test in patients but rather thinking through the presumptive diagnosis, the presumptive stage, and the need for further confirmatory staging tests first.

In general, patients with lung cancer can be separated into four groups (Table 2) with respect to intrathoracic radiographic characteristics (including both the primary tumor and the mediastinum), as was discussed in chapter 12 on noninvasive staging.

Table 2—*Definition of Radiographic Groups With Respect to Intrathoracic Radiographic Characteristics*

Group	Description	Definition
A	Mediastinal infiltration	Tumor mass within the mediastinum such that discrete lymph nodes cannot be distinguished or measured*
B	Enlarged discrete mediastinal nodes	Discrete mediastinal nodes ≥ 1 cm in short-axis diameter on a transverse CT scan image
C	Clinical stage II or central stage I tumor	Normal mediastinal nodes (< 1 cm) but enlarged N1 nodes (≥ 1 cm) or a central tumor (within proximal one third of the hemithorax)
D	Peripheral clinical stage I tumor	Normal mediastinal and N1 nodes (< 1 cm) and a peripheral tumor (within outer two thirds of hemithorax)

*This does not include a tumor mass within the lung that is abutting the mediastinum and tangentially involving the mediastinal pleura or fat (this situation pertains to the T stage of the primary tumor and not the N stage of the mediastinum).

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Briefly, the groups consist of patients with extensive mediastinal infiltration (radiographic group A), patients with enlargement of discrete mediastinal nodes the size of which can be measured (radiographic group B), patients with normal mediastinal nodes determined by CT scan but with a central tumor or suspected N1 disease (radiographic group C), and patients with normal mediastinal nodes and a peripheral clinical stage I tumor (radiographic group D).

The definition of the four radiographic groups is useful for several reasons. As described in chapter 12, it is helpful in determining the chance of finding distant metastases despite a negative clinical evaluation, as well as the FP and FN rates of the CT and PET scan predictions of mediastinal node involvement. In addition, the separation into radiographic groups helps to guide the choice of an invasive test and the performance characteristics of these tests. The radiographic groups are defined by the anatomic characteristics found on a CT scan for several reasons. First, a CT scan is relatively inexpensive and is essentially always performed as a preliminary step in order to define the nature of a pulmonary abnormality and to arrive at a clinical diagnosis of suspected lung cancer. Second, the technical reasons for choosing one invasive approach over another are governed primarily by anatomic factors (*ie*, the location and size of the nodes) rather than by metabolic factors (*ie*, PET scan uptake).

The interpretation and application of the results of invasive staging procedures are difficult because the published data are defined by patients who have undergone a particular test, rather than by radiographic or clinical criteria that could be used prospectively to select patients for a particular approach. The patients who have undergone a particular procedure are a mix of the different radiographic groups just discussed, and often include patients in whom the primary issue was confirmation of the diagnosis, those in whom it was confirmation of nodal involvement, and those in whom it was confirmation of the lack of nodal involvement. Furthermore, the location of suspected nodal involvement influences which test is performed because some nodal stations are easily accessible by one test and not by another. Therefore, the patient cohorts included in series of particular invasive procedures are likely not the same. This makes a comparison of the sensitivity and specificity of the different tests inappropriate. However, we have attempted to make a loose comparison for patients in particular radiographic subgroups, with recognition that this assessment must be taken with a large grain of salt. In addition, the amount of experience is very likely to affect the performance characteristics of a procedure and must also be taken into account in choosing an invasive staging procedure in a specific practice setting. At any rate, it is best to view the different invasive staging tests as complementary and not competitive.

The approach taken in this chapter is to summarize the performance characteristics of each invasive test first, with the recognition that the patients included in studies of a particular test are generally poorly defined, and that direct comparisons between tests are inappropriate. This is followed by a somewhat speculative discussion about which types of patients were included and an analysis of the test results for particular subgroups, whenever this is possible. Finally, the last section uses the available data and the nuances of patient subgroups to attempt to define an integrated approach for use in invasive staging tests of the mediastinum.

It must be emphasized that all of the tests discussed in this chapter are used to refine the clinical stage as defined by the American Joint Committee on Cancer. The clinical stage is the stage that is determined using all information available prior to any treatment, and thus is the most useful staging classification in actual practice. The information available may be limited (*ie*, involving only a chest CT scan) or extensive (*ie*, involving invasive procedures). An invasive staging procedure is still considered to be part of clinical staging, even though it may involve a surgical procedure (*ie*, mediastinoscopy) and evaluation by a pathologist. The pathologic stage is applicable only to patients who have undergone surgical resection, including an accurate assessment of potential areas of spread (such as lymph nodes) by the surgeon and the pathologist. In general, the pathologic stage is viewed as the closest approximation to the true stage, but is useful only for postoperative prognostication, and is not applicable during patient evaluation and selection of a treatment strategy.

Materials and Methods

The data presented here are based on a systematic search and evaluation of the published literature from January 1980 through June 2006. Articles published prior to July 2001 were identified according to the criteria laid out in the previous version of the American College of Chest Physicians lung cancer guidelines.[1] Subsequent literature was identified by the authors using the same search strategy and selection criteria (briefly, studies published in the English language, peer-reviewed, nonoverlapping, having at least 20 patients, containing an adequate assessment of the true nodal status, and with the ability to calculate performance characteristics).[1]

The data abstraction was performed for patients suspected of having lung cancer (*eg*, non-small cell lung cancer [NSCLC] and small cell lung cancer [SCLC]). Patients suspected of a diagnosis other than lung cancer were excluded from the study, where possible. A definite diagnosis of any lung cancer in the medias-

tinal tissues was considered to be positive, while other diagnoses (*eg*, benign disease or lymphoma) were coded as negative for lung cancer. Equivocal test results were considered to be negative. Biopsies that were aborted or yielded insufficient tissue are included as negative findings and are counted as such in the statistics. The reported feasibility of the test is also reported (*ie*, the proportion of patients undergoing the test in whom an adequate biopsy was able to be obtained) in order to have an assessment of the technical success rate. The calculation of the subtotal or total summary performance characteristics was accomplished by the calculation of an average of the values (*eg*, of sensitivity and specificity) from each study; in other words, no weighting according to study size was performed. This was chosen for simplicity, and because a comparison of the results using both methods revealed minimal differences (*ie*, 1 to 2 percentage points).

Various parameters can be used to assess the reliability of a test, including sensitivity, specificity, and FN and FP rates (typically expressed as a percentage). The latter two measures are sometimes expressed in a less intuitive manner as the converse, known as the negative predictive value (1 – FN rate) or the positive predictive value (1 – FP rate). Sensitivity and specificity are derived from patient populations in whom the true disease status is already known, who either all have or do not have the condition in question. These parameters provide data about how often the test results will be positive or negative for these respective populations. Thus, these measures provide information about the test, because the disease status has already been determined in the patients. In theory, these measures can be used to compare different tests, provided the patient populations in which the tests are used are the same. Unfortunately, particularly with regard to invasive staging tests, the patients selected for different tests are not the same, limiting the value of the measures of sensitivity and specificity. Furthermore, the FN and FP rates are of much greater practical use to the clinician, who must interpret the reliability of a test result (positive or negative) in an individual patient. The clinician does not know the true disease status of the patient, only that the patient falls within the group of those with a negative or positive test result. It is important to point out that the FN rate or FP rate of the test cannot be estimated from the sensitivity or specificity, because these are each derived from different formulas. This is a common misconception that frequently creates confusion and inappropriate interpretation of the test results. The only exception to this fact is in the case of "perfect" test performance (*ie*, a sensitivity of 100% does, in fact, imply an FN rate of 0%, and a specificity of 100% implies an FP rate of 0%).

This chapter focuses on the clinician's viewpoint and therefore places an emphasis on the FN and FP rates. The clinician is caring for individual patients. From this perspective, a test is useful if one is comfortable basing treatment decisions on the result, because it is sufficiently predictive of the true disease status in that patient.

Techniques of Invasive Mediastinal Staging

Mediastinoscopy

Mediastinoscopy is performed in the operating room, usually under general anesthesia, and in most United States centers patients are discharged from the hospital the same day.[2–4] The procedure involves an incision just above the suprasternal notch, insertion of a mediastinoscope alongside the trachea, and biopsy of the mediastinal nodes. Rates of morbidity and mortality as a result of this procedure are low (2% and 0.08%, respectively).[5] Right and left high and low paratracheal nodes (stations 2R, 2L, 4R, and 4L), pretracheal nodes (stations 1 and 3), and anterior subcarinal nodes (station 7) are accessible via this approach. Node groups that cannot be biopsied with this technique include posterior subcarinal nodes (station 7), inferior mediastinal nodes (stations 8 and 9), aortopulmonary window (APW) nodes (station 5), and anterior mediastinal nodes (station 6). The availability of a videomediastinoscope allows better visualization, more extensive sampling (including posterior station 7), and even performance of a complete lymph node dissection through this approach.[6,7]

The average sensitivity of mediastinoscopy to detect mediastinal node involvement from cancer is approximately 80%, and the average FN rate is approximately 10% (Table 3).[6,8,12,13,15,16,77–88] Several authors[8–13] have shown that approximately half (range, 42 to 57%) of the FN cases were due to nodes that were not accessible by the mediastinoscope. The FN rate at mediastinoscopy is probably also affected by the diligence with which nodes are dissected and sampled at mediastinoscopy. Ideally, five nodal stations (stations 2R, 4R, 7, 4L, and 2L) should routinely be examined, with at least one node sampled from each station unless none are present after actual dissection in the region of a particular node station. Videomediastinoscopy appears to yield some improvement in sensitivity (90%) and FN rates (7%).[6,13,14] The specificity and the FP rates of mediastinoscopy are reported to be 100% and 0%, respectively. Strictly speaking, these values cannot really be assessed because patients with a positive biopsy finding were not subjected to any further procedures (such as thoracotomy) to confirm the results. Nevertheless, it seems reasonable to assume that the FP rate is low. Few studies have reported feasibility, but in general it appears to be quite high.

The patients included in these series have had potentially operable, nonmetastatic lung cancer with very few exceptions. The majority of these patients were in the radiographic groups B, C, and D. Only a few studies have reported on specific subgroups of patients. In patients with peripheral clinical stage I tumors, the sensitivity was found to be approximately 45%, the FN rate 8%, and the prevalence 15%.[15,16] Thus, mediastinoscopy appears to be very good in ruling out mediastinal node involvement in patients with normal-sized nodes (because of the low FN rate). An explanation for the lower sensitivity in this population is not readily apparent, but underscores

Table 3—*Cervical Mediastinoscopy in Lung Cancer Patients

Study/Year	Patients, No.	Patient Type	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Hammoud et al[12]/1999	1,369	cI–III	100	85	100	0	8	36	?% SCLC
Coughlin et al[8]/1985	1,259	cI–III		92	100	0	3	29	4% SCLC
Luke et al[77]/1986	1,000	cI–III		85	100	0	9	39	12% SCLC
De Leyn et al[78]/1996	500	cI–III		76	100	0	13	39	NSCLC only
Lardinois[13]/2003	181	cI–III		87	100	0	8	34	VMS
Brion et al[79]/1985	153	cI–III		67	100	0	15	35	5% SCLC
Jolly et al[80]/1991	136	cI–III		92	100	0	9	54	7% SCLC
Ratto et al[81]/1990	123	cI–III		88	100	0	6	33	NSCLC only
Ebner et al[82]/1999	116	cI–III	96	81	100	0	18	50	11% SCLC
Gdeedo et al[83]/1997	100	cI–III		78	100	0	9	32	NSCLC only
Deneffe et al[84]/1983	124	cI–III	100	68	100	0	12	31	NSCLC only
Aaby et al[85]/1995	57	cI–III		84	100	0	11	44	NSCLC only
Subtotal	5,118	cI–III		82	100	0	10	38	
Pagé et al[86]/1987	345	cII–III†		73	100	0	20	48	18% SCLC
Dillemans et al[87]/1994	331	cII,III†		72	100	0	16	41	NSCLC only
Kimura[14]/2003	125	cII–III		85	100	0	8	36	VMS
Ríordáin et al[88]/1991	74	cII–III†		81	100	0	16	50	3% SCLC
Vennisac[6]/2003	154	cIII	100	97	100	0	6	71	VMS
Subtotal	1,029	cII–III		82	100	0	13	49	
Choi et al[15]/2003	291	cI		44	100	0	9	15	NSCLC
Gürses[16]/2002	67	cN0		40	100	0	7	15	
Subtotal	358	cI		42	100	0	8	15	
Total	6,505			78	100	0	11	39	

*VMS = videomediastinoscopy; ? = not defined.
†Excluded peripheral cI; included central, cII, and cIII.

the need for caution in extrapolating the performance characteristics of a test derived from one patient population to another population.

EUS-NA

EUS-NA of mediastinal lymph nodes through the wall of the esophagus has been performed with a negligible risk of infection or bleeding. Only one complication (transient fever) has been reported among 6 studies involving 369 patients.[17–22] No mortality has been reported. This technique is particularly useful for inferior pulmonary ligament, esophageal, subcarinal, and APW nodes (stations 9, 8, 7, and 5). Nodes that are anterolateral to the trachea (stations 2R, 2L, 4R, and 4L) are difficult to sample reliably (but are more commonly involved with lung cancer). This procedure requires a skilled endoscopist with specific experience and the necessary equipment, which is becoming more commonly available at many tertiary referral centers.

Sixteen studies[17–24,26–29,31,34,89,90] met the inclusion criteria and assessed the use of EUS-NA in the mediastinal staging of 973 evaluable lung cancer patients (Table 4). There are no data regarding the feasibility of EUS-NA, but it is assumed to be high for well-selected patients at experienced centers. For the detection of malignant mediastinal (*ie*, N2 or N3) lymph nodes, the overall sensitivity was 84%, and the overall FN rate was 19% (range, 0 to 61%). The overall specificity was 99.5%, and the overall FP rate was 0.4%, but only one study[23] truly allowed the evaluation of these performance characteristics because it is the only study in which a positive result was investigated further. In this study, a surgical excision of lymph nodes that were positive, as determined by EUS-NA, was performed; a specificity of 97% and an FP rate of 7% were found.[23] Interestingly, this is the same as the average FP rate for TBNA in those studies that have assessed this.

The patients included in these studies had NSCLC without evidence of distant metastases. Most of the patients had enlarged lymph nodes, which is further corroborated by an overall prevalence of disease of 61% (exactly what is predicted by a CT scan FP rate of 40%). Furthermore, it must be remembered that patients undergoing EUS were generally selected because they had suspected nodal involvement in locations amenable to EUS-NA. Thus, the population undergoing EUS has been

Table 4—*EUS-NA of the Mediastinum in Lung Cancer Patients

Study/Year	Patients, No.	Patient Type	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Annema et al[34]/2005	193	cN0–3†	100	90	100	0	27	79	
Annema et al[29]/2004	36	?		93	100	0	20	78	All PET+
Caddy et al[89]/2005	33	?	100	91	100	0	15	67	
Fritscher-Ravens et al[90]/2003	33	cN0–3†	100	88	100	0	11	48	Excluding bulky nodes
Larsen et al[27]/2005	55	cN0–3†		92	100	0	6	47	
Subtotal	350	cN0–3	100	91	100	0	16	64	
Wallace et al[22]/2001	107	cN2,3‡	100	87	100	0	32	79	7% SCLC
Annema et al[23]/2005	93	cN2,3	100	71	97	7	15	38	
Kramer et al[21]/2004	81	cN2,3‡	100	72	100	0	61	85	
Wiersema et al[20]/2001	33	cN2,3	100	100	88	4	0	76	9% SCLC
Larsen et al[28]/2002	29	cN2,3		90	100	0	18	69	
Silvestri et al[19]/1996	26	cN2,3‡		88	100	0	18	65	19% SCLC
Fritscher-Ravens et al[18]/2000	25	cN2,3		96	§	§	§	§	42% SCLC
Gress et al[17]/1997	24	cN2,3	100	93	100	0	10	63	
Subtotal	418	cN2,3	100	87	98	2	22	68	
Eloubeidi et al[26]/2005	104	cN0,1‖	100	93	100	0	4	38	Prior negative mediastinoscopy findings
Wallace et al[24]/2004	64	cN0,1	100	61	100	0	18	36	
LeBlanc et al[31]/2005	67	cN0,1	100	45	100	0	21	33	
Subtotal	235	cN0,1	100	66	100	0	14	36	
Total	1,003			84	99.5	0.7	19	61	

*See Table 3 for abbreviations not used in the text.
†Approximately 60% cN,3.
‡80% cN2,3.
§Not defined because all subjects had mediastinal disease.
‖Some patients had enlarged nodes but negative mediastinoscopy findings.

primarily in radiographic group B, only some in group C, and probably fewer in group A. However, it is clear that nodes that are < 1 cm can be sampled using this technique.[18,22]

Some studies[17,19–22,24–30] have reported on more specific groups of patients. Among patients with enlarged lymph nodes seen on CT scan, the sensitivity is 87% and the FN rate is 22% (specificity, 98%; FP rate, 2%). In these studies, the prevalence of N2,3 involvement was 68%. Among patients with normal-sized lymph nodes seen on CT scans, the sensitivity is 66% and the FN rate is 14% (specificity, 100%; FP rate, 0%).[24,31] In these studies, the prevalence of N2 or N3 disease was 36%, which is higher than the expected rate (20 to 25%) based on the CT scan data for normal-sized mediastinal nodes, even for patients with central tumors or cN1 involvement.[32] Thus, it can be surmised that many of these patients were selected based on PET scan positivity. Nevertheless, it is reasonable to assume that the performance characteristics of EUS-NA apply broadly to patients with cN0,1 tumors, because the technical issues are probably governed by the size of the nodes and should be relatively unaffected by PET scan results.

Emerging data suggest that the combination of EUS-NA and EBUS-NA may allow complementary and nearly complete access to all mediastinal lymph node stations. One study found a sensitivity of 97% and an FN rate of 2% for combined EUS and EBUS in a population with a prevalence of mediastinal metastases of 42%.[33] The ability to perform both procedures in a single session is appealing, although there are many unresolved issues regarding the training and availability of personnel with combined endoscopic and bronchoscopic expertise.

EUS-FNA is also capable of detecting metastatic disease to subdiaphragmatic sites such as the left adrenal gland, celiac lymph nodes, and the liver. The overall yield is 4% (37 of 834 patients) for such M1 disease detected by EUS-NA.[18,20,23,24,26,27,31,34] The actual performance characteristics for the detection of M1 disease by EUS-NA cannot be calculated because patients generally do no undergo exploration of the abdomen.

EUS is also capable of evaluating the presence of direct tumor invasion into the mediastinum (T4). Eight studies[18,23,24,26,27,31,34,35] have evaluated the prevalence of T4 disease, but only one study[35] has

specifically evaluated the reliability of EUS for T staging. This study found a sensitivity of 88%, a specificity of 98%, an FN rate of 1%, and an FP rate of 30%. Overstaging appeared to occur when a tumor was seen only to invade the mediastinal soft tissues. The FP rate was 0% if a tumor was seen within a blood vessel or the esophagus. Thus, although EUS can be helpful in determining the T stage, the high FP rate, in general, limits the basing of treatment decisions on this test.

The cost of EUS is less than surgical staging procedures, probably due to the ability to perform EUS without general anesthesia in an ambulatory setting. Two studies[36,37] have suggested that EUS may be more cost-effective compared to mediastinoscopy, although these studies assumed that mediastinoscopy frequently required inpatient hospital admission.

TBNA

TBNA, also known as a Wang NA, can be performed safely with no significant morbidity. It can be performed on an outpatient basis, as is the case with most bronchoscopic procedures. TBNA is used most frequently to assess subcarinal nodes. Paratracheal lymph nodes may also be biopsied with TBNA, but these are sometimes more difficult to access, due to the difficulty in sufficiently angulating the bronchoscope and the needle. It has been reported[38–41] that it is feasible to obtain adequate specimens via TBNA in approximately 80 to 90% of cases.

Seventeen studies[38–42,44,91–101] met the inclusion criteria for mediastinal staging with TBNA (Table 5). The overall sensitivity was 78% with values ranging from 14 to 100%. The average FN rate was approximately 28% (range, 0 to 66%). The reported specificity and FP rates were 100% and 0%, respectively, although few studies confirmed positive TBNA results with further invasive procedures. Occasional FP results have been reported in series[42–44] in which this has been specifically examined with a confirmatory test (average, 7%).

The patients included in studies of TBNA have

Table 5—*TBNA of the Mediastinum in Lung Cancer Patients**

Study/Year	Patients, No.	Patient Type	Technique	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Harrow et al[91]/2000	264	cN1–3	Flex TBNA (various ga)	100	93	100	0	16	72	22% SCLC
Bilaceroglu et al[38]/1998	134	cN1–3	Rigid/flex TBNA (18 and 21 ga)	100	75	100	0	64	88	18% SCLC
Hermens et al[92]/2003	106	cN1–3	Flex TBNA (19 ga)	100	98	100	0	7	60	26% SCLC
Rong and Cui[93]/1998	44	cN1–3	CT-guided flex TBNA (? ga)	100	100	100	0	0	66	10% SCLC
Patelli et al[94]/2002†	183	cN2.3	Flex TBNA (19 and 22 ga)	100	98	100	0	17	67	0% SCLC
Schenk et al[44]/1986	88	cN2.3	Flex TBNA (22 ga)	100	50	96	11	25	39	17% SCLC
Vansteenkiste et al[39]/1994	80	cN2	Transcarin rigid TBNA (17 ga)	100	79	100	0	45	79	18% SCLC
Katis et al[95]/1998	76	cN2.3	Flex TBNA (20 and 21 ga)	100	74	100	0	(90)‡	95	50% SCLC
Schenk et al[111]/1993	64	cN2.3	Flex TBNA (19 vs 22 ga)	100	91	100	0	18	86	27% SCLC
Utz et al[96]/1993§	61	cN2	Transcarin flex TBNA (cyto vs histo needle)	100	56	100	0	(100)‡	100	33% SCLC
Rodríguez de Castro et al[40]/1995	56	cN2.3	Flex TBNA (22 ga)	100	77	100	0	19	70	23% SCLC
Ratto et al[42]/1988	47	cN2	Transcarin flex TBNA (21 ga)	100	14	100	0	27	30	8% SCLC
Wang et al[97]/1983	39	cN2.3	Flex TBNA	100	76	100	0	29	86	21% SCLC
Schenk et al[98]/1989	29	cN2.3	Flexible TBNA (18 ga)	100	80	100	0	66	86	28% SCLC
Selcuk and Firat[99]/2003	27	cN2,3	Flex TBNA (22 ga)	100	100	100	0	(0)‡	100	56% SCLC
Garpestad et al[41]/2001	21	cN2.3	CT scan fluoro-guided flex TBNA (22 and 19 ga)	86	83	100	0	33	57	17% SCLC
Wilsher and Gurley[100]/1996	20	cN2,3	Rigid TBNA (? ga)	100	90	100	0	(100)‡	100	15% SCLC
Summary	1,339				78	99	1	28	75	

*cyto = cytology; flex = flexible; fluoro = fluoroscopy; ga = gauge; histo = histology; transcarin = transcarinal; transtrach = transtracheal. See Table 3 for abbreviation not used in the text.

†Analyzed by the number of TBNA biopsies performed rather than the number of patients.

‡Excluded from calculations because NPV is relatively less reliable with a prevalence of > 90%.

§Patients with negative TBNA findings and lack of surgical confirmation were excluded from analysis.

generally had a very high prevalence of N2,3 involvement, and the general implication is that the mediastinal nodes have been markedly enlarged, although the specifics about node size are generally vague. The results should not be applied to patients without extensive mediastinal involvement. Furthermore, the high FN rate makes this test less useful for staging of the mediastinum in patients with normal-sized nodes. Positive TBNA results fairly reliably demonstrate mediastinal node involvement. Negative TBNA results, however, cannot sufficiently exclude mediastinal nodal involvement, and additional staging procedures should be performed.

EBUS-NA

EBUS-NA is a relatively new technique for mediastinal staging. Initially, EBUS was accomplished by introducing a catheter with an ultrasound transducer at the tip of the catheter through the working channel of the bronchoscope. The lymph node was localized with the probe, and the catheter was then withdrawn. The lymph node would then be sampled with TBNA without real-time guidance. More recently, a bronchoscope with a convex ultrasound probe has been developed that allows for real-time ultrasound-guided TBNA.[45] EBUS-NA can be used to sample the highest mediastinal, upper and lower paratracheal, and subcarinal lymph nodes, as well as hilar lymph nodes.

Eight studies[46,47,101–105,112] met the inclusion criteria for mediastinal staging with EBUS-NA (see Table 6). The overall sensitivity was 90%, with values ranging from 79 to 95%. The average FN rate in general was 24% (range, 1 to 37%). One study[46] with an extremely high FN rate (89%) was excluded from this calculation. This FN rate is explained by an extremely high disease prevalence (98%), because extremely high (or low) prevalence makes the FN rate (or FP rate) unreliable purely on mathematical grounds.[32] The specificity and FP rates were 100% and 0%, respectively, but these values are artificial because positive EBUS-NA results were not confirmed.

The studies using EBUS have for the most part involved patients with discrete lymph node enlargement (patients in radiographic group B and some in groups A and C), which is consistent with a disease prevalence of approximately 70%. Although including many patients with lymph nodes < 2 cm, studies to date have not published performance characteristics of EBUS-NA in lymph nodes 1 to 2 cm in size vs lymph nodes > 2 cm in size. One multiinstitutional study[47] has specifically focused on patients with lymph nodes between 0.5 and 1 cm. This study demonstrated an extremely low FN rate of 1%. This supports a general sense that real-time imaging of nodes with EBUS and the immediate proximity of nodes to the airway holds a great deal of promise for this staging method, even in small nodes. However, at this point the experience with this technique is limited to only a few centers, and whether such excellent results in normal-sized nodes can be corroborated in other studies is not known. It is counterintuitive that the FN rate would be so low in normal-sized nodes if it has generally been found to be around 25% with this technique in studies that have primarily included patients with enlarged nodes. Until this is better defined, it is suggested that negative EBUS-NA biopsy results in most centers be confirmed by additional staging modalities.

TTNA

TTNA or biopsy for the diagnosis and staging of the mediastinum is distinct from TTNA of parenchy-

Table 6—*EBUS-NA of the Mediastinum in Lung Cancer Patients**

Study/Year	Patients, No.	Patient Type	Technique	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Herth et al[46]/2006	502	cI-III	RT-US bronch (22 ga)		94	100	0	(89)†	98	25% SCLC
Yasufuku et al[101]/2005	108	cII–III	RT-US bronch (22 ga)	100	95	100	0	11	69	16% SCLC
Yasufuku et al[102]/2004	70	cII–III	RT-US bronch (22 ga)	100	95	100	0	10	67	14% SCLC, 22% other cancers
Vilmann et al[103]/2005‡	31	cII–III	RT-US bronch (22 ga)	100	85	100	0	28	65	?% of SCLC
Rintoul et al[112]/2005	20	cII–III	RT-US bronch (22 ga)	100	79	100	0	30	70	14% SCLC
Kanoh et al[104]/2005	54	cII–III	Catheter probe (19 ga)	100	86	100	0	37	81	30% SCLC
Plat et al[105]/2006	33	cII–III	Catheter (histo needle)		93	100	0	25	82	19% SCLC
Herth et al[47]/2006	100	cI	RT-US bronch 22 ga		94	100	0	1	17	
Summary	918				90	100	0	20	68	

*RT-US bronch = real-time ultrasound bronchoscope. See Tables 3 and 5 for abbreviations not used in the text.

†Excluded from calculations because NPV is relatively less reliable with a prevalence of $> 90\%$.

‡Both EBUS-NA and EUS-NA were performed in each patient. Only values from EBUS-NA were used in calculating the summary statistics.

Table 7—*TTNA of the Mediastinum in Lung Cancer Patients**

Study/Year	Patients, No.	Patient Type	Technique	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Westcott[106]/1981	72	cN2,3†	CT scan-guided (20–22 ga)		94	‡	‡	‡	‡	?% SCLC
de Gregorio et al[107]/1991	48	cN2,3†	Fluoro-guided (18–22 ga)	92	72	100	0	(58)§	90	SCLC + other cancer
Moinuddin et al[108]/1984	40	cN2,3†	CT scan-guided (18–20 ga)	91	100	100	0	0	78	48% SCLC
Protopapas and Westcott[109]/1996	32	cN2,3	CT scan-guided (20 ga)		100	100	0	(0)§	91	16% SCLC
Böcking et al[110]/1995	23	cN2,3	CT scan-guided (22 ga)	87	80	100	0	0	65	
Summary	215				89	100	0		81	

*See Tables 3 and 5 for abbreviation not used in the text.
†Bulky masses, corresponding to radiographic group A.
‡Not defined because all subjects had mediastinal disease.
§Excluded from calculations because NPV is relatively less reliable with a prevalence of > 90%.

mal masses to achieve a diagnosis. The ability to carry out TTNA for the diagnosis and staging of cancer in the mediastinum has generally been reported to be high (*ie*, > 90%), although approximately 10% of patients require the placement of a catheter for the evacuation of a pneumothorax.[32] The sensitivity has generally been reported to be approximately 90% (see Table 7).[106–110]

Patients selected for this procedure have generally had quite extensive mediastinal involvement (patients in radiographic group A, with some patients in group B). The mediastinal lymph nodes have generally been at least 1.5 cm in size. This is also supported by the fact that the prevalence of cancer in the mediastinal nodes was very high (*ie*, > 80%). Furthermore, only about 75% of the patients had lung cancer (despite excluding studies in which only a minority of patients had lung cancer). Therefore, these results are most applicable to patients with mediastinal infiltration or bulky mediastinal involvement, in whom the purpose of the procedure was probably primarily to confirm the diagnosis and less likely to confirm the stage. Extrapolation of these results to patients with lesser amounts of mediastinal spread for staging purposes may be inappropriate. Furthermore, the practical aspects of TTNA make this test unsuited for the biopsy of multiple mediastinal nodes such as would be needed in patients in radiographic groups C, D, and even B.

VATS

Thoracoscopy, also known as VATS, can be used to access mediastinal nodes. This is done under general anesthesia and in general is limited to an assessment of only one side of the mediastinum. Access to the R-sided nodes is straightforward, but access to the L paratracheal nodes is more difficult. Several series have shown the feasibility of this technique. No mortality has been reported from VATS for mediastinal staging, and complications were noted in only 12 of 669 patients (average, 2%; range, 0 to 9%).[48–55]

The performance characteristics of VATS mediastinal node biopsy for N2 node staging are shown in Table 8. The sensitivity varies widely, from 37 to 100%. The reason for this variation is not entirely clear. Even if the studies are restricted to patients with enlarged nodes, the sensitivity still ranges from 50 to 100%. The low sensitivity comes primarily from a study by Sebastian-Quetglas et al[49] This study is the only prospective, multiinstitutional study, and may perhaps be more generally applicable than the results from single institutions with a focused interest and extensive experience. It should be noted that VATS staging was feasible in only 75% of patients in this series. The performance characteristics recorded here are those that apply specifically to determination of mediastinal node status. The FN rate is 15% both in enlarged and normal-sized nodes. In all reports, the specificity is reported as 100% and the FP rate as 0%, but this is technically not evaluable because no further testing was done in the event of a positive VATS result.

VATS can also be useful for further evaluation of the T stage as determined radiographically. This is primarily useful in detecting or ruling out T4 lesions that preclude resection. In patients with radiographically suspected T4 involvement this has been shown to be absent in 38% of patients (29 to 50%) in three studies.[49,50,55] Furthermore, in patients with a cytologically negative pleural effusion, 40% were shown

Table 8—*Thoracoscopic (VATS) Assessment of the Mediastinal Nodes in Lung Cancer Patients*

Study/Year	Patients, No.	Patient Type	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Sebastian-Quetglas et al[49]/2003	105	All	75	37	100	0	20	29	
Roberts et al[53]/1999	50	All	100	38	100	0	11	16	All had negative mediastinoscopy results
Subtotal	155			38	100	0	15	25	
Sebastian-Quetglas et al[49]/2003	30	cN2	63	50	100	0	58	73	
Eggeling et al[50]/2002	73	cN2, cT4	100	99	100	0	4	70	VATS combined with medication
Massone et al[48]/2003	53	cN2		100	100	0	0	64	
Landreneau et al[52]/1993	33	cN2		100	100	0	0	42	All had negative mediastinoscopy results
Subtotal	189			87	100	0	15	64	
Sebastian-Quetglas et al[49]/2003	75	cN0	80	0			32	11	
Total*	419			75	100	0	7	44	

*Patients depicted in several different rows from the same study were not counted twice in the calculations.

not to be due to malignant involvement by VATS.[55] On the other hand, routine VATS found unsuspected pleural studding in 4% of patients (0 to 5%) in several studies.[48–51,54,56] An unsuspected malignant pleural effusion was also found in 6% of patients in one study.[53] Most of the patients in these studies regarding pleural involvement had CT scan evidence of discrete node enlargement.

Assessment of APW Lymph Nodes

Cancers in the left upper lobe (LUL) have a predilection for involvement of the nodes in the APW (station 5). These nodes are classified as mediastinal nodes and represent the most important group of N2 nodes that are not accessible by standard cervical mediastinoscopy. It has been suggested[57] that nodes in this region should not be viewed as mediastinal nodes and that the resection of patients should be performed regardless of APW node involvement, making the assessment of these nodes superfluous. This was based on a selected subgroup of 23 completely resected patients who had APW node involvement as the only site of N2 disease. However, the analysis of all of the data in this regard shows that the survival of patients with only APW node involvement is not substantially different than that of patients with involvement of only a single N2 node station in another location.[58] Therefore, the issue is more a matter of whether patients with involvement of a single mediastinal node station should undergo surgical resection, and not whether APW nodes should be classified as N2 nodes.

The classic way of invasively assessing this area is a Chamberlain procedure (also known as an *anterior mediastinotomy*), which involves an incision in the second or third intercostal space just to the left of the sternum. Traditionally, an overnight hospital stay has been necessary, but in many institutions this is no longer found to be necessary, especially as surgeons have used visualization between the ribs more frequently as opposed to removal of a costal cartilage.

Table 9—*Anterior Mediastinotomy in Lung Cancer Patients*

Study/Year	Patients, No.	Patient Type	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Anterior mediastinotomy alone									
Best et al[60]/1987	39	cIII		63	100	0	0	77	> 21% SCLC
Pagé et al[86]/1987	45	cII–III		86	100	0	11	47	18% SCLC
Standard cervical mediastinoscopy alone									
Pagé et al[86]/1987	345	cII–III		73	100	0	20	48	18% SCLC
Deneffe et al[84]/1983	124	cII–III	100	68	100	0	12	31	NSCLC only
Anterior mediastinotomy + standard cervical mediastinoscopy									
Pagé et al[86]/987	32	cII–III		87	100	0	11	47	18% SCLC
Deneffe et al[84]/1983	39	cII–III	100	87	100	0	8	38	NSCLC only

The reliability of this procedure has not been extensively documented, despite its common use. The sensitivity of a Chamberlain procedure in addition to standard cervical mediastinoscopy in patients with LUL tumors is approximately 87%, and the FN rate is approximately 10% (Table 9). Two additional studies[59,60] regarding this procedure have not really addressed the reliability of the procedure for the staging of NSCLC. In one study,[59] no actual biopsies were performed in most patients, and the procedure was used to assess resectability (in this series, resectable patients included those with bulky APW nodal involvement). The other study[60] used anterior mediastinotomy primarily for diagnosis (not staging), and included pulmonary biopsies and evaluation of patients with mediastinal masses. In fact, only a minority of patients included in this study had lung cancer.

Extended cervical mediastinoscopy offers an alternative method for the invasive assessment of APW nodes, but it is used in only a few institutions (see Table 10). With this procedure, a mediastinoscope is inserted through the suprasternal notch and is directed lateral to the aortic arch.[61] In 100 consecutive patients with LUL cancers, standard mediastinoscopy and extended mediastinoscopy were found to have a sensitivity of 69% and an FN rate of 11% for the detection of N2,3 disease (prevalence, 29%).[61] Similar results (sensitivity, 81%; FN rate, 9%) were reported in another series[62] of 93 such patients, all of whom had enlarged APW nodes. In approximately 550 patients who were undergoing extended cervical mediastinoscopy, two major complications (stroke, 1 patient; aortic injury, 1 patient) have been reported.[61–65]

Thoracoscopy has been used to assess APW lymph nodes. The general results for this technique are reported in Table 8. Specific results for stations 5 and 6 have not been reported, but are likely to be better because these node stations are much easier to access than any of the other mediastinal node stations. EUS-NA also provides an alternative method of sampling APW nodes (see previous "EUS-NA" subsection). Data addressing the reliability of this procedure specifically for APW nodes in patients with LUL tumors are not available. In general, however, the sensitivity of this test is very high, although the FN rate is high enough to potentially be an issue.

The patients included in these series of Chamberlain procedure or extended cervical mediastinoscopy have had potentially operable lung cancer with very few exceptions. These patients are primarily from radiographic group B, with probably a few from group C. The reported results provide data regarding the reliability of these tests for the staging of mediastinal nodes compared to thoracotomy in patients with lung cancer.

Other Staging Procedures

In patients with signs of advanced disease, clinical scenarios often occur that indicate the need for other invasive procedures to be performed, such as NA of a supraclavicular lymph node, thoracentesis or thoracoscopy of a pleural effusion, or NA or biopsy of a metastatic site such as an enlarged adrenal or hepatic mass. The indications for such procedures are covered in more detail in the chapters on diagnosis[9] and noninvasive staging,[12] and specific recommendations regarding such procedures can be found in these chapters as well. In brief, if an enlarged supraclavicular lymph node or a pleural effusion is present, it is generally prudent to pursue a diagnosis of these lesions. When the clinical presentation is entirely consistent with locally advanced disease (stage IIIb), these procedures are usually indicated because they represent the easiest way to confirm the diagnosis of lung cancer. When the clinical presentation is otherwise not consistent with locally advanced disease,

Table 10—*Extended Cervical Mediastinoscopy in Lung Cancer Patients

Study/Year	Patients, No.	Patient Type	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Anterior mediastinotomy alone									
Freixinet Gilart et al[62]/2000	106	cII,III	NR	33	100	0	38	0.48	5% SCLC
Ginsberg et al[61]/1987	100			52	100	0	16	0.29	LUL NSCLC only
Standard cervical mediastinoscopy alone									
Freixinet Gilart et al[62]/2000	106	cII,III	NR	51	100	0	31	0.48	5% SCLC
Ginsberg et al[61]/1987	100			45	100	0	18	0.29	LUL NSCLC only
Anterior mediastinotomy + standard cervical mediastinoscopy									
Freixinet Gilart et al[62]/2000	106	cII,III	NR	76	100	0	18	0.48	5% SCLC
Ginsberg et al[61]/1987	100			69	100	0	11	0.29	LUL NSCLC only

*See Table 9 for abbreviation not used in the text.

the etiology of these lesions must be established in order to accurately define the stage. However, the procedures used to diagnose an enlarged supraclavicular node (*ie*, NA or surgical biopsy) are the same regardless of whether the issue is to confirm the diagnosis or to define the stage. Similarly, in patients with a clinical presentation that is consistent with advanced disease (stage IV), an invasive procedure may be indicated as the easiest way to confirm the diagnosis and establish the cell type of the lung cancer. In patients with a solitary site that is suspicious for a distant metastasis or in patients with a clinical presentation that seems inconsistent with advanced disease, an invasive procedure is indicated to accurately define the stage. The procedures used to assess possible distant sites are the same regardless of the clinical presentation, and are dictated primarily by technical and anatomic factors that are specific to the particular patient.

No data are available to assess the sensitivity, specificity, and FN and FP rates of NA of a supraclavicular node. General experience indicates that this procedure is usually successful; in addition, surgical biopsy of such a node is easily accomplished if a NA procedure is not diagnostic. The reliability of procedures to diagnose a pleural effusion is covered in the chapter on diagnosis. Thoracentesis has a sensitivity of approximately 60%; thoracoscopy has a sensitivity of $>95\%$. Procedures to diagnose suspected distant metastatic sites are too varied to discuss in detail; furthermore, no data are available that expressly assesses the reliability of these tests in patients with lung cancer.

Approach to Patients

Mediastinal Infiltration

In patients with extensive mediastinal infiltration, the radiographic evidence of mediastinal involvement is quite universally considered adequate. There are no data to prove this, because invasive confirmation is not done. However, even though staging is not an issue, tissue is needed to confirm the diagnosis and to establish what type of cancer is present (*eg*, NSCLC vs SCLC). In this case, it does not matter whether tissue is obtained from the primary tumor or from a mediastinal site.

In patients in whom the diagnosis is the primary issue, tissues should be obtained by whatever method is easiest to perform. In other words, the choice of procedure will be governed primarily by patient-specific factors (*ie*, anatomic, convenience, and comorbidity factors) instead of the performance characteristics of a test. For example, it is still likely that a test of relatively low sensitivity such as sputum cytology or cytology of a pleural effusion will be chosen first simply because it is easiest to perform. It is rare that such a patient will undergo TBNA, EUS-NA, or mediastinoscopy. Details of the performance characteristics of diagnostics tests of the primary tumor are summarized in chapter 9, and performance characteristics of the invasive mediastinal tests are summarized in the tables here. However, as noted above, the determining factor concerning which test to choose will be governed primarily by patient-specific issues.

Recommendation

1. For patients with extensive mediastinal infiltration of tumor and no distant metastases, radiographic (CT scan) assessment of the mediastinal stage is usually sufficient without invasive confirmation. Grade of recommendation, 2C

Discrete Mediastinal Lymph Node Enlargement

Many patients present with a CT scan demonstrating the enlargement of discrete mediastinal (N2,3) lymph nodes. An extensive literature[32] demonstrates that enlargement seen on CT scan alone carries an FP rate of approximately 40% (see chapter 12). The PET scan literature has only recently become detailed enough to begin to define FN and FP rates in subgroups of patients such as those with discrete nodal enlargement seen on a CT scan. The FP rate for PET scanning in the mediastinum has been widely shown to be around 15 to 20%, although this has not been defined for this particular subgroup of patients. Two metaanalyses[66,67] have estimated the PET FN rate to be 13 to 25% in patients with nodal enlargement detected by CT scan, although these estimates are not based on direct data or clearly defined patients. Direct data from studies[68,69] in patients with mediastinal or hilar nodal enlargement (radiographic groups B and C combined) have found a PET FN rate of 20 to 28% for N2,3 involvement. Thus, it appears that in patients with enlarged mediastinal nodes detected by CT scanning, the CT scan alone cannot be relied on, and invasive biopsy is needed whether a PET scan finding is positive or negative.

In choosing an invasive staging test, several issues must be considered. First is the availability of different procedures. All of the invasive tests require some specialized experience and skill, and people who perform these procedures only occasionally may not be able to achieve the performance characteristics published in studies performed at high-volume institutions. Second, the location of the suspicious nodes is important, because nodes in one location may be

accessible only by a particular approach. There may be factors related to patient comorbidity that may argue against certain approaches, such as mediastinoscopy, which usually requires general anesthesia. However, patients who are unable to tolerate a general anesthetic for such a small procedure as mediastinoscopy are likely not to be well enough to tolerate definitive treatment for lung cancer anyhow. The morbidity and mortality of invasive procedures may be a consideration, although all of the available procedures generally have an excellent safety profile. Finally, cost may be a consideration.

The sensitivity of various invasive mediastinal staging tests in cN2,3 patients appears to be similar. A strict comparison is not justified because the patients undergoing these procedures are not comparable due to differences in how they are selected for a particular procedure (*eg*, the location of the nodes). The primary issue is the variability in FN rates. If a NA technique is chosen, it must be remembered that a negative result is not very reliable. A NA procedure may well be a good first choice because these procedures are less invasive than mediastinoscopy. However, a negative needle biopsy finding should be followed up in general with mediastinoscopy.

An option for the treatment of patients with stage III NSCLC is induction therapy followed by surgery (see chapter 17). If this approach is chosen, the role of mediastinal restaging after induction therapy is very unclear. However, some people have argued that the approach should include surgery only in those patients who have a response in the mediastinum to induction therapy. It has been shown repeatedly[70] that CT scan evidence of tumor shrinkage is notoriously misleading. PET scanning for mediastinal restaging has also been shown to have high FP and FN rates.[70] A repeat mediastinoscopy is generally safe and feasible (82 to 100%) but has mediocre results (sensitivity, 70 to 82%; FN rate, 15 to 25%),[13,71–73] and most surgeons are uncomfortable with this procedure. Because a first-time mediastinoscopy is probably the best way to accomplish mediastinal restaging, an argument can be made to use a NA technique initially to document N2,3 involvement and to save mediastinoscopy for the restaging procedure after induction therapy. All of this only applies if the adopted treatment policy is one of induction therapy, with subsequent therapy to be determined by the results of mediastinal restaging (despite the lack of data defining the role of surgery and restaging).

Recommendations

2. For patients with discrete mediastinal lymph node enlargement (and no distant metastases), invasive confirmation of the radiographic stage is recommended (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes). Grade of recommendation, 1B

3. For patients with discrete mediastinal lymph node enlargement (and no distant metastases), many invasive techniques for the confirmation of the N2,3 node status are suggested as reasonable approaches (*eg*, mediastinoscopy, EUS-NA, TBNA, EBUS-NA, or TTNA), given the appropriate experience and skill (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes). Grade of recommendation, 1B

4. For patients with discrete mediastinal lymph node enlargement (and no distant metastases), a nonmalignant result from a needle technique (*eg*, EUS-NA, TBNA, EBUS-NA, or TTNA) should be further confirmed by mediastinoscopy (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes). Grade of recommendation, 1C

Central and Clinical N1 Tumors

Patients with no evidence of mediastinal node enlargement but with a central tumor or N1 node involvement represent another distinct group (group C). It is reasonable to consider patients with central tumors together with those with N1 node enlargement, because it is usually difficult to assess the N1 nodes in the case of a central tumor. Extensive data indicate that the FN rate of a CT scan with respect to the mediastinal nodes is 20 to 25% (see chapter 12 on noninvasive staging).[32] More limited data demonstrate that the FN rate for PET scanning in the mediastinal nodes in this situation is similarly high (24 to 83%).[68,69,74,75] Thus, invasive staging is required in these patients despite the negative CT scan result and even a negative PET scan result.

In patients with normal-sized mediastinal lymph nodes in whom invasive staging is needed, mediastinoscopy remains the "gold standard." The general experience with mediastinoscopy suggests that the FN rate (approximately 10%) is low in these patients, and those studies[15,16] that have specifically reported on these patients substantiate this. Although it cannot be directly compared to mediastinoscopy, the FN rate (20%) of EUS-NA demonstrates that a significant number of patients with negative EUS-NA finding may still harbor metastases. Subgroup analysis in the study by Wallace et al[24] has suggested that approximately one half of these FN cases were due to malignant lymph nodes in the anterior mediastinum, which may be more accessible by mediastinoscopy or, theoretically, EBUS-NA, although to date this area has not been carefully

studied. The other half of FN cases were often due to very small deposits that may be more subject to sampling error of the needle or small biopsy methods.

Other methods of mediastinal staging have generally not been used much in this patient population (*ie*, TTNA, TBNA, and EBUS-NA). However, the performance characteristics of these tests, especially the FN rates, in patients with enlarged mediastinal nodes would suggest that TTNA, TBNA, and EBUS-NA are likely not to perform as well as mediastinoscopy in patients with normal-sized nodes. This is particularly true with regard to the FN rates. Because the goal of invasive staging in this situation is to confirm the absence of mediastinal disease, the FN rate is the parameter of greatest importance. It does not appear that the NA techniques can confirm a negative mediastinum finding with sufficient reliability. EBUS-NA may turn out to be sufficiently reliable to rule out mediastinal node involvement in small nodes, but the data are too preliminary to justify a firm recommendation.[47]

Recommendations

5. For patients with a radiographically normal mediastinum (by CT scan) and a central tumor or N1 lymph node enlargement (and no distant metastases), invasive confirmation of the radiographic stage is recommended (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes). Grade of recommendation, 1C

6. For patients with a central tumor or N1 lymph node enlargement (and no distant metastases), invasive staging is recommended. In general, mediastinoscopy is suggested, but EUS-NA or EBUS-NA may be a reasonable alternative if nondiagnostic results are followed by mediastinoscopy. Grade of recommendation, 2C

Peripheral Clinical Stage I Tumors

Patients with peripheral tumors in whom there is no enlargement of N1 or N2,3 nodes seen on CT scans, the FN rate of this radiographic assessment in the mediastinum is approximately 10%.[32] The incidence is lower in patients with T1 tumors (9%) than in those with T2 tumors (13%).[32] Whether this incidence is viewed as being high enough to justify performing mediastinoscopy or PET scanning is a matter of judgment. A negative PET scan finding in the mediastinum carries a FN rate of approximately 5% (range, 3 to 6%) in this group of patients.[68,74–76] Thus, invasive staging is probably not needed in this patient group if the findings of a PET scan of the mediastinum are negative. A PET scan is generally not needed in the case of a cT1N0M0 tumor (see chapter 12). Invasive staging of the mediastinum is also generally not indicated in these cases.

If invasive staging is deemed to be necessary, it appears that mediastinoscopy is the best choice because of a low FN rate compared to techniques involving NA. The arguments raised concerning the invasive staging of normal mediastinal nodes in cN1 or central tumors (group C) applies to this group (group D) as well, since these arguments are a function primarily of the size of the mediastinal nodes.

Recommendations

7. For patients with a peripheral clinical stage I tumor in whom a PET scan shows uptake in mediastinal nodes (and not distant metastases), invasive staging is recommended. In general, mediastinoscopy is suggested, but EUS-NA or EBUS-NA may be a reasonable alternative if nondiagnostic results are followed by mediastinoscopy. Grade of recommendation, 1C

8. For patients with a peripheral clinical stage I tumor, invasive confirmation of the mediastinal nodes is not needed if the findings of a PET scan of the mediastinum are negative. Grade of recommendation, 1C

Patients With LUL Tumors

Patients with tumors in the LUL deserve special mention because the aortic arch raises technical issues of access to the mediastinal nodes in the APW (station 5). This node station is the most likely mediastinal nodal area to be involved in the case of an LUL tumor, whereas it is extremely unlikely to be involved in patients with a tumor in any of the other lobes. Of course, mediastinal nodal involvement from an LUL tumor can also extend to other node stations such as the subcarinal (station 7) or paratracheal areas (stations 4L, 4R, 2L, and 2 R). A full assessment of potentially involved mediastinal node stations in the case of an LUL tumor requires investigation of the paratracheal and subcarinal nodes, as well as a separate procedure to access the APW area. The technical issues of access to the APW nodes raises questions about whether a separate invasive test for the assessment of these nodes is really necessary.

The definition of radiographic groups (groups A, B, C and D) is the same no matter which lobe of the lung is involved. In addition, the indications for invasive staging of the mediastinum in patients with

LUL tumors should follow the same guidelines as in patients with a tumor in a different lobe (patients with enlarged mediastinal nodes, a central tumor or N1 nodal enlargement and a normal mediastinum, or with evidence of PET scan uptake in mediastinal areas should undergo invasive mediastinal staging).

If the usual mediastinal node stations are found to be negative (stations 2R, 4R, 7, 2L, and 4L), it is controversial whether a separate procedure to assess the station 5 area is needed. However, given the lack of clear data that involvement of only this station carries a different prognosis than involvement of a different single mediastinal node station, and with the availability of techniques of assessing the APW area that are easier for patients to undergo (*eg*, EUS-NA, EBUS-NA, extended cervical mediastinoscopy, and VATS), the guidelines committee favors pursuing an invasive assessment of the APW nodes. A finding of involvement in one mediastinal area may preclude the necessity of biopsying other areas, especially if an additional procedure would be necessary (*eg*, a positive EUS-NA finding for station 5 may preclude the assessment of paratracheal nodes, or a positive mediastinoscopy result would obviate the need for an anterior mediastinotomy).

A comparative assessment of different invasive tests for APW nodes is not possible. A reasonable extrapolation from the data for other node stations would be to pursue a needle technique for enlarged APW nodes and a surgical biopsy (*eg*, Chamberlain procedure, VATS, or extended cervical mediastinoscopy) for normal-sized APW nodes. However, it is also a reasonable compromise to accept a negative NA finding without adding an additional surgical biopsy, given the controversy over the need to assess the APW nodes. Modification of these suggestions may be necessary due to the availability of expertise with the invasive procedures. However, it is suggested that referral to a larger center be considered if there is not a fair amount of expertise with at least one invasive APW staging procedure.

Recommendation

9. For patients with an LUL cancer in whom invasive mediastinal staging is indicated, as defined by the previous recommendations, it is suggested that invasive mediastinal staging include assessment of the APW nodes (via Chamberlain procedure, thoracoscopy, extended cervical mediastinoscopy, EUS-NA, or EBUS-NA) if other mediastinal node stations are found to be uninvolved. Grade of recommendation, 2C

Conclusion

Accurate mediastinal staging is crucial to the selection of the optimal therapy for patients without distant metastases. Imaging studies are not sufficiently reliable in many situations, making invasive staging tests an important part of appropriate staging. Many different invasive staging tests, which should be viewed as complementary to one another because they are applicable to particular nodal stations and patient groups, are available. It is helpful to separate patients into different groups based on the extent of mediastinal involvement by CT scan and whether the primary tumor is central or peripheral. In general, needle techniques are most useful in patients with enlarged mediastinal nodes, while mediastinoscopy remains the "gold standard" in patients with normal-sized nodes.

Summary of Recommendations

1. For patients with extensive mediastinal infiltration of tumor (and no distant metastases), radiographic (CT scan) assessment of the mediastinal stage is usually sufficient without invasive confirmation. Grade of recommendation, 2C

2. For patients with discrete mediastinal lymph node enlargement (and no distant metastases), invasive confirmation of the radiographic stage is recommended (regardless of whether the findings of a PET scan of the mediastinal nodes are positive or negative). Grade of recommendation, 1B

3. For patients with discrete mediastinal lymph node enlargement (and no distant metastases), many invasive techniques for confirmation of the N2,3 node status are suggested as reasonable approaches (mediastinoscopy, EUS-NA, TBNA, EBUS-NA, TTNA), given the availability of personnel with appropriate experience and skill. Grade of recommendation, 1B

4. For patients with discrete mediastinal lymph node enlargement (and no distant metastases), a nonmalignant result from a needle technique (*eg*, EUS-NA, TBNA, EBUS-NA, or TTNA) should be further confirmed by mediastinoscopy (regardless of whether the findings of a PET scan of the mediastinal nodes are positive or negative). Grade of recommendation, 1C **5. For patients with a radiographically normal mediastinum (determined by CT scan) and a**

central tumor or N1 lymph node enlargement (and no distant metastases), invasive-confirmation of the radiographic stage is recommended (regardless of whether the findings of a PET scan of the mediastinal nodes are positive or negative). Grade of recommendation, 1C

6. For patients with a central tumor or N1 lymph node enlargement (and no distant metastases), invasive staging is recommended. In general, mediastinoscopy is suggested, but EUS-NA or EBUS-NA may be a reasonable alternative if nondiagnostic results are followed by mediastinoscopy. Grade of recommendation, 2C

7. For patients with a peripheral clinical stage I tumor in whom a PET scan shows uptake in the mediastinal nodes (and no distant metastases), invasive staging is recommended. In general, mediastinoscopy is suggested, but EUS-NA or EBUS-NA may be a reasonable alternative if nondiagnostic results are followed by mediastinoscopy. Grade of recommendation, 1C

8. For patients with a peripheral clinical stage I tumor, invasive confirmation of the mediastinal nodes is not needed if the findings of a PET scan of the mediastinum are negative. Grade of recommendation, 1C

9. For patients with an LUL cancer in whom invasive mediastinal staging is indicated, as defined by the previous recommendations, it is suggested that invasive mediastinal staging include the assessment of the APW nodes (via Chamberlain procedure, thoracoscopy, extended cervical mediastinoscopy, EUS-NA, or EBUS-NA) if other mediastinal node stations are found to be uninvolved. Grade of recommendation, 2C

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Bronchial Intraepithelial Neoplasia/Early Central Airways Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **An evidence-based approach is necessary for the localization and management of intraepithelial and microinvasive non-small cell lung cancer in the central airways.**
Methods: **Material appropriate to this topic was obtained by literature search of a computerized database. Recommendations were developed by the writing committee and then reviewed by the entire guidelines panel. The final recommendations were made by the Chair and were voted on by the entire committee.**
Results: **White light bronchoscopy has diagnostic limitations in the detection of microinvasive lesions. Autofluorescence bronchoscopy (AFB) is a technique that has been shown to be a sensitive method for detecting these lesions. In patients with moderate dysplasia or worse on sputum cytology and normal chest radiographic findings, bronchoscopy should be performed. If moderate/severe dysplasia or carcinoma *in situ* (CIS) is detected in the central airways, then bronchoscopic surveillance is recommended. The use of AFB is preferred if available. In a patient being considered for curative endobronchial therapy to treat microinvasive lesions, AFB is useful. A number of endobronchial techniques as therapeutic options are available for the management of CIS and can be recommended to patients with inoperable disease. In patients with operable disease, surgery remains the mainstay of treatment, although patients may be counseled about these techniques.**
Conclusions: **AFB is a useful tool for the localization of microinvasive neoplasia. A number of endobronchial techniques available for the curative treatment can be considered first-line therapy in inoperable cases. For operable cases, the techniques may be considered and discussed with the patients.**
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Key words: angiogenic squamous dysplasia; autofluorescence bronchoscopy; carcinoma *in situ*; fiberoptic bronchoscopy; Nd-YAG; photodynamic therapy; radiographically occult lung cancer

Abbreviations: AFB = autofluorescence bronchoscopy; ASD = angiogenic squamous dysplasia; CCD = charged-couple device; CIS = carcinoma *in situ*; FVB = flexible videobronchoscopy; LIFE = light-induced fluorescence endoscopy; NBI = narrow band imaging; NSCLC = non-small cell lung cancer; PDT = photodynamic therapy; SqCC = squamous cell carcinoma; WLB = white light bronchoscopy

The majority of lung cancer cases are diagnosed in a late stage, when nonspecific symptoms such as cough, dyspnea, and hemoptysis are present. Fewer than 15% of patients with invasive lung cancer survive 5 years after treatment. Advances in early diagnostic and treatment options have the potential to manage lung carcinoma while still in an intraepithelial and microinvasive or minimally invasive stage.

White light bronchoscopy (WLB) is one of the most commonly used diagnostic tools for obtaining a definitive diagnosis of lung cancer. However, WLB is limited in its ability to detect small intraepithelial and microinvasive preinvasive lesions, which may be only a few cells thick and might only have a surface diameter of a few millimeters. Autofluorescence bronchoscopy (AFB) was developed to address this limitation by WLB in detecting intraepithelial and microinvasive or preinvasive lung cancer lesions. AFB is now an established technique that has been shown to be a far more sensitive method of detecting these lesions than WLB.

In addition to the development of AFB for the

early diagnosis of intraepithelial and microinvasive or minimally invasive lung carcinoma, there are five techniques available being used to ablate intraepithelial malignant and microinvasive endobronchial malignant lesions without surgical excision. These modalities include Nd-YAG laser therapy, photodynamic therapy (PDT), electrocautery, cryotherapy, and high-dose rate brachytherapy. These may be particularly appropriate treatment options in patients with limited cardiopulmonary reserve.

Materials and Methods

To update previous recommendations on bronchial intraepithelial neoplasia/early central airways lung cancer, guidelines on lung cancer diagnosis and management were identified by a systematic review of the literature (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter). Supplemental material appropriate to this topic was obtained by literature search of a computerized database (MEDLINE) and review of the Thoracic Oncology NetWork reference lists of relevant articles. Recommendations were developed by the section editor and writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), and then reviewed by the entire guidelines panel, including the Chair and the Vice Chair. The final recommendations were developed by the Chair and were voted on by the entire committee. All members of the lung cancer panel approved the chapter before approval by the Thoracic Oncology Network, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.

Material appropriate to this topic was obtained by literature search of a computerized database (MEDLINE) in the English language from January 1966 to January 2006, and review of the relevant articles. The search words that were used were as follows: "carcinoma *in situ*" (CIS), "angiogenic squamous dysplasia" (ASD), "radiographically occult lung cancer," "neodymium yttrium-aluminum-garnet," "photodynamic therapy," "electrocautery," "cryotherapy," "non-small cell lung cancer" (NSCLC), "light-induced fluorescence endoscopy," "white light bronchoscopy," (WLB) "autofluorescence bronchoscopy," (AFB) "flexible videobronchoscopy" (FVB), and "narrow band imaging" (NBI).

For the purposes of this chapter, the reviewed literature was limited to diagnostic and treatment approaches to early stage lung cancer. The definition of an early stage cancer is a roentgenographically occult squamous cell carcinoma (SqCC) that is < 2 cm in surface area, appears superficial endoscopically, has clearly visible margins, and demonstrates no invasion beyond the bronchial cartilage assessed either by histopathology or by available imaging including high-resolution CT or endobronchial ultrasound. Although there is an extensive literature on the detection and treatment of early stage lung cancer, the reported studies consist of small to moderate-size case series. Clinical outcomes in these studies were defined as response to treatment and included complete, partial, or no response. Complete response was defined as no evidence of disease visually as well as on histology and cytology examination. Some studies also included time to tumor recurrence. Relative sensitivity is commonly used in these reports to express the additional value of AFB over WLB when, as in most reports, WLB was performed before AFB by the same observer and the actual prevalence of lesions was unknown. Relative sensitivity is defined as the ratio of the sensitivity of WLB alone or WLB combined with AFB divided by the sensitivity of WLB alone.

Diagnosis of Early Stage Lung Cancer

AFB

Imaging of the central airway mucosa with AFB was developed in the early 1990s at the British Columbia Cancer Research Centre in Vancouver, BC, and proposed as a method to localize high-grade dysplasia (moderate and severe dysplasia), CIS, and minimally invasive SqCC.[1–4] The underlying premise of this technology was that the large area of the central tracheobronchial mucosa comprises the substantial site of the origin of SqCC and early disease in the central airways might not be detected by WLB. This is an important issue because SqCC comprises 17 to 29% of all lung cancers.[5] Previous efforts at imaging these lesions used porphyrin products, which, while allowing better imaging, was limited by skin photosensitivity reactions and did not gain significant acceptance by clinicians.[6]

After Lam et al[7] introduced AFB in 1992, the light-induced fluorescence endoscopy (LIFE) device (Xillix Technologies; Vancouver, BC, Canada) became commercially available in 1998. This system used a helium-cadmium laser to illuminate the bronchial mucosa with 442-nm light. The red and green autofluorescence emitted light was captured by a photomultiplier camera, and a pseudocolor image of the relative red-green intensity in an area is generated in real time by computer. The image was displayed green in normal areas and red-brown in abnormal areas, because of reduced green autofluorescence in abnormal and preneoplastic mucosal lesions.

A multiinstitutional trial[7] of 173 subjects with a total of 700 lesions showed that AFB with the LIFE device identified more abnormalities than WLB. It

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Table 1—*Comparison of WLB vs Combined White Light and LIFE-Lung Bronchoscopy for the Detection of Moderate/Severe Dysplasia and CIS*

Study	Patients, No.	Lesions, No.	Sensitivity, %		Relative Sensitivity	Specificity, %	
			WLB	WLB + AFB		WLB	WLB + AFB
Lam et al[32]	94	77	48	73	1.5	94	94
Lam et al[94]	223	113	39	79	2.0	91	87
Lam et al[7]	173	102	9	56	6.2	90	66
Weigal et al[95]	36	3	0	67		87	48
Kurie et al[96]	39	60		43			57
Kennedy et al[97]	55	77	21	76	3.6		
Venmans et al[98]	33	9	78	100	1.3	88	60
Venmans et al[99]	95	40	70	85	1.2	86	67
Vermylen et al[100]	34	16	25	94	3.8	87	21
Khanavkhar[101]	243	50	28	78	2.8	84	59
Metwally et al[102]	87	14	50	86	1.7	86	63
Thiberville et al[103]	138	76	57	84	1.5	72	48
van Rens et al[104]	72	15	20	100	5	51	4
Yokomise et al[105]	30	14	65	90	1.4	71	77
Ikeda et al[106]	158	84	58	92	1.6	62	66
Shibuya et al[23]	64	45	69	91	1.3	57	32
Sato et al[10]	63	46	61	89	1.5	38	33
Lee et al[107]	62	17	41	100	2.4	89	67
Overall	1,699	858	40	80	2	81	60

was established that AFB provided a 2.71 increase in relative sensitivity compared to WLB alone for localization of moderate dysplasia, severe dysplasia, CIS, and invasive carcinoma.[7] The final World Health Organization classifications of these lesions have been reviewed by a panel of pathologists. When lesions of invasive carcinoma were excluded, the relative sensitivity increased to 6.2. Based on this study,[7] the LIFE device was approved for clinical use by the Food and Drug Administration in 1998 and was subsequently widely used in the United States, Canada, Europe, and Japan (Table 1).[7,10,23,32,94–107] Kurie et al[8] reported no benefit of AFB for the localization of metaplasia or mild dysplasia in a population with relatively low prevalence for high-grade dysplastic lesions or lung cancer.[8] However, many other groups confirmed that AFB provides a significantly increased relative sensitivity for localizing moderate dysplasia, severe dysplasia, and CIS (Table 1). This system is no longer commercially available in the United States. Lam and McWilliams[9] summarized the different methods of inducing and imaging autofluorescence by the current commercially available products.

The populations studied with AFB included patients with symptoms of lung cancer (hemoptysis, cough, chest pain); patients with radiologic evidence of lung cancer; preoperative patients with lung cancer; postoperative patients with no recurrence of tumor after 2 years; patients with postoperative head and neck cancer; and patients with abnormal sputum cytology,[10,11] or abnormal DNA content based on automated microscopy.[12] The patients examined by AFB because of abnormal sputum tended to have the highest yield of high-grade dysplasia (moderate or severe dysplasia) or CIS,[10,13–15] ranging from 19 to 39% of the biopsy specimens.

There are currently three AFB devices approved for use in the United States (Table 2). The Onco-LIFE device (Xillix Technologies; Richmond, BC, Canada) uses a combination of reflectance and fluorescence imaging. A red reflectance image is used in combination with the green fluorescence image to enhance the contrast between malignant and normal

Table 2—*North American Commercially Available Autofluorescence Imaging Systems*

Device	Excitation Light, nm	Detection Range, nm	Image Composition	Suspicious Mucosa
Onco-LIFE	395–445	470–710	Green fluorescence, red reflectance	Brown-red against green background
Storz D-light	380–440	475–800	Dual fluorescence, blue reflectance	Blue-brown against green background
SAFE 1000	420–450	490–590	Green fluorescence	Dark green against lighter green background

tissues. Using reflected red light as a reference has the theoretical advantage over reflected blue light in that it is less absorbed by hemoglobin and, hence, is less influenced by changes in vascularity associated with inflammation. The Storz D-Light system consists of a charged-coupled device (CCD) camera and a filtered Xe lamp (380 to 440 nm). It combines a fluorescence image with a blue reflectance image.[16] The lesions appear purple against a blue-green background. Frame averaging is used to amplify the weak autofluorescence. This system appeared to have similar results to the LIFE system in a comparison study.[17] The Pentax SAFE-1000 system uses a filtered Xe lamp in the 420- to 450-nm range to produce the excitation light, but only detects fluorescence in the green spectrum (490 to 590 nm) using a single image-intensified CCD sensor. Two systems not yet commercially available in the United States include the Pentax SAFE-3000 system (Pentax Medical Co.; Lincoln Park, NJ) and the Wolf system (Richard Wolf Medical Instruments Corp.; Vernon Hills, IL).

The Pentax SAFE-3000 system uses a semiconductor laser diode that emits 408-nm wavelength light for excitation of bronchial mucosa and detects autofluorescence using a single high-sensitivity CCD sensor in the fluorescence spectrum 430 to 700 nm. The Wolf system is similar to the Xillix LIFE-Lung system, with a filtered 300-W Xe lamp in the violet-blue range (390 to 460 nm) and slightly different band-pass filters for detection being 500 to 590 nm (green region) and 600 to 700 nm (red region).[18]

Most of the published data regarding autofluorescence bronchoscopy are with the use of the LIFE-Lung device. However, a large, randomized, controlled, multicenter trial[16] in Europe using the Storz device was recently published, in which subjects were enrolled who were current smokers > 40 years old with at least 20 pack-years of smoking and had either symptoms concerning for lung carcinoma (new cough, hemoptysis, or new dyspnea) or radiologic suspicion for carcinoma. The study[16] randomized 1,173 subjects to WLB only, or to WLB plus AFB examination. The authors reported a low overall yield of high-grade dysplasia or CIS (3.9%) but reaffirmed the increased relative sensitivity of AFB with WLB (5.1%) compared to WLB alone (2.7%) [Tables 3, 4]. The sensitivity for localizing CIS, however, only increased by a factor of 1.24 ($p = 0.75$) with AFB, and only 12 of 2,907 biopsies (0.4%) performed revealed CIS. These highly experienced bronchoscopists likely were able to detect CIS fairly well with WLB. Possible reasons for the low yield may have been the relatively low smoking histories and younger age limit of the patients included, as well as pathology interpretation and quality control by a panel of pathologists, which were not specified.

All studies appear to show a lower specificity with AFB compared to WLB at the expense of higher sensitivity. Although low specificity is seen for most screening technologies, such as mammography and prostate-specific antigen, lower specificity with AFB is somewhat problematic because it might result in more biopsy specimens with AFB and there is a greater cost with AFB than with a minimally invasive screening diagnostic procedure. However, data[19] regarding lesions that are positive on autofluorescence but negative on pathology (false-positive findings) suggest that these lesions are not entirely normal. Increased amounts of chromosomal aberration have been found, suggesting that these lesions may have potential for progression and therefore may not truly be benign lesions (Tables 3, 4).[19] The presence of multiple areas of abnormal autofluorescence, notwithstanding the histopathology grade, appears to be a risk factor for subsequent development of lung cancer. Pasic et al[20] evaluated a group of 46 subjects with either previous aerodigestive cancer or sputum atypia and reported that the presence of two areas of abnormal autofluorescence increased the risk of subsequent lung cancer over the next 4 years compared to subjects with only one suspicious area (50% vs 8%).[20] Therefore, the presence of autofluorescence abnormalities alone may be an indicator of cancer risk and field carcinogenesis.

Videobronchoscopy

The use of AFB and incorporation of the technique into routine clinical practice may improve recognition of bronchial pathology under white light examination. The development of improved white

Table 3—*Comparison of WLB vs Combined White Light and Storz D-Light Bronchoscopy for the Detection of Moderate/Severe Dysplasia and CIS in the Same Patient Group*

Study	Patients, No.	Lesions, No.	Sensitivity, %		Relative Sensitivity	Specificity, %	
			WLB	WLB + AFB		WLB	WLB + AFB
Haussinger et al[16]	589	34	70	82	1.2	59	58

Table 4—*Comparison of WLB vs Combined White Light and Storz D-Light Bronchoscopy for the Detection of Moderate/Severe Dysplasia and CIS in Different Patient Groups*

Study	Patients, No.	Lesions, No.	Sensitivity, %		Relative Sensitivity	Specificity, %	
			WLB	WLB + AFB		WLB	WLB + AFB
Haussinger et al[16]	1,173	53	58	82	1.4	62	58

light imaging technology with videoendoscopy and magnification has challenged the role of AFB. A recent comparison of these two techniques was published by Chhajed et al.[21] The recently evaluated the diagnostic yield with FVB (Olympus BF240; Olympus; Tokyo, Japan) was compared to AFB using the LIFE system and an Olympus BF40 flexible bronchoscope in 151 patients at high risk with sputum atypia of a grade of moderate dysplasia or worse. FVB detected 72% lesions of moderate dysplasia or worse, compared to 96% with AFB. The use of AFB significantly increased the yield of abnormal pathology in areas that were classified as either normal or abnormal using FVB.

There have been further advances in endoscopic imaging technology with the incorporation of optical zoom or magnifying lenses to enhance the examination of the bronchial mucosa. The ability to provide a fourfold-magnified view up to 110 times compared with conventional FVB enabled investigators to better visualize and characterize mucosal vascular patterns that may be secondary to early lung cancer angiogenesis. Shibuya et al[22] performed sequential examinations using WLB and AFB followed by high-magnification FVB in 31 subjects at high risk with an average of 62–pack-year smoking history who presented with dysplasia or carcinoma in their sputum. In biopsies of 43 sites with abnormal AFB findings, a tortuous vascular pattern and high vascular area ratio distinguished between dysplasia in 15 of 21 sites vs bronchitis inflammation in 20 of 22 sites with less tortuous vascular pattern and a lower vascular area ratio.[22–24]

In a follow-up study[25] by the same group involving an additional 48 subjects at high risk with sputum suspicious or diagnostic for malignancy, NBI with selective spectral filtering was added to high-magnification FVB in sequential WLB-AFB, high-magnification FVB, and high-magnification FVB-NBI examinations. NBI conferred additional visual information in the detection of capillary blood vessels seen in ASD.[25] In 67 biopsy samples taken from AFB abnormal sites, a specific "dot" vascular pattern seen under high-magnification FVB-NBI identified ASD with a 78% sensitivity in 18 ASD lesions.[24] Collectively, these studies suggest that improvement in optical and digital imaging by the incorporation of high magnification and selective bandwidth filtering of white light may be complementary to AFB. These techniques may help to identify specific subsets of high-risk preinvasive early lung cancer lesions such as ASD. The introduction of ever higher resolution CCD chips will further enhance the resolution of airway mucosal details.

There may be considerable interobserver variation in the reporting of pathology of these early stage lesions and, despite advancement in molecular biology techniques, as yet there are no accurate predictors of risk of malignant progression. The value of localizing intraepithelial neoplasia is related to the natural history of these lesions, with the possibility of their presence being a marker of malignant risk and the potential for cure by local intervention when malignancy is detected at the earliest possible stage.

Proposed Indications for AFB

Evaluation of Patients with High-Grade Sputum Atypia

Moderate dysplasia, severe dysplasia, CIS, and invasive carcinoma grades in sputum cytology have commonly been used as indicators for AFB examination.[10] Historical studies[26] on sputum cytology showed that 11% of subjects with moderate dysplasia and 19 to 46% with severe dysplasia in sputum progressed to SqCC. Patients with high-grade dysplasia or worse have a high prevalence of preneoplasia and/or neoplasia found with AFB examination.[27] The yield of invasive malignancy is positively related to the cytology grade. There is no controversy that a sputum cytology reading of either invasive cancer or CIS requires further investigation, usually with WLB and CT. Sato et al[28] reported a marked improvement in survival of patients who had a sputum diagnosis of SqCC but who had no radiographic abnormalities. One group was treated with surgical resection (n = 207), and another group with the same diagnosis declined treatment (n = 44). The treated group had a 94.9% survival at 10 years, and the untreated group had a 33.5% survival in the same time period. Severe dysplasia has also been reported to portend a high likelihood of impending clinical cancer.[29,30] Prindiville et al[30] reported that

adjusted risks of lung cancer development for increasing grades of cytologic atypia were 1.0 (normal), 1.10 (mild atypia), 1.68 (moderate atypia), 3.18 (moderate atypia or worse), and 31.4 (worse than moderate atypia). Moderate dysplasia has been associated with increased risk of subsequent cancer in the National Cancer Institute studies.[26] Kennedy et al[14] reported that 79 consecutive subjects with no evidence of malignancy on chest radiograph but moderate dysplasia in sputum who had AFB examination showed lung cancer in 5 subjects (6.3%), with 3 subjects having invasive SqCC and 2 subjects with CIS. An additional seven subjects (8.9%) were found to have severe dysplasia. McWilliams et al[31] reported finding seven cases of CT occult central SqCC in four subjects (CIS, n = 6; microinvasive, n = 1; 1.3%), and a significant yield of high-grade dysplasia (5.7%) with AFB in asymptomatic smokers whose sputum had epithelial cells with an elevated DNA index (> 1.2) when evaluated by quantitative image cytometry.

Recommendation

1. For patients with severe dysplasia, CIS, or carcinoma in sputum cytology but with chest imaging studies showing no localizing abnormality, standard WLB is recommended. AFB should be used when available. Grade of recommendation, 1B

Evaluation of Patients with Suspected, Known or Previous Lung Cancer

AFB can play a useful role in both the delineation of tumor margins and the assessment of the presence of synchronous lesions in patients with early lung cancer who are being evaluated for curative surgical resection.[32–35] Synchronous cancer can be found on AFB in up to 17% of these patients, and up to 44% of patients may also have other moderate/severe dysplastic lesions that will require bronchoscopic follow-up.[32,34,36–38]

Lam et al[32] reported that at least one synchronous site of CIS was detected in 15% of 53 subjects with known lung cancer. Venmans et al[33] detected other sites of moderate dysplasia or worse in 44% subjects with a known site of CIS referred for endobronchial therapy. Pierard et al[38] found that in 43 preoperative lung cancer patients, 9.3% had a synchronous occult CIS, and 19% had dysplasia or worse. Pierard et al[34,38] also found that 23% of 26 patients referred for treatment with high-grade preinvasive lesions or CIS/microinvasive cancer had synchronous severe dysplasia/CIS/microinvasive cancer on AFB. van Rens et al[35] reported the preoperative evaluation of 72 NSCLC patients and found three synchronous NSCLC in three patients (4.2%) and 13 high-grade dysplasia in 10 patients (14%). The discovery of the synchronous carcinoma altered the therapeutic plan in these patients.

After successful curative resection of NSCLC, a high rate (1 to 3%/yr) of second primary (metachronous) tumors has been reported.[40] It is also estimated that 2 to 13% of patients surviving small cell carcinoma per patient per year will have NSCLC develop. In a subset of patients with previous early central SqCC, the reported rate of metachronous lesions appears even higher with up to nearly 30% having a second central carcinoma develop within 4 years.[41,42] Weigel et al[43] reported findings in 31 AFB examinations on 25 patients after complete resection of NSCLC, in which three lesions of moderate/severe dysplasia and one microinvasive cancer developed during an average of 20.5 months postoperative follow-up in 12% of patients The relative sensitivity of AFB over WLB was 3.0. A follow-up report[44] by the same authors with a total of 51 patients found one invasive cancer and three high-grade dysplastic lesions (6% yield) after a median of 13 months after surgery. Three of the four lesions were found in patients with previous SqCC. Pasic et al[20] found that 28% of patients with a previous lung cancer had metachronous central SqCC develop during AFB surveillance within a median of 47 months of follow-up. Moro-Sibilot et al[45] reported that in patients with a previous resected SqCC, 30% had high-grade dysplasia or worse compared to only 4% with a previously resected adenocarcinoma, or 20% overall of resected NSCLC on AFB examination.

Patients who have had either a previous curative resection for NSCLC or successful chemoradiotherapy for small cell lung cancer are at high risk for second lung cancers. Whether AFB may be useful in the long-term follow-up and surveillance in these patients has not been adequately studied (see chapter on "Follow-up and Surveillance of the Lung Cancer Patient Following Curative Intent Therapy"). Patients with previous SqCC may be particularly at high risk for subsequent intraepithelial neoplasia and multiple metachronous central carcinomas.

Patients With Early Central Lung Cancer Eligible for Curative Endobronchial Therapy

When considering an early central carcinoma for curative endobronchial therapy, AFB may play a role in correctly determining the size of the lesion and whether all margins can be visualized. These factors have an important impact on the success of endobronchial treatment, and may not be accurately assessed with WLB. Sutedja et al[46] performed AFB on 23 patients referred for intraluminal therapy of

NSCLC after WLB. In four patients, CT showed the lesions to be too extensive for intraluminal therapy. In the remaining 19 patients, 13 patients (68%) were found to have lesions too extensive for intraluminal therapy by AFB examination. Ikeda et al[47] reported careful dissection of the airways of 30 patients with NSCLC who had preoperative AFB examination and subsequently underwent resection with curative intent. There was better correlation between margins determined by AFB than WLB with histopathologically determined margins.

Recommendation

2. For patients being considered for curative endobronchial therapy to treat CIS in centers where it is available, AFB may be considered to guide therapy. Grade of recommendation, 2C

Follow-up of High-Grade Bronchial Intraepithelial Neoplasia

Longitudinal data using serial bronchoscopy and biopsy in patients with intraepithelial neoplasia detected by AFB have now been reported by a number of authors. In a study by Breuer et al,[48] 52 subjects with either positive sputum cytology findings, previously resected upper respiratory tract cancer, or clinical suspicion for lung cancer had AFB. A total of 134 lesions were followed up: squamous metaplasia (n = 45), mild/moderate dysplasia (n = 64), and severe dysplasia (n = 25). The highest progression rates to CIS/invasive carcinoma were seen in severe dysplasia (32%) vs mild/moderate dysplasia (9%) and metaplasia (9%). The median time to progression was most rapid with severe dysplasia at 16.5 months compared to 21.5 months with all other lesions. Interestingly, many sites were found to show nonstepwise fluctuations between the histologic grades.

In another series published by Bota et al,[49] AFB was performed in 104 patients who were either smokers, had previous asbestos exposure, had a previous curative lung cancer resection, or had a current operable aerodigestive cancer. A total of 380 lesions including hyperplasia/metaplasia (n = 152), mild/moderate dysplasia (n = 169), severe dysplasia (n = 27), and CIS (n = 32) were found and observed for 24 months, although persistent severe dysplasia/CIS lesions were treated at 3 months of follow-up. Severe dysplasia had high rates of progression, with 11% showing progression to CIS/invasive cancer, whereas 3.5% of mild/moderate dysplasia progressed to severe dysplasia, and 2% of hyperplasia/metaplasia showed progression to carcinoma. Many lesions showed regression, including 37% hyperplasia/metaplasia, 60% mild/moderate dysplasia, and 63% of severe dysplasia. In contrast, 75% of CIS persisted and were treated with endobronchial therapy.

The outcome of CIS was also evaluated by Venmans et al[33] when he reported the short-term follow-up of nine subjects with CIS. Some lesions (67%) had initial endobronchial therapy to attempt cure. Overall, 67% of lesions progressed to invasive carcinoma. It is likely that the progression rate would have been higher if some of the lesions had not been treated at initial diagnosis. The same group[20] subsequently reported that a higher prevalence of abnormal AFB sites in a patient predicted a higher probability for development of invasive carcinoma.

Lam et al[50] reported the follow-up of 2,346 lesions detected in 566 subjects who had at least a 20–pack-year smoking history but no previous or current aerodigestive cancer. Lesions ranged from hyperplasia (n = 892), metaplasia (n = 459), mild dysplasia (n = 787), moderate dysplasia (n = 157), and severe dysplasia (n = 51), and there was a mean follow-up of 4.7 years. Eight subjects were found to have eight CIS and two invasive cancers (n = 3) from sites that showed hyperplasia, metaplasia (n = 3), moderate dysplasia (n = 2), or severe dysplasia (n = 3) in their first bronchoscopy. These tumors developed over a median interval of 21 months. Therefore, the progression rate of severe dysplasia to CIS/invasive carcinoma was 6%, and moderate dysplasia was only 1.3%.

Hoshino et al[51] reported follow-up of 99 lesions in 50 subjects who had AFB performed because of either suspicious sputum cytology or previous lung cancer. The lesions included 11 severe, 56 moderate, and 32 mild cases of dysplasia. Overall, only three lesions progressed to carcinoma: two severe (18%), and one moderate (1.7%). However, the mean duration of follow-up was only 6.9 months. Lesions with increased telomerase activity, Ki-67 labeling, and p53 immunoreactivity tended to persist as dysplasia.

George et al[52] reported the results of observation of 51 lesions in 22 subjects with a median follow-up of 23 months (range, 12 to 85 months). The majority of the patients had previous asbestos exposure, known COPD, or previous lung cancer (82%), and they were referred for AFB. High-grade lesions included 7 severe dysplasias and 29 CIS, and low-grade lesions included 17 mild/moderate dysplasias. Progression to invasive cancer was seen in 17% (6 of 36 high-grade lesions), and all of these were previous sites of CIS. Therefore, the progression of CIS to invasive cancer was 21% (6 of 29 lesions) in this series. Only half of these progressive CIS were successfully treated, raising concerns that delay in treatment resulted in a poorer outcome for these patients. Indolence was observed in 64% of

high-grade lesions. However, observation was discontinued early in a significant proportion of these persistent lesions because the subjects underwent other therapy that could have influenced outcomes (*eg*, lobectomy and radiotherapy). No progression was seen in low-grade lesions. Interestingly, five subjects (14%) with high-grade bronchial lesions had remote lung cancers that were detected by CT during the period of observation, suggesting that the presence of bronchial dysplasia may be a marker for overall lung cancer risk as previously noted by Pasic et al.[20]

The variable rates in progression of these preneoplastic lesions may have been attributable to differences in the patient populations evaluated or histopathology reporting. In the report of Lam et al,[50] with lower rates of progression of moderate/severe dysplasia to carcinoma, the subjects were current/former smokers who had no history of aerodigestive cancer or clinical suspicion of cancer. In the study by George et al,[52] who also documented lower rates of progression of intraepithelial neoplasia, only 40% of study subjects had previous lung cancer, and the remainder had either COPD, significant smoking history, or asbestos exposure. Subjects were excluded if they had a clinical suspicion of lung cancer. In the series published,[39,48–51,53] subjects with previous or current aerodigestive cancers or clinical suspicion of lung cancer were included and contributed a significant proportion or all of the population studied. It is well known that patients with a diagnosis of lung cancer or other aerodigestive cancers are at risk for second primary lung cancers, and this subset likely represents a very high-risk group, with subsequent higher observed rates of progression.[48,49,52,53]

Overall, the observed rates of progression to invasive carcinoma of moderate dysplasia range is 0 to 9%, and to severe dysplasia from 0 to 32%. CIS lesions are seen to either persist in $>$ 60% cases with no regression or progress to invasive carcinoma in 20 to 60% cases, despite stopping smoking in some instances. When severe dysplasia and CIS are found, it is suggested that additional focused biopsies in the area of concern be performed to ensure microinvasive carcinoma is not an element of the lesion.

Recommendation

3. For patients with known severe dysplasia or CIS in the central airways, standard WLB is recommended at periodic intervals (3 to 6 months) for follow-up. AFB should be used when available. Grade of recommendation, 2C

Treatment of Early Stage NSCLC

Roentgenographically occult lung cancers can be detected in patients at high risk with either sputum cytology or bronchoscopic inspection. Traditionally, the only treatment available for these cancers was surgical resection. Even though these cancers are small because of their central location, on average approximately 70% of cases require a lobectomy, and the remaining 30% require either a bilobectomy or pneumonectomy for curative intent resection.[54] There are patients with reduced cardiopulmonary reserve who are not candidates for these surgical options. Additionally, 1 to 4% of these patients will have a synchronous lung cancer.[55] Some studies[56–58] report up to 17% of newly diagnosed early lung cancer cases have a synchronous lesion. The risk for second lung cancer ranges from 1 to 25%/yr.[59]

Endobronchial therapies that preserve lung function have been developed and include PDT,[60] brachytherapy,[61] electrocautery,[62] cryotherapy,[58] and Nd-YAG laser therapy.[63] Most roentgenographically occult cancers (*ie*, lung cancers) not detected by either chest radiography or CT are histopathologically SqCC and are located in relatively large central bronchi.[64] The majority of these occult cancers invade the bronchial wall but are not metastatic.[65]

In early stage SqCC, estimating the depth of intrabronchial invasion is a significant challenge, but bronchoscopic evaluation can provide valuable information regarding depth of invasion. Both the size of the lesion and its topographic appearance may determine the depth of penetration. Lesions $<$ 10 mm in greatest dimension with only superficial thickening of the epithelium have been reported to invade beyond the bronchial cartilage in $<$ 5% of cases examined. Those with a nodular or polypoid appearance showed invasion in 18% and 27%, respectively.[66]

Fujimura et al[59] found that in surgically resected roentgenographically occult lesions with endoscopically visible margins, 10% of lesions were $<$ 10 mm in length, 23% of lesions were 10 to 29 mm in length, and 67% lesions were $>$ 30 mm in length and had lymph node involvement. Lesions with margins beyond endoscopic visibility had an increased risk of lymph node involvement. Nakamura et al[41,67] also reported that increasing tumor dimension was associated with increased depth of mural invasion, decreased cure rates, and increased lymph node involvement. Endobronchial ultrasound is available to determine depth of invasion. The accuracy of this approach has been reported to be quite good in determining appropriate candidates for endobronchial therapy.[68,69]

PDT

PDT is based on the interaction of a photosensitizer with light of narrow bandwidth. In the presence of oxygen, tumor death occurs by several mechanisms including vascular shutdown, cell cycle apoptosis, and direct singlet oxygen membrane injury. The majority of clinical data using PDT in early lung cancer have been for treatment of patients who were deemed nonsurgical candidates. The greatest experience has emerged from Japan in the past 2 decades.[55,60,70–78] One hundred forty-five patients with 191 early NSCLCs have been treated with PDT since 1980. This includes 99 patients with stage 0 and 56 patients with stage IA disease. There were 141 men and 4 women. The majority of cases (98%) were SqCC. Complete response was achieved in 86% of lesions, with a recurrence rate of 13%, thereby resulting in a long-term response of 75%. When success of treatment was evaluated according to lesion size, lesions < 1.0 cm had a complete response of 95%, and lesions ≥ 2 cm had a complete response of only 46%. Treatment success was also related to whether the distal margin of the tumor could be clearly seen bronchoscopically. If the margin were visible, a complete response rate of 92% was achieved, compared to 67% if the margins were not visible. If the lesion was < 1.0 cm and the margins were visible, complete response was achieved in 98% of cases.[72,76,77]

Imamura et al[56] studied 29 patients (39 cancers) and achieved complete response in 64% of lesions. Recurrence occurred in 36%, giving a long-term response of 41%. On evaluation of lesion size, 72% of lesions that were < 3 cm^2 achieved a complete response. Ono et al[78] studied 36 patients (39 cancers) and achieved a complete response rate of only 31%, with a recurrence in 33%. Therefore, the long-term response was only 21%. A number of smaller studies[79–82] from Europe and Canada reported complete response rates of 62 to 91%. A multicenter investigator-initiated experience[83] was collated and presented to the Food and Drug Administration for approval of porfimer sodium in the treatment of early superficial SqCC. A total of 102 patients with radiologically occult (stages 0, IA, and IB) SqCC were treated. An overall immediate complete response rate of 78% was achieved (95% confidence interval, 7 to 87%). Forty-four percent of the patients had recurrent tumor on follow-up, giving a long-term response rate of 43%. The median time to tumor recurrence was 2.8 years (range, 0.1 to 10 years). Analysis of the subgroup of the 24 inoperable patients revealed a complete response of 92% (95% confidence interval, 81 to 100%). A similar recurrence rate of 46%, a long-term response rate of 50%, and a median time to tumor recurrence of 2.7 years were observed.

The Mayo Clinic has reported treatment of 58 nonsurgical patients with early lung cancer.[84–90] An 84% complete response rate was achieved after one treatment. Nineteen patients (39%) recurred and had a second PDT treatment. The median time to tumor recurrence after the first treatment was 4.1 years. After the second treatment, 11 patients (22%) had recurrence. The long-term complete response rate was 66%. PDT as an alternative to surgical resection was studied in 21 patients with small bronchial cancers.[88] A 71% complete response (15 of 21 patients) was achieved, with 11 patients (52%) maintaining a complete response > 12 months. Patients who did not respond or recurred were offered surgery. Of the 10 patients who underwent surgery, 3 were found to have N1 disease. Two patients refused surgery. A total of nine patients (43%) were spared surgery.

In summary, PDT is effective in managing small superficial SqCC. The worldwide data showed that patients with early lung cancer treated with PDT achieve a complete response in approximately 75% cases, with a recurrence rate of approximately 30%. Complete response rates $> 90\%$ can be achieved when lesions are small (< 1 cm in diameter), superficial, and all margins can be visualized. Experience remains limited using PDT for patients who are surgical candidates.

Electrocautery

Bronchoscopic electrocautery is the use of high-frequency electrical current that generates heat caused by tissue resistance, resulting in destruction of tissue. A small study[62] in early lung cancer of 13 patients (15 cancers) showed a complete response in 80% of lesions with no recurrence at 22 months of follow-up. Endoscopic treatment has a curative potential for patients with intraluminal microinvasive radiographically occult lung cancer. This is discussed in the report[91] of the long-term follow-up of in a group of 32 patients ineligible for surgery who were treated with endobronchoscopic therapy. Treated tumors were ≤ 1 cm in size, intraluminally located in the central airways, with no bronchial wall invasion or extraluminal tumor growth on high-resolution CT, and with visible distal margin under conventional and AFB. Endoscopic therapy was performed with curative intent, and consecutive patients were treated with PDT (5 patients), Nd-YAG laser (1 patient), electrocautery (24 patients), and argon plasma coagulation (2 patients). Follow-up evaluation at 3- to 4-month intervals included high-resolution CT and both WLB and AFB, which allowed biopsies and brush

cytology for histologic evaluation. The average follow-up period was 5 years (range, 2 to 10 years). In three patients, local recurrence was again successfully treated with electrocautery. Sixteen patients died during follow-up. Eight of the nine patients who died because of lung cancer had a previous resection of a more advanced stage lung cancer up to 5 years before endoscopic treatment of the radiographically occult lung cancer. The cause of death in the remaining seven patients was not related to lung cancer. Sixteen patients are still alive without tumor recurrence. These data showed that bronchoscopic therapy is an effective treatment modality for patients at high risk with early lung cancer, who are not eligible for surgical resection.[91]

Cryotherapy

Cryotherapy is a technique in which tissue is destroyed by freezing and is the least expensive treatment option for early lung cancer. A report[58] included 35 patients (41 cancers) with early stage lung cancer. A complete response after cryotherapy was obtained in 91% of the patients with a recurrence rate of 28% within 4 years. A long-term response of 63% was achieved, similar to that of PDT.[58]

Brachytherapy

Brachytherapy refers to the placement of a radioactive source within or near an endobronchial malignancy to deliver local irradiation. This requires the insertion of an afterloading polyurethane catheter into the airway adjacent to the tumor during fiberoptic bronchoscopy.[192] Ir is generally used. In two small studies,[61,92] the use of high-dose brachytherapy in three to six sessions resulted in response rates similar to PDT. Marsiglia et al[92] reported 34 patients with early stage lung cancer with a complete response of 85% seen $>$ 2 years after follow-up. Perol et al[61] reported 19 patients with early stage lung cancer with a complete response rate of 83%, which decreased to 75% at 1-year follow-up.

Nd-YAG Laser Therapy

Nd-YAG laser therapy is used for direct thermal ablation of tissue in endobronchial malignancy. It has been used extensively as a palliative measure to relieve airway obstruction. The use of laser treatment for early lung cancer has not been widely studied. A study by Cavaliere et al[63] showed a complete response rate of 100% in 22 patients with small bronchial cancers. The long-term outcome of these patients was not reported. Nd-YAG laser therapy is not indicated for tumors that are located in the bronchial wall parallel to the bronchoscope or for tumors involving smaller bronchial branches because of the risk of perforation.[93] This would occur because of heat sink effect and absorption of heat by the tissue.

After endobronchial treatment for early lung cancer, patients should be closely monitored for recurrent disease and development of metachronous lesions. Reevaluation at 3 to 6 months with WLB and AFB, if available, is reasonable (see chapter of "Follow-up and Surveillance of the Lung Cancer Patient Following Curative Intent Therapy").

Recommendation

4. For patients with superficial SqCC who are not surgical candidates, PDT, electrocautery, cryotherapy, and brachytherapy are recommended as treatment options. Use of Nd-YAG laser is not recommended because of the risk of perforation. Grade of recommendation, 1C

Conclusions

The detection and assessment of intraepithelial and microinvasive neoplasia in the central airways is significantly improved by the use of autofluorescence imaging. The range of its clinical application is still being explored but includes investigation of patients with abnormal sputum cytology, longitudinal surveillance of bronchial dysplasia, and assessment of early central lung cancer being considered for curative endobronchial therapy. A number of techniques are now available for curative endobronchial therapy in select central lesions.

PDT is the most extensively studied endobronchial treatment for early lung cancer for patients who are not candidates for surgical resection. Suitable lesions require careful assessment bronchoscopically and radiographically. The data for use of PDT for patients who are surgical candidates currently are limited. Other endobronchial treatments such as electrocautery, cryotherapy, and brachytherapy are not as well studied but appear to have similar response rates to PDT. The best response is seen in highly selected patients with small lesions and visible margins.

Summary of Recommendations

1. For patients with severe dysplasia, CIS, or carcinoma in sputum cytology but with chest imaging studies showing no localizing

abnormality, standard WLB is recommended. AFB should be used when available. Grade of recommendation, 1B

2. For patients being considered for curative endobronchial therapy to treat CIS in centers where it is available, AFB may be considered to guide therapy. Grade of recommendation, 2C

3. For patients with known severe dysplasia or CIS in the central airways, standard WLB is recommended at periodic intervals (3 to 6 months) for follow-up. AFB should be used when available. Grade of recommendation, 2C

4. For patients with SqCC who are not surgical candidates, PDT, electrocautery, cryotherapy, and brachytherapy are recommended as treatment options. Use of Nd-YAG laser therapy is not recommended because of the risk of perforation. Grade of recommendation, 1C

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Treatment of Non-small Cell Lung Cancer Stage I and Stage II*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **The surgical treatment of stage I and II non-small cell lung cancer (NSCLC) continues to evolve in the areas of intraoperative lymph node staging (specifically the issue of lymph node dissection vs sampling), the role of sublobar resections instead of lobectomy for treatment of smaller tumors, and the use of video-assisted techniques to perform anatomic lobectomy. Adjuvant therapy (both chemotherapy and radiation therapy) and the use of larger fractions of radiotherapy delivered to a smaller area for nonoperative treatment of early stage NSCLC have shown promising results.**

Methods: **The panel selected the following areas for review based on clinical relevance and the amount and quality of data available for analysis: surgical approaches to resecting early stage NSCLC, methods of lymph node staging at the time of surgical resection, adjuvant chemotherapy in the treatment of early stage NSCLC, and the use of radiation therapy for primary treatment of early stage NSCLC as well as in the adjuvant setting. Recommendations by the multidisciplinary writing committee were based on literature review using established methods.**

Results and conclusions: **Surgical resection remains the treatment of choice for stage I and II NSCLC, although surgical methods continue to evolve. Adjuvant chemotherapy for patients with stage II, but not stage I, NSCLC is well established. Radiotherapy remains an important treatment for either cases of early stage NSCLC that are medically inoperable or patients who refuse surgery.** ***(CHEST 2007; 132:234S–242S)***

Key words: ablative therapy; adjuvant therapy; chemotherapy; metaanalyses; non-small cell lung cancer; radiotherapy; stage I and II; surgery; video-assisted thoracic surgery

Abbreviations: ACCP = American College of Chest Physicians; ACOSOG = American College of Surgeons Oncology Group; NSCLC = non-small cell lung cancer; SBRT = stereotactic body radiation therapy; UFT = tegafur/uracil; VATS = video-assisted thoracic surgery

Patients with stage I or stage II non-small cell lung cancer (NSCLC) are considered to have early stage disease. Unfortunately, these two stages combined account for only 25 to 30% of all patients with lung cancer. Stage I NSCLC is defined by the American Joint Commission on Cancer as a T1 or T2 tumor in the parenchyma of the lung, no more proximal than 2 cm from the carina, and not invading chest wall or parietal pleura. In addition, patients in

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this stage grouping have hilar (N1) and mediastinal (N2) lymph node stations negative for tumor, and no metastatic (M1) disease. Stage II NSCLC is defined as a T1 or T2 cancer with N1 nodal metastasis and no distant metastasis (T1-2N1M0) or a T3 cancer with no nodal or distant metastasis (T3N0M0). Stage IIA consists of T1N1 cancers.

For review, T1 tumors by definition are ≤3 cm and do not involve the visceral pleura or a main bronchus. N1 denotes metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes involved by direct extension of the primary tumor. Stage IIB includes T2N1 and T3N0 cancers. T2 denotes a tumor with any of the following features: >3 cm in greatest dimension, or involves a main bronchus >2 cm distal to the carina, or invades the visceral pleura, or is associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung. T3 denotes a tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pleura, parietal pericardium, or tumor in the main bronchus <2 cm distal to the carina without involvement of the carina, or associated atelectasis or obstructive pneumonitis of the entire lung.

We refer the reader to the last version of these *Guidelines* for those aspects of the treatment of stage I and stage II NSCLC that were well reviewed there and also for important background information (see previous "Stage I" and "Stage II" chapters, *CHEST* 2003). In the current version of the *Guidelines*, treatment recommendations regarding tumors of the chest wall (T3N0, part of stage IIB), formerly discussed in the chapter on the treatment of stage II NSCLC, are instead included in the chapter on special situations (see chapter on "Special Treatment Issues in Lung Cancer"). Since the last version of these *Guidelines*, a number of trends in the treatment of patients with stage I and stage II NSCLC have become evident. These trends include increased experience with video-assisted thoracic surgical (VATS) lobectomy in the treatment of patients with clinical stage I NSCLC; the growing recognition that patients with smaller tumors (≤2.0 cm) are a favorable subset of patients with stage I NSCLC; growing consideration of sublobar resection for patients with small stage I NSCLC; increasing use of stereotactic radiation and other ablative therapies in nonsurgical candidates; and recent controversy about the use of adjuvant chemotherapy for completely resected patients with stage IB NSCLC, among others. These trends and others are the subjects of ongoing or planned clinical trials. These issues will be covered in this chapter when there are sufficient data to make evidence-based recommendations.

Materials and Methods

The Duke Evidence-based Clinical Practice Center searched the literature for studies regarding the issues of lymph node staging vs dissection, surgical treatment of early stage lung cancer, the use of adjuvant chemotherapy in the treatment of early stage lung cancer, and the use of radiation therapy for primary treatment of early stage lung cancer as well as in the adjuvant setting. The Duke Evidence-based Practice Center found insufficient data were available regarding ablative therapies such as radiofrequency ablation, cryotherapy, and ablation of tumors using microwave emitting probes, and these areas were not included in this evidence-based review. They then provided evidence tables, summaries of studies, and references to other recently published guidelines authored by other organizations for the panel members to review. The panel of authors for this chapter devised an initial set of recommendations. A larger multidisciplinary panel including thoracic surgeons, radiation oncologists, pulmonologists, and medical oncologists reviewed these and made additional recommendations. Grades were assigned to each recommendation using a standardized method (see chapter on "Methodology for Lung Cancer Evidence Review and Guideline Development"). The entire document was then reviewed and approved by the Health and Science Policy committee of the American College of Chest Physicians (ACCP) and ultimately the Board of Regents of the ACCP.

Results

Surgical Treatment of Stage I and II NSCLC

There are no randomized clinical trials comparing surgery alone to radiation therapy alone or chemotherapy alone in the treatment of early stage (stage I and II) NSCLC. The concept that surgery offers the best hope of a cure is based on retrospective data ("clinical experience") as reported in the literature. Based on large series of resected stage I and stage II NSCLC, the prognoses for stage IA, IB, IIA and IIB NSCLC, expressed in terms of 5-year survival rates, are commonly accepted to be 60 to 80% for stage I and 40 to 50% for stage II NSCLC.

Silvestri et al[1] retrospectively reviewed mortality rates of 1,416 patients who underwent lobectomy in South Carolina. Mortality was less for those patients whose operation was performed by a board-certified thoracic surgeon as opposed to a general surgeon (21 of 705 patients [3.0%] for thoracic surgeons, vs 38 of 711 patients [5.3%] for general surgeons). In a large retrospective review of the Medicare database, similar findings were noted.[2] Of 25,545 patients who underwent either lobectomy or pneumonectomy for lung cancer in 1998 to 1999, operative mortality rates were significantly lower for cardiothoracic (5.6%) and general thoracic (5.8%) surgeons than general

surgeons (7.6%). In order to participate in modern, multimodality treatment approaches, thoracic surgeons must be aware of the indications for adjuvant therapies, the required preoperative and intraoperative staging that facilitate that approach, and the available treatment alternatives. No less should be required of programs that offer newer image-guided ablative therapies such as radiofrequency ablation, cryoablation, or stereotatic radiation therapy. At present, surgical resection remains the recommended treatment approach for patients with stage I and II NSCLC. As such, all patients with early stage NSCLC should be seen and evaluated by a thoracic surgeon to determine whether they are a candidate for surgical exploration and resection. Other local therapies such as stereotactic radiation or radiofrequency ablation may be appropriate for patients who are medically inoperable. The use of these techniques in patients who are surgical candidates should not occur outside of the context of a clinical research study.

Recommendations

1. For patients with clinical stage I and II NSCLC and no medical contraindication to operative intervention, surgical resection is recommended. Grade of recommendation, 1A

2. For patients with clinical stage I and II NSCLC, it is recommended that they be evaluated by a thoracic surgical oncologist with a prominent part of his/her practice focused on lung cancer, even if patients are being considered for nonsurgical therapies such as percutaneous ablation or stereotactic body radiation therapy (SBRT). Grade of recommendation, 1B

The Lung Cancer Study Group[3] reported in 1995 the results of a prospective randomized trial comparing limited resection to lobectomy in patients with peripheral T1 lung cancers. In this study, patients treated with limited resection had a threefold increase in local recurrence, a 75% increase in combined local and distant recurrence, and a 50% increase in death with cancer rate. There was no difference in operative mortality between the limited resection and lobectomy treatment groups, although there was a higher rate of postoperative respiratory failure requiring ventilator support in the lobectomy group.

Most clinicians treating lung cancer agree that complete surgical resection of stage I lung cancer offers the best chance for cure. Questions still arise as to the risk-benefit relationship between lobectomy and lesser resections (segmentectomy or wedge resection) in selected groups of patients with stage I lung cancer. One group of patients in whom limited resection has been advocated includes those with poor pulmonary function (see chapter on "Physiologic Evaluation of Patients With Lung Cancer Being Considered for Resectional Surgery"). Linden et al[4] reported the results of resection in 100 patients with poor lung function (preoperative FEV_1 <35% of predicted). There were no operative (30 days) deaths in 14 lung cancer patients treated with lobectomy via thoracotomy (n = 10) or VATS (n = 4) approaches. A small, case-matched control study by Martin-Ucar et al[5] compared stage I NSCLC patients with a predicted postoperative FEV_1 of <40% treatment with either segmental resection or anatomic lobectomy. In this report of 34 patients,[5] there was identical hospital mortality (5.9%) for the two types of resection. Unlike the Lung Cancer Study Group trial, there was no significant difference in local recurrence or overall survival comparing segmental resection to lobectomy. This trial surprisingly showed an increased incidence of local recurrence in the lobectomy arm and only distant recurrence in the segmentectomy arm, calling in to question the overall validity of the findings.

In a large retrospective review from Japan, Watanabe et al[6] analyzed the data on 3,270 consecutive patients treated with resection for primary lung cancer between January 1987 and December 2002. The authors compared outcomes between 1,615 patients treated in an earlier period (from 1987 to 1996) to 1,655 patients treated in a later period (from 1997 to 2002). The authors reported very low 30-day (0.5%) and in-hospital (0.8%) mortality rates in patients treated with surgical resection for lung cancer between 1997 and 2002. They did not see a significant difference in either 30-day (0.3% vs 0.3%) or in-hospital mortality (1.3% vs 0.9%) between lesser resection and lobectomy. As expected, there was a significantly increased 30-day (3.1%) and in-hospital (5.9%) mortality in patients treated with pneumonectomy.

In a retrospective review of 1,137 patients treated surgically for lung cancer, Jackevicius et al[7] reported on the outcomes of 42 patients treated with limited resection (segmentectomy or wedge) between 1980 and 1997. The overall actual 5-year survival rate was a disappointing 29%. The authors found the best survival among patients with T1N0 cancers treated with surgical resection alone with a median survival in these patients of 45.7 months. The authors found no survival benefit with adjuvant radiation therapy in stage I or II patients. Not surprisingly, patients with N2 stage IIIA disease fared the worst, with a median survival of only 9 months. The authors rightly concluded that limited resection should only be per-

formed in case of T1-2N0 lung cancer. There is no role for limited resection in patients with known N1 or N2 disease.

Tsubota et al[8] reported the early results of a prospective multicenter trial of limited surgical resection of peripheral tumors <2 cm in diameter. The investigators excluded patients with N1 or N2 disease identified by frozen section. There were no perioperative deaths in 55 patients treated with segmentectomy, and the overall 5-year survival was 85%. Local recurrence rate was 4%.

Landreneau et al[9] analyzed the outcomes of a series of patients with peripheral stage IA (T1N0M0) lung cancer treated with open lobectomy (n = 117), open wedge resection (n = 42), or VATS wedge resection (n = 60) between January 1989 and July 1994. Postoperative complications occurred in 16% of patients undergoing VATS wedge resection in contrast to 28% of patients undergoing open wedge resection and 31% of patients treated with open lobectomy. While there was no significant difference in overall survival between patients treated with VATS wedge resection compared to open lobectomy, there was a significant decrease in overall survival for patients treated with open wedge resection. There was a trend toward increased local recurrence in the wedge resection groups (19%) compared to the open lobectomy group (9%), although this difference was not statistically significant. The 5-year actuarial survival in the wedge resection groups (open and VATS) was 48%, vs 67% in the open lobectomy group. All patients in this analysis had T1 (<3 cm) tumors located in the outer third of the lung with no evidence of endobronchial extension and had clear margins on frozen section and intraoperative mediastinal and hilar nodal staging.

Fernando et al[10] reported on a multicenter retrospective outcome study of 291 patients with stage IA (T1N0) NSCLC treated with either sublobar resection (n = 124) or lobar resection (n = 167). Brachytherapy was used in 48% (n = 60) of the sublobar resection cases. Brachytherapy decreased the local recurrence rate in the sublobar resection group from 17% (11 of 64 patients) to 3.3% (2 of 60 patients). There was no survival difference between sublobar and lobar resection in tumors <2 cm in diameter. In contrast, median survival was significantly better for patients with larger tumors (2 to 3 cm) undergoing lobar resection group (70 months) than for similar patients treated with sublobar resection (44.7 months).

Birdas et al[11] retrospectively reviewed the outcomes of 167 patients with stage IB lung cancer treated with lobectomy (n = 126) or sublobar resection (n = 41) with ^{125}I brachytherapy over the resection staple line. The local recurrence rate was similar between the sublobar with brachytherapy group (4.8%) and the lobectomy group (3.4%). At 4 years, the disease-free survival was equivalent for sublobar (43.0%) and lobectomy (42.8%) patients. Overall survival did not differ for sublobar patients (54.1%; median, 50.2 months) and lobectomy patients (51.8%; median, 56.9 months; p = 0.38).

Currently, the American College of Surgeons Oncology Group (ACOSOG) is conducting a phase III clinical trial (ACOSOG Z4032) designed to determine whether the addition of ^{125}I brachytherapy to sublobar resection improves local control in patients with stage I NSCLC compared to sublobar resection alone. Eligible patients must be considered to be at high risk for standard surgical therapy (lobectomy) based on well-defined criteria including decreased lung function or other comorbid factors.

Recommendations

3. In patients with stage I and II NSCLC who are medically fit for conventional surgical resection, lobectomy or greater resection are recommended rather than sublobar resections (wedge or segmentectomy). Grade of recommendation, 1A

4. In patients with stage I NSCLC who may tolerate operative intervention but not a lobar or greater lung resection because of comorbid disease or decreased pulmonary function, sublobar resection is recommended over nonsurgical interventions. Grade of recommendation, 1B

As thoracic surgeons have gained further experience with VATS techniques, they have been applied at an increasing number of centers for the performance of anatomic lung resections (lobectomy and segmentectomy) in patients with clinical stage I NSCLC.[12] Data from an exploratory early series[13] have found VATS resection safe and with complication rates similar to that of open lobectomy. More recently, large series[14] have reported long-term follow-up confirming that VATS lobectomy can achieve cure rates similar to those performed via thoracotomy.

Recommendation

5. In patients with stage I NSCLC who are considered appropriate candidates for thoracoscopic anatomic lung resection (lobectomy or segmentectomy), the use of VATS by surgeons experienced in these techniques is an acceptable alternative to open thoracotomy. Grade of recommendation, 1B

The extent of lymph node evaluation at the time of surgical resection of stage I and stage II NSCLC continues to be a matter of debate. Clinical practice varies from visual inspection alone to radical lymphadenectomy. Questions remain regarding the extent of lymph node removal (sampling vs dissection) or the minimum number of lymph node stations or nodes sampled.

Two randomized trials[15,16] have found no difference in overall survival in patients undergoing lymphadenectomy compared to those undergoing lymph node sampling at the time of resection for NSCLC. In contrast, a third randomized trial by Wu et al[17] found improved survival for patients with clinical stage I to III NSCLC who underwent resection with mediastinal lymph node dissection rather than sampling.

The Cochrane collaboration reviewed 11 randomized trials with a total of 1,910 patients who underwent treatment for early stage (I to IIIA) lung cancer. From a pooled analysis of three trials, they reported that 4-year survival was superior in patients who underwent resection and complete mediastinal lymph node dissection compared with those undergoing resection and lymph node sampling, with the hazard ratio estimated to be 0.78 (95% confidence interval, 0.65 to 0.93; $p = 0.005$).[18]

Data from a prospective, multiinstitutional, randomized trial[19] conducted by the ACOSOG have been reported. This trial was designed to determine if survival after lung resection was impacted by lymph node dissection versus lymph node sampling (ACOSOG Z0030). Preliminary analysis has found no difference in operative mortality based on lymph node procedure. Lymph node dissection was associated with longer operative time and greater volume of postoperative chest tube drainage. However, length of hospital stay did not differ between the two surgical approaches (median stay, 6 days). Both lymph node dissection and sampling are safe procedures and provide critical staging information that will influence recommendations regarding postoperative adjuvant therapy. At present, there is insufficient information to recommend one technique as superior.

Recommendation

6. In patients undergoing resection for stage I and II NSCLC, it is recommended that intraoperative systematic mediastinal lymph node sampling or dissection be performed for accurate pathologic staging. Grade of recommendation, 1B

No randomized trials comparing sleeve lobectomy to pneumonectomy have been reported in the literature. The data available consist of retrospective reviews of the outcomes in patients treated with sleeve lobectomy compared with matched or unmatched control subjects treated with pneumonectomy. For example, Suen et al[20] reported a series of 58 patients with NSCLC treated with sleeve lobectomy or pneumonectomy. After sleeve lobectomy, the operative mortality was 5.2% and the overall 5-year survival rate was 37.5%. For patients treated with pneumonectomy, operative mortality rate was 4.9% and the overall 5-year survival rate was 35.8%.

Recommendations

7. For patients with centrally or locally advanced NSCLC in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy. Grade of recommendation, 1B

8. For patients with N1 lymph node metastases (stage II NSCLC) in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy. Grade of recommendation, 1B

Adjuvant Chemotherapy

Despite complete resection, many stage I and II NSCLC patients experience recurrence. The majority of these relapses are distant, and studies have addressed the role of postoperative chemotherapy. Although the majority of randomized trials have included a range of surgical stages, there are sufficient data to make recommendations about the use of adjuvant chemotherapy in stage I and II NSCLC. Several excellent reviews[21–23] of this topic are available.

For patients with completely resected stage IA NSCLC, postoperative chemotherapy is not recommended. There are very little data available on this subset of patients because most randomized adjuvant trials have excluded patients with stage IA disease extent. From the lung adjuvant cisplatin evaluation metaanalysis,[24] there was no benefit for postoperative adjuvant cisplatin-based chemotherapy among 347 stage IA NSCLC patients.

For patients with stage IB NSCLC, the majority of recent studies[25–27] have not found a statistically significant benefit for this subset of patients. One study[28] has reported benefit, although the results were so different from the other trials as to call into question the validity of its findings. The lung adjuvant cisplatin evaluation metaanalysis[24] found a trend toward improvement in survival in 1,371 stage IB patients randomized to postoperative cisplatin-based

chemotherapy over surgery alone, with an 8% reduction in the risk of death associated with chemotherapy, but this difference was not statistically significant. The Cancer and Leukemia Group B investigators conducted an exploratory analysis of the effectiveness of adjuvant paclitaxel/carboplatin chemotherapy in those patients with primary tumors >4 cm. In this analysis,[27] there continued to be a statistically significant benefit for these stage IB patients.

Studies from Japan have evaluated the use of oral uracil/tegafur (UFT) as an adjuvant therapy to surgery in early stage NSCLC. UFT, a fluoropyrimidine, is a well-tolerated oral agent. Results from these randomized adjuvant trials have been mixed. The single largest trial[28] randomized completely resected stage I adenocarcinoma patients to oral UFT for 2 years or no postoperative therapy. With a median follow-up of >6 years, the 5-year survival rates were 88% in the UFT group and 85% in the control group ($p = 0.047$). Subset analyses found the greatest benefit in the T2N0, stage IB patients. Of concern was the lack of benefit for disease-free survival.[29] A metaanalysis[30] of the effectiveness of adjuvant UFT has also been conducted. This included results from 2,003 patients and compared outcome of single-agent adjuvant oral UFT to surgery alone. UFT was associated with a significant improvement in overall survival (hazard ratio, 0.74; 95% confidence interval, 0.61 to 0.88; $p = 0.001$).[30] There are no confirmatory data on the use of adjuvant oral UFT outside of Japan. Although the results are encouraging, oral UFT or another oral fluoropyrimidine cannot be recommended as adjuvant therapy at this time.

Data for the use of adjuvant cisplatin-based chemotherapy in stage II NSCLC are strong. The International Adjuvant Lung Trial, National Cancer Institute of Canada JBR.10, and Adjuvant Navelbine International Trialists Association studies all found significant benefit for the use of adjuvant chemotherapy in the general population of NSCLC studied, as well as in the stage II patient subsets.[31] The lung adjuvant cisplatin evaluation metaanalysis[24] of the 1,616 stage II patient subset found a 27% reduction in the risk of death (hazard ratio, 0.83; 95% confidence interval, 0.73 to 0.95).

Recommendations

9. For patients with completely resected stage IA NSCLC, the use of adjuvant chemotherapy is not recommended for routine use outside the setting of a clinical trial. Grade of recommendation, 1A

10. For patients with completely resected stage IB NSCLC, the use of adjuvant chemotherapy is not recommended for routine use. Grade of recommendation, 1B

11. For patients with completely resected stage II NSCLC and good performance status, the use of platinum-based adjuvant chemotherapy is recommended. Grade of recommendation, 1A

Definitive Radiation Therapy for Stage I and II NSCLC

While surgery is the preferred treatment for early stage lung cancer, for those patients who are not candidates for surgery because of comorbid conditions ("medically inoperable") or who refuse surgery, experience has generally shown that radiotherapy is effective in obtaining local control with some longer-term survivors. Data suggest that medically inoperable patients still mainly die from lung cancer despite their other medical problems, so treatment of the tumor is justified as opposed to supportive care. Qiao et al[32] reviewed 18 articles between 1988 and 2000. Local recurrence was noted to be the predominant mode of failure and occurred at a median rate of 40%. Median survival in these studies was 18 to 33 months.

Accelerated therapy (54 Gy in 12 days) was superior to conventional radiotherapy (60 Gy in 6 weeks) in the randomized phase III continuous hyperfractionated accelerated therapy study conducted in the United Kingdom.[33] A subset of 169 patients with stage I/II NSCLC were included. Four-year survival was significantly improved with continuous accelerated hyperfractionated radiation therapy (18% vs 12%).

More recently, radiation oncologists have administered radiotherapy in larger doses, fewer fractions, and smaller fields first with three-dimensional conformal therapies and more recently with the use of SBRT, with relatively large series reported from Japan and smaller series from the United States.[34,35] Onishi et al[34] noted local recurrence rates of 14.5% (9.7% for T1 tumors and 20.0% for T2 tumors) during follow-up (median, 24 mo). In a series of 70 patients, Timmerman et al[35] noted excessive toxicity when treating central tumors, but reported 2-year freedom from severe toxicity of 83% for patients with peripheral lung tumors. A 3-month major response rate of 60% was reported. Kaplan-Meier estimated local control rate at 2 years was 95%. Data are awaited from Radiation Therapy Oncology Group trial 0236, a phase II trial of SBRT in the treatment of patients with medically inoperable stage I/II NSCLC, which recently achieved its accrual goals and closed.

Recommendation

12. For patients with stage I or II NSCLC who are not candidates for surgery ("medically inoperable") or who refuse surgery, curative intent fractionated radiotherapy is recommended. Grade of recommendation, 1B

Adjuvant (Postoperative) Radiation Therapy for Stage I and II NSCLC

Postoperative radiotherapy after complete resection of stage I or II NSCLC has been proposed with the goal of decreasing local recurrence rates and improving long-term survival. The Cochrane collaboration had recently updated its well-known postoperative radiotherapy metaanalysis.[36] The current metaanalysis is based on the results of 10 randomized control trials and 2,232 patients. There continues to be evidence that postoperative radiotherapy is associated with a decrease in survival for patients with stage I (N0) and stage II (N1) NSCLC. Critics note that the metaanalysis includes a number of older studies that used radiotherapy methods that are known to be inferior to current standards.

Analyzing similar data for patients with stage II and III NSCLC, Cancer Care Ontario found that postoperative radiation therapy was "mainly detrimental to survival in patients with stage II NSCLC," while no benefit or detriment was seen for postoperative radiation therapy administered to patients with completely resected stage III NSCLC.[37]

Recommendations

13. For patients with completely resected stage IA or IB NSCLC, postoperative radiotherapy is associated with a decreased survival and is not recommended. Grade of recommendation, 1B

14. For patients with completely resected stage II NSCLC, postoperative radiotherapy decreases local recurrence but a survival benefit has not been clearly shown; therefore, postoperative radiotherapy is not recommended. Grade of recommendation, 1B

Conclusions

Although there are no clinical trials comparing surgical resection to other forms of therapy for treating stage I and II lung cancer, extensive clinical experience indicates that the best chance of cure for these tumors comes with surgical resection. Operative outcomes have been found to be better with thoracic surgeons performing lung resection than general surgeons. In patients who can tolerate conventional surgical resection, lobectomy is preferred over sublobar resections. In patients who cannot tolerate conventional surgical resection, sublobar resection is recommended over nonsurgical interventions. For the appropriately trained thoracic surgeon, VATS is an acceptable alternative to open thoracotomy. Whether VATS or open thoracotomy are performed, either systematic mediastinal lymph node sampling or lymph node dissection is recommended at the time of surgical resection. Sleeve lobectomy is preferred over pneumonectomy, when technically possible, in patients with either centrally advanced disease or N1 metastases. Cisplatin-based adjuvant chemotherapy is recommended for completely resected stage II, but not stage I, NSCLC. Curative intent radiotherapy is recommended for patients with stage I or II NSCLC that is either medically inoperable or in patients who refuse surgery. Radiotherapy is not recommended postoperatively after complete surgical resection.

Summary of Recommendations

1. For patients with clinical stage I and II NSCLC and no medical contraindication to operative intervention, surgical resection is recommended. Grade of recommendation, 1A

2. For patients with clinical stage I and II NSCLC, it is recommended that they be evaluated by a thoracic surgical oncologist with a prominent part of his/her practice focused on lung cancer, even if they are being considered for nonsurgical therapies such as percutaneous ablation or SBRT. Grade of recommendation, 1B

3. In patients with stage I and II NSCLC who are medically fit for conventional surgical resection, lobectomy or greater resection are recommended rather than sublobar resections (wedge or segmentectomy). Grade of recommendation, 1A

4. In patients with stage I NSCLC who may tolerate operative intervention but not a lobar or greater lung resection due to comorbid disease or decreased pulmonary function, sublobar resection is recom-mended over nonsurgical interventions. Grade of recommendation, 1B

5. In patients with stage I NSCLC who are considered appropriate candidates for thoracoscopic anatomic lung resection (lobectomy orsegmentectomy), the use of VATS by surgeons experienced in these techniques is an acceptable alternative to open thoracotomy. Grade of recommendation, 1B

6. In patients undergoing resection for stage I and II NSCLC, it is recommended that intraoperative systematic mediastinal lymph node sampling or dissection be performed for accurate pathologic staging. Grade of recommendation, 1B.

7. For patients with centrally or locally advanced NSCLC in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy. Grade of recommendation, 1B

8. For patients with N1 lymph node metastases (stage II NSCLC) in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy. Grade of recommendation, 1B

9. For patients with completely resected stage IA NSCLC, the use of adjuvant chemotherapy is not recommended for routine use outside the setting of a clinical trial. Grade of recommendation, 1A

10. For patients with completely resected stage IB NSCLC, the use of adjuvant chemotherapy is not recommended for routine use. Grade of recommendation, 1B

11. For patients with completely resected stage II NSCLC and good performance status, the use of platinum-based adjuvant chemotherapy is recommended. Grade of recommendation, 1A

12. For patients with stage I or II NSCLC who are not candidates for surgery ("medically inoperable") or who refuse surgery, curative intent fractionated radiotherapy is recommended. Grade of recommendation, 1B

13. For patients with completely resected stage IA or IB NSCLC, postoperative radiotherapy is associated with a decreased survival and is not recommended. Grade of recommendation, 1B

14. For patients with completely resected stage II NSCLC, postoperative radiotherapy decreases local recurrence but a survivalbenefit has not been clearly shown; therefore, postoperative radiotherapy is not recommended. Grade of recommendation, 1B

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Treatment of Non-small Cell Lung Cancer-Stage IIIA*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Study objectives: **Stage IIIA non-small cell lung cancer represents a relatively heterogeneous group of patients with metastatic disease to the ipsilateral mediastinal (N2) lymph nodes and also includes T3N1 patients. Presentations of disease range from apparently resectable tumors with occult microscopic nodal metastases to unresectable, bulky multistation nodal disease. This review explores the published clinical trials to make treatment recommendations in this controversial subset of lung cancer.**

Design, setting, and participants: **Systematic searches were made of MEDLINE, HealthStar, and Cochrane Library databases up to May 2006, focusing primarily on randomized trials, with inclusion of selected metaanalyses, practice guidelines, and reviews. Study designs and results are summarized in evidence tables.**

Measurement and results: **The evidence derived from the literature now appears to support routine adjuvant chemotherapy after complete resection of stage IIIA lung cancer encountered unexpectedly at surgery. However, using neoadjuvant therapy followed by surgery for known stage IIIA lung cancer as a routine therapeutic option is not supported by current published randomized trials. Combination chemoradiotherapy, especially delivered concurrently, is still the preferred treatment for prospectively recognized stage IIIA lung cancer with all degrees of mediastinal lymph node involvement. Current and future trials may modify these recommendations.**

Conclusions: **Multimodality therapy of some type appears to be preferable in all subsets of stage IIIA patients. However, because of the relative lack of consistent randomized trial data in this subset, the following evidence-based treatment guidelines lack compelling evidence in most scenarios.** ***(CHEST 2007; 132:243S–265S)***

Key words: adjuvant chemotherapy; adjuvant radiotherapy; chemotherapy; guidelines; lung carcinoma; neoadjuvant therapy; non-small cell lung cancer; pulmonary surgical procedures; radiation therapy

Abbreviations: ALPI = Adjuvant Lung Project Italy; CALGB = Cancer and Leukemia Group B; CAP = cyclophosphamide-doxorubicin-cisplatin; CHART = continuous hyperfractionated accelerated radiation therapy; ECOG = Eastern Cooperative Oncology Group; HART = hyperfractionated accelerated radiation therapy; MaxSUV = percentage change in the standardized uptake value; NSCLC = non-small cell lung cancer; PET = positron emission tomography; RTOG = Radiation Therapy Oncology Group; SUV = standardized uptake value

The evidence-based guidelines that follow are written primarily to provide a succinct synthesis of the medical literature and provide specific treatment guidelines that can serve as a useful tool for the clinician who deals directly with locally advanced non-small cell lung cancer (NSCLC). Exhaustive detail about published trials are avoided to make this a more readable and useable guide. To develop the following guidelines for stage IIIA disease, the authors conducted a systematic search of MEDLINE, HealthStar, and Cochrane Library databases up to May 2006, reviewing 15 other published clinical guidelines, 10 metaanalyses, 12 systematic reviews, and 91 primary articles with clinical trials on this topic, focusing on the

most well-designed, largest peer-reviewed reports. Selected key references are included in the bibliography.

Based on the collected series of 5,230 NSCLC patients seen in the period from 1975 to 1988 at the MD Anderson Cancer Center reported by Dr. Clifford Mountain in the 1997 revision of lung cancer staging criteria,[1] 30% of all patients have locally advanced disease at initial presentation. Of those, one third (10% of the total) have stage IIIA with ipsilateral N2 lymph node metastases, which in the United States would then encompass approximately 17,000 new patients yearly. This group forms perhaps the most therapeutically challenging and controversial subset of lung cancer patients, with a published 5-year survival rate of only 23%.[1]

This border-zone subset of stage IIIA patients, which lies between the generally resectable stage I and II tumors and unresectable stage IIIB patients, has been the subject of a wide variety of clinical trials incorporating various combinations of chemotherapy, radiotherapy, and surgery. Unfortunately, most published studies have significant limitations because they are not randomized, lack rigorous pretreatment staging, or involve significant inhomogeneity in the study population, making interpretation of the results difficult. There are a few more rigorous randomized trials, which are discussed subsequently, that strongly suggest a combined modality approach is beneficial in stage IIIA disease. The approach showing promise in selected patients uses initial treatment (induction or neoadjuvant therapy) with chemotherapy or chemoradiotherapy followed by surgery. Nevertheless, more widespread use of induction therapy followed by surgery for lung cancer has been used for only 12 years, and as a result there are limited reliable data with larger patient groups. In addition, the few larger randomized trials show conflicting data that further confounds our attempts to propose specific guidelines. Therefore, treatment recommendations for stage IIIA in this chapter are generally weak in many recommendations. This lack of consistent, larger, randomized data underscores the importance of enrolling patients in clinical trials whenever possible.

Because staging and treatment are so interdependent, intraoperative staging with systematic mediastinal node sampling or dissection is critically important. Unless histologic conformation of mediastinal node status is obtained at the time of surgery, postoperative pathologic staging will be inaccurate, as will further treatment recommendations and the discussion of prognosis. Therefore, the standard of care in modern thoracic surgery dictates that mediastinal node sampling or dissection must be performed at the time of every lung resection for lung cancer.

Under the 1997 revised lung cancer staging system,[1] stage IIIA encompasses all tumors with ipsilateral mediastinal lymph node metastases (T1–3, N2). Also included in this stage are tumors with resectable chest wall or mediastinal involvement and hilar node metastases (T3N1), added primarily because of similar survival rates. However, the treatment recommendations and applicable clinical trials for T3N1 are the same as for stage II. Therefore, for the purposes of these current guidelines, T3N1 tumors are discussed in the preceding chapter on stage I and II tumors. The present chapter will deal only with N2 disease. Furthermore, in patients with resectable T3 tumors (chest wall involvement, but not superior sulcus Pancoast tumors) who are found at surgery or preoperatively to have N2 mediastinal lymph node involvement, the following treatment recommendations apply in every respect.

Nevertheless, the patients with stage IIIA (N2) tumors present substantial heterogeneity in clinical presentation, treatment, and prognosis. Therefore, for the purposes of generating rational treatment guidelines, we have chosen to classify N2 tumors into four subsets (Table 1), which have been published

Table 1—*Subsets of Stage IIIA(N_2)**

Subset	Description
$IIIA_1$	Incidental nodal metastases found on final pathology examination of the resection specimen
$IIIA_2$	Nodal (single station) metastases recognized intraoperatively
$IIIA_3$	Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)
$IIIA_4$	Bulky or fixed multistation N2 disease

*Adapted from Ruckdeschel.[2]

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previously.[2] The subsequent discussion of the literature and treatment guidelines will be broken down into these four subsets.

Treatment of Specific Patient Groups

Incidental N2 Disease (Stage IIIA$_{1-2}$)

Despite careful preoperative staging including CT scan, positron emission tomography (PET), and mediastinoscopy, some patients will be found to have metastases to mediastinal N2 lymph nodes at thoracotomy. In some, metastatic nodal disease will be found as a surprise a number of days postoperatively on the final pathologic examination of the surgical specimen (stage IIIA$_1$). In others, metastases will be found intraoperatively as an unexpected finding at thoracotomy with a frozen section pathologic examination of mediastinal nodes (stage IIIA$_2$). Unexpected nodal metastases in this setting are not that unusual. In the era before PET scanning, one surgical series of 102 patients in 1990 from the Brompton Hospital in London who had no clinical evidence of mediastinal adenopathy at thoracotomy, 24% of patients had pathologically positive nodes.[3,4] With current preoperative staging including PET scans, finding unexpected N2 involvement at surgery is an uncommon event.

Surgery

Despite negative preoperative staging studies including mediastinoscopy, as many as one fourth of patients will be found at surgery to have occult N2 metastatic disease.[3,4] If only one nodal station is unexpectedly found to be involved with metastatic lung cancer at open thoracotomy, and all of the involved nodes are technically resectable and the primary tumor is also technically resectable, then the surgeon should proceed at that time with the planned lung resection along with a mediastinal lymphadenectomy. If a complete resection is not possible or there is multistation or bulky unresectable extracapsular nodal disease, then the planned lung resection should be aborted. Although incomplete resection rarely results in long-term survival, collected results of surgery alone in stage IIIA (N2 disease) provides a 14 to 30% 5-year survival rate, with the best survivals seen in minimal N2 disease and complete resection.[5–12]

At least 27 to 36% of patients with metastatic disease to the mediastinal N2 nodes will not have involvement of the hilar or lobar lymph nodes.[13,14] In other words, in approximately one third of patients, metastatic tumor cells bypass the N1 hilar lymph nodes and spread directly to the mediastinal N2 nodes. If resection of clinically negative mediastinal lymph nodes is not performed at the time of lung resection, it is possible that occult, subclinical metastatic disease to the N2 nodes will be missed, which will provide inaccurate pathologic staging and may alter the clinical course.

The optimal intraoperative approach to deal with the mediastinal lymph nodes remains unsettled. There is general agreement that systematic invasive harvesting of nodes from all possible lymph node stations is essential for accurate staging, but controversy arises as to whether complete mediastinal lymph node dissection is of therapeutic benefit in improving long-term survival rates. Theoretically, mediastinal lymph node dissection will harvest more nodes and thereby provide more accurate staging. Few published randomized studies have addressed the sampling versus dissection question. In a prospective randomized trial, Izbicki et al[15] found no survival benefit of an *en bloc* mediastinal lymph node dissection compared to systematic lymph node sampling in NSCLC. However, data from the North American Intergroup trial[16] comparing adjuvant postoperative radiotherapy with chemoradiotherapy in N1 and N2 node-positive patients shows a mild significant benefit for mediastinal dissection, although this analysis was retrospective and the choice of the approach to nodes in the mediastinum was left to the surgeon. In a companion analysis[17] of lymph node harvesting techniques and results from this Intergroup trial, mediastinal lymph node dissection resulted in a significantly longer median survival than systematic lymph node sampling, but interestingly the survival advantage was limited to patients with right lung tumors (66.4 mo vs 24.5 mo; $p < 0.001$). Realistically, the distinction between what constitutes a mediastinal lymphadenectomy as opposed to systematic mediastinal lymph node sampling is technically somewhat blurred and is quite surgeon dependent.

However, if metastatic disease is found in the N2 nodes at mediastinoscopy before thoracotomy, for example, then further surgery at that time should be avoided based on the poor results of primary resection for stage IIIA disease. If appropriate, induction therapy first is more advantageous, followed later in selected patients by definitive surgical resection of the primary lung cancer along with as complete a mediastinal lymphadenectomy if possible. This topic is discussed in a subsequent section.

Recommendations

1. *Surgical Considerations*: In patients with NSCLC who have incidental (occult) N2 disease (IIIA$_2$) found at surgical resection and in whom complete resection of the lymph nodes and primary tumor is technically possible, completion of

the planned lung resection and mediastinal lymphadenectomy is recommended. Grade of recommendation, 2C

2. In patients with NSCLC undergoing surgical resection, systematic mediastinal lymph node sampling or complete mediastinal lymph node dissection is recommended. Grade of recommendation, 1B

Adjuvant Radiotherapy

Although it is recognized that the finding of regional metastatic N2 disease at surgery is a poor prognostic feature, there is little consensus as to the appropriate postthoracotomy management of these patients. Despite the great frequency of lung cancer, there have been relatively few patients entered into prospective trials evaluating the role of adjuvant postoperative radiation therapy, chemotherapy, or both.

The role of postoperative radiation therapy in patients with NSCLC has been debated for many years. The ability of postoperative radiation therapy in moderate doses, 45 to 55 Gy, to eradicate microscopic residual disease and reduce rates of local recurrence was strongly suggested in several early single-institution trials.[18–20] What has remained controversial is whether the reduction in locoregional recurrence also leads to an improvement in overall survival. While the nonrandomized, single institution trials suggested that this was the case, data from the prospective trials have been less supportive. Two separate issues are likely involved. First, how large is the group of patients who have residual disease locally in the chest without occult distant metastatic disease, the subgroup for whom adjuvant mediastinal radiation therapy might be curative? Second, what is the morbidity and mortality of adjuvant mediastinal radiotherapy with modern treatment planning techniques?

The Lung Cancer Study Group conducted a phase III trial[21] in which patients with resected squamous cell carcinoma of the lung were randomized between observation and mediastinal irradiation to 50 Gy in 5 weeks. Entry into the study was restricted to patients with squamous cell carcinoma because of the greater tendency of this tumor to fail locally rather than distantly, compared with adenocarcinoma and large cell carcinoma. The majority of patients had N1 disease, but smaller proportions had N2 or T3N0 disease. The results of the trial were striking. Local failure as a first site of relapse was seen in 20% of patients on the observation arm but was seen in only 1% of those randomized to adjuvant nodal irradiation. The Lung Cancer Study Group and other trials of adjuvant postoperative radiation have been criticized for their small sample size, their mixture of N1 and N2 patients, and for the reliance on data on the site of first failure. It should be remembered that these deficiencies did not prevent the demonstration of a striking effect of radiotherapy on local control. What was lacking was the efficacy of good local control to result in long-term freedom from disease.

Several other randomized trials have addressed the same issue in patients with resected NSCLC of all histologies and have consistently failed to demonstrate a significant survival advantage (Table 2). In some trials, there have been poorer survivals for patients who have undergone irradiation, most likely attributable to increased cardiopulmonary toxicity. In both the Lung Cancer Study Group and Medical Research Council trials, there was a trend to improved survival for the irradiated N2 but not N1 patients, but these survival differences did not reach statistical significance.

The recently published postoperative radiation therapy meta-analysis[29] (PORT Meta-analysis Trialist Group) of 2,128 patients treated in nine randomized trials (six previously published series and three unpublished series) of postoperative radiation therapy concluded that this treatment was associated with a highly significant increase in the risk of death. Overall, the risk ratio was 1.21 ($p = 0.001$). The

Table 2—*Randomized Controlled Trials of Surgery Plus Adjuvant Radiotherapy vs Surgery Alone**

Source	Year	Patients, No.	XRT Dose, Gy	Stage	Survival	Local Recurrence, Surgery Plus XRT/Surgery, %
Paterson and Russel[22]	1962	202	45	Any	NS	
Bagma[23]	1971	73	46	Any	NS	
Van Houtte et al[24]	1980	224	60	I, II	NS	4.8/20.7 ($p = 0.002$)
Weisenberger, LCSG 773[25]	1985	210	50	II, IIIA	NS	1/19 ($p = 0.02$)
Stephens et al[26]	1996	308	40	II, IIIA	NS	18/29 ($p = 0.003$)
Debevec et al[27]	1996	74	30	IIIA	NS	
Dautzenberg et al[28]	1999	728	60	II, IIIA	Worse for XRT group ($p = 0.002$)	

*NS = no significant difference; XRT = radiotherapy.

authors[29] concluded that postoperative radiotherapy as used in these studies was detrimental and should not be used. It is important to recognize that there are several significant differences between the treatment administered in a number of the trials included in this metaanalysis and current practice patterns in the United States. First, a substantial portion of the patients included in this study, 562 of 2,128 patients (26.4%), had stage I disease without demonstrated nodal metastases. There has never been a strong case favoring the postoperative irradiation of these stage I patients, and there is little suggestion from patterns of their failure after surgery that such treatment would be beneficial. Thus one fourth of the patients in this analysis stood to gain little from treatment. Second, the details of treatment, including preoperative staging, surgical technique, and radiation dose and dose delivery differed substantially from current practice. Several of the trials required or allowed very large daily fraction sizes > 2.0 Gy, with the Medical Research Council trial using 2.6 Gy/d and the Slovenian trial using 3.0 Gy/d. Such larger fraction sizes would be expected to have an increase in acute and late complications compared to slower fractionation. Seven of the nine trials also allowed the use of ^{60}Co treatment beams, with their poorer depth-dose characteristics than higher energy accelerator beams, and only one study included CT scan-based treatment planning. Therefore, compared with present standards of treatment, the likelihood is great that postoperative radiation therapy would lead to excess deaths from cardiac and pulmonary damage.

In such a metaanalysis that included patients with little chance of benefit of treatment, this would likely result in an overall survival detriment. It is notable that in this metaanalysis, the increased risk of death was most marked in those patients with stage I disease and was not significant for patients with N2 disease. This is consistent with, although it does not prove a potential benefit for properly delivered radiotherapy for resected N2 patients.

A later review and practice guidelines on postoperative radiotherapy in stage II and IIIA were developed and published in 2004 by the Lung Cancer Disease Site Group of Cancer Care Ontario Program of Evidence-Based Care.[30] After their review of the literature including metaanalyses, they concluded also that no survival benefit was found with postoperative radiotherapy in completely resected stage IIIA disease and that the data for improved local control were conflicting. They therefore recommended that the decision regarding postoperative radiotherapy be assessed in an individual case basis.

At present, postoperative radiation therapy cannot be recommended on the basis of any proof of improved survival, but it should be considered in selected patients to reduce the risk of local recurrence, particularly when there is involvement of multiple nodal stations, extracapsular tumor spread, or close or microscopically positive resection margins, especially as assessed by the surgeon performing the resection. While adjuvant mediastinal radiotherapy has often been viewed as routine, it can be associated with significant cardiac and pulmonary toxicity and care in treatment planning and delivery is essential.

Adjuvant Chemotherapy

Because the predominant pattern of failure is systemic recurrence of metastatic disease in patients with fully resected stage IIIA lung cancer, numerous trials of adjuvant postoperative chemotherapy have been performed over the past 3 decades. These trials have been hampered by a number of problems including inconsistent staging especially in the earlier trials, lack of effective chemotherapeutic agents until recently, and the poor tolerance of postthoracotomy patients to chemotherapy because of GI toxicity in an era lacking strong antiemetic agents.

In the 1970s and 1980s, a number of adjuvant chemotherapy trials used drug combinations that predated cisplatin-containing regimens. Most of these trials used alkylating agents and provided no survival advantage to patients, and in fact in most there was a detrimental effect resulting in a relative 15% increase in death in patients receiving adjuvant chemotherapy.[31]

In the 1990s, a number of controlled, randomized trials were published using a variety of cisplatin-based chemotherapy regimens, commonly using cyclophosphamide-doxorubicin-cisplatin (CAP). Most of these trials (Table 3) of adjuvant chemotherapy after lung resection had a mixture of stages. Common to most trials was significant GI toxicity (studies predated availability of serotonin-receptor antagonist antiemetics), and few patients received the full planned course of chemotherapy. Almost all trials showed no advantage in disease-free survival or overall survival with postoperative adjuvant chemotherapy. Niiranen et al[32] did find a significant increase in survival in resected T1–3N0 patients with adjuvant CAP chemotherapy. However, the surgery-only control arm had a high proportion of pneumonectomy cases, and when the pneumonectomy cases were excluded from analysis the survival advantage disappeared.

A metaanalysis by the Nonsmall Cell Lung Cancer Collaborative Group in 1995 analyzed the results of five non-cisplatin-based adjuvant chemotherapy regimens and found no survival benefit.[31] The Nonsmall Cell Lung Cancer Collaborative Group also

Table 3—*Randomized Controlled Trials of Surgery Plus Adjuvant Cisplatin-Based Chemotherapy vs Surgery Alone (With or Without Adjuvant Radiotherapy)

Source	Year	Patients, No.	Adjuvant Chemotherapy	Stage	Disease-Free Survival	Long-Term Survival (5 yr) in Surgery-Chemo/ Surgery, %
Niiranen et al[32]	1992	110	CAP	I–III (I, 90%)	NS	67/56 (p = 0.05 for stage I)
Ohta et al[33]	1993	181	CDDP/Vd	III	NS	35/41 (p = 0.86)
Feld et al[34]	1993	269	CAP	I–II (I, 84%)	NS	53/57 (p = 0.92)
Figlin and Piantodosi[35]	1994	188	CAP	II–III	NS	NS
SGACLC[36]	1995	333	CDDP/A/UFT	I–III (I, 61%)	NS	68.7/58.1 (p = 0.35)
Wada et al[37]	1996	323	CDDP/Vd/UFT vs UFT alone vs Surg alone	I–III		60.6/64.1/49 (p = 0.1)
Scagliotti et al[38]	2003	1209	Surg/MVP/RT vs Surg/RT	I–III (IIIA, 29%)	NS; HR, 0.89 (p = 0.13)	NS; HR, 0.96 (p = 0.59)
Waller et al[39]	2003	381	CV, MIC, MVP or NP for 3 cycles	I–III (IIIA, 34%)	54% both arms (p = 0.98)	NS
Arriagada et al[40]	2004	1867	CDDP + Et, Vn, or Vb 3–4 cycles	I–IIIA (IIIA, 39%)	39.4% (chemo) vs 34.3% at 5 yr; HR, 0.83 (p < 0.003)	44.5% (chemo) vs 40.4% at 5 yr; HR, 0.86 (p < 0.03)
Douillard et al[41] ANITA	2005	840	NP 4 cycles	I–IIIA (IIIA, 35%)		42% (chemo) vs 26% (p = 0.013)

*SGACLC = Study Group of Adjuvant Chemotherapy for Lung Cancer. A = doxorubicin; CAP = cyclophosphamide-doxorubicin-cisplatin; CDDP = cisplatin; Chemo = chemotherapy; CV = cisplatin, vindesine; Et = etoposide; HR = hazard ratio; MIC = mitomycin C, ifosphamide, cisplatin; MVP = mitomycin C, vindesine, cisplatin; NP = vinorelbine, cisplatin; RT = radiotherapy; Surg = surgery; Vb = vinblastine; UFT = uracil-tegafur; Vd = vindesine; Vn = vinorelbine. See Table 2 for expansion of abbreviations not used in the text.

analyzed eight cisplatin-based adjuvant chemotherapy trials and found a 13% decrease in the relative risk of death with chemotherapy and an absolute survival benefit of 3% at 3 years and 5% at 5 years, but all of the differences were not statistically significant. A later meta-analysis by Le Chevalier et al[42] in 1998 of all randomized, controlled adjuvant chemotherapy trials also suggested a small 5% survival benefit with cisplatin-based regimens.

A persistent problem with postoperative chemotherapy has been administering the planned doses and cycles of chemotherapy. However, with the elimination of drugs such as doxorubicin and the introduction of better supportive care drugs such as improved antiemetics and cytokine support of hematologic toxicity, there would theoretically be improved chemotherapy dose compliance. Unfortunately, the experience of ongoing trials shows that the problem has not resolved and only approximately 65% of the planned dose of chemotherapy is actually received. The positive Japanese experience in 1996 with low-dose, minimally toxic, prolonged adjuvant therapy with uracil-tegafur suggests that the "standard" short-term, dose-intense adjuvant therapy may not be the best or only approach to consider.[37]

In the 2000s, a number of larger randomized trials of cisplatin-based adjuvant chemotherapy trials have matured providing data to review. All compared surgery with postoperative chemotherapy (some with adjuvant radiotherapy) to surgery (with or without adjuvant radiotherapy) in resected stages IB-IIIA. The Adjuvant Lung Project Italy (ALPI) trial[38] published in 2003 enlisted the enrollment of 1,209 patients (28.5% stage IIIA) from 66 Italian centers and 5 other European centers outside of Italy who were randomized within 42 days after surgery to three cycles of adjuvant chemotherapy with mitomycin C, vindesine, and cisplatin versus no chemotherapy. Adjuvant radiotherapy was given to 65% of patients in the mitomycin C, vindesine, and cisplatin arm and 82% of patients in the control arm. Sixty-nine percent of patients in the mitomycin C, vindesine, and cisplatin arm completed all chemotherapy doses. After a median 64.5-month follow-up, the combined results showed no significant improvement in overall survival (hazard ratio, 0.96) or progression-free survival (hazard ratio, 0.89). Similarly negative results were also presented in 2003 with the much smaller Big Lung Trial (Medical Research Council), in which 381 patients (34% stage IIIA) underwent surgical resection with randomization to adjuvant chemotherapy with three cycles of one of four cisplatin-based regimens vs no chemotherapy.[39] Of the chemotherapy arm, only 64% received all planned cycles. On analysis

of results, there was no survival benefit with adjuvant chemotherapy (hazard ratio, 1.00; p = 0.98), confirming the ALPI findings.[38]

However, 2004 saw the publication of the larger International Adjuvant Lung Cancer Trial of 1,867 patients with stages IB to IIIA (39% stage IIIA),[40] which randomized patients to three to four cycles of postoperative cisplatin-based chemotherapy versus the control group of surgery alone (with adjuvant 60 Gy radiotherapy given in both arms of stage IIIA patients). After a median 56-month follow-up, the overall survival rate was significantly higher in the chemotherapy group (hazard ratio, 0.86), with a 5-year survival rate of 44.5% in the chemotherapy group versus 40.4% in the control arm, with the strongest benefit in patients with stage III disease. The disease-free survival rate was likewise significantly higher in the chemotherapy group (hazard ratio, 0.83).

The most recently presented adjuvant chemotherapy trial is the Adjuvant Navelbine International Trialist Association study that randomized 840 completely resected patients with stages I to IIIA (35% stage IIIA) to four postoperative cycles of cisplatin and navelbine vs observation (patients received postoperative radiotherapy per preference of each participating center).[41] After a median follow-up of > 70 months, the long-term 5-year survival of stage IIIA patients in the chemotherapy arm was significantly greater at 42% vs 26% in the observation arm (p = 0.013). The benefit of adjuvant chemotherapy was also seen in stage II patients but not in stage I.

The most recent metaanalysis of adjuvant chemotherapy published in 2005 by Berghmans et al[43] involved 19 trials totaling 7,644 patients (12 studies included some stage IIIA patients). Their analysis did include the International Adjuvant Lung Cancer Trial and ALPI trial but not the strongly positive Adjuvant Navelbine International Trialist Association trial. Although the combined results for all stages of disease significantly favored adjuvant chemotherapy over observation alone (hazard ratio, 0.85; 95% confidence interval, 0.79 to 0.91), the subgroup analysis with stage III (N2 positive) patients showed a trend favoring adjuvant treatment but it did not quite reach statistical significance (combined hazard ratio with fixed-effects, 0.84; 95% confidence interval, 0.74 to 0.95; p = 0.07). The authors suggest that future trials consider clearly separating resected stage III from the earlier stages to better address the role of adjuvant chemotherapy in this controversial advanced stage.

Adjuvant Combination Chemoradiotherapy

With the lack of any clear-cut survival advantage in adjuvant radiotherapy and the possible positive benefit of adjuvant chemotherapy in resected N2 lung cancer, attention turned to question the potential benefit of combination chemoradiotherapy postoperatively. Adjuvant radiotherapy appears to decrease local recurrence but failure with distant metastases is a predominant pattern, which theoretically should be complementary to the addition of adjuvant systemic chemotherapy.

To date there have been five published randomized controlled trials involving patients with N2 disease (Table 4) with adjuvant combined chemotherapy and radiotherapy, beginning in 1988 with the Lung Cancer Study group 791.[44] This trial involved patients who had incomplete resections (positive margins or involvement of the most proximal lymph node in the mediastinum) and compared postoperative split course radiotherapy with the same radiotherapy plus CAP chemotherapy. There was an increase in the recurrence-free survival favoring the chemotherapy arm (p = 0.004), but overall survival was not increased.

Later trials failed to demonstrate any improvement in disease-free survival or overall survival with the addition of adjuvant chemotherapy to radiotherapy. The most recently published report in 2000 is

Table 4—*Randomized Controlled Trials of Surgery Plus Adjuvant Chemoradiotherapy vs Surgery Plus Adjuvant Radiotherapy

Source	Year	Patients, No.	Stage	Chemotherapy Radiotherapy Regimens	Disease-Free Survival	Long-term Survival Surgery-XRT vs Surgery-XRT/Chemotherapy, %
Lad et al[44]	1988	164	II–III	CAP40 Gy (split course)	Chemo favored (p = 0.004)	54/68 (p = 0.1); 1 yr
Sawamura et al[45]	1988	52	II–III	Tegafur-CDDP 50 Gy	NS	NS
Pisters et al[46]	1994	72	III	Vd-CDDP 40 Gy	NS	44/31 (p = 0.42); 2 yr
Dautzenberg et al[47]	1995	267	I–III	A-C-CCNU-CDDP-V 60 Gy	NS	12/13 (p = 0.68); 10 yr
Keller et al[16] (Intergroup E3590)	2000	488	II–IIIA	CDDP-VP-16 50.4 Gy	NS	39 mo/38 mo (p = 0.56 median)

*CCNU = lomustine; V = vincristine; VP-16 = etoposide; see Tables 2 and 3 for other abbreviations.

the Intergroup trial (E3590), which included 488 patient and failed to demonstrate any increase in median survival or disease-free survival. In a companion laboratory subset analysis, Schiller et al[48] found a nonsignificant trend toward improved median survival in adjuvant chemoradiotherapy patients who had normal (wild-type) *K-ras* expression compared to mutant *K-ras* patients (median survival, 42 mo vs 25 mo; p = 0.09). Nevertheless, evidence is yet to be established substantiating the benefit of the routine addition of adjuvant chemotherapy to postoperative radiotherapy in stage IIIA lung cancer.

Looking from the other direction, little data are available addressing the question of the survival advantage of adding adjuvant radiotherapy to adjuvant chemotherapy in fully resected stage IIIA patient. The only recent randomized study designed to answer this question was the Phase III Cancer and Leukemia Group B (CALGB) 9734 trial presented in 2003.[49] This small study of 40 patients (closed early because of poor accrual) with resected stage IIIA disease compared four cycles of adjuvant carboplatin and paclitaxel with or without 50-Gy adjuvant radiotherapy. One-year survival rates were not significantly different at 70% in the chemotherapy arm, vs 72% in the chemotherapy/radiotherapy arm. The authors concluded that there was no benefit to adding adjuvant radiotherapy to adjuvant chemotherapy in completely resected stage IIIA NSCLC.

Recommendation

3. *Adjuvant Chemotherapy*: In patients with resected NSCLC who were found to have incidental (occult) N2 disease ($IIIA_{1-2}$) and who have good performance status, adjuvant platinum-based chemotherapy is recommended. Grade of recommendation, 1A

Recommendation

4. *Adjuvant Radiotherapy*: In patients with resected NSCLC who were found to have incidental (occult) N2 disease ($IIIA_{1-2}$), adjuvant postoperative radiotherapy should be considered after adjuvant chemotherapy to reduce local recurrence. Grade of recommendation, 2C

Recommendation

5. *Adjuvant Chemoradiotherapy*: In patients with resected NSCLC who were found to have incidental (occult) N2 disease ($IIIA_{1-2}$), combined postoperative concurrent chemotherapy and radiotherapy is not recommended except as part of a clinical trial. Grade of recommendation, 1B

Potentially Resectable N2 Disease (Stage $IIIA_3$)

Traditionally, the finding of any metastasis whatsoever to the mediastinal N2 nodes deemed that patient to have an unresectable lung cancer. With the development of chemotherapeutic agents with significant activity against lung cancer, beginning with cisplatin in the early 1980s, and with the development of modern radiotherapy techniques, studies have appeared suggesting that combining chemotherapy and/or radiotherapy followed by surgery in selected stage IIIA patients may offer therapeutic benefit. The poor survival rates with surgery alone in N2 disease, even with adjuvant postoperative chemotherapy or radiotherapy, has led to efforts at giving initial nonsurgical (radiotherapy and/or chemotherapy) therapy first, with hopes to convert the unresectable tumor to resectable and, as well, to improve long-term survival. After a number of initial phase II trials with various drugs and radiotherapy doses given before surgery in the neoadjuvant or induction setting, there were enough positive results to persuade even the most pessimistic that this approach may have value, warranting randomized trials.

Induction (Neoadjuvant) Therapy

The majority of stage IIIA patients have enlarged (> 1.0 cm short axis diameter) N2 nodes (our stage $IIIA_3$) on chest CT. Mediastinoscopy should generally be performed in this setting to document that these nodes actually contain metastatic tumor, because approximately 40% of moderately enlarged nodes may be benign, especially if there is an associated recent pneumonitis. Adverse prognostic factors associated with positive mediastinal nodes include extracapsular spread of tumor, multiple levels of involved lymph nodes, and bulky enlarged nodes.[50] Of special note is the location of the N_2 nodes, in that involvement of the higher, superior mediastinal nodes (nodes found positive that are generally available for biopsy at mediastinoscopy) portends a worse prognosis than patients with a negative mediastinoscopy yet who are found to have positive nodes at thoracotomy.[51] However, other studies contradict this finding. Naruke et al[52] found that metastatic disease to the subcarinal lymph nodes adversely affected prognosis compared to other lymph node locations. The Lung Cancer Study Group[53] retrospectively analyzed 163 patients with stage III disease from their postoperative treatment protocols and found that the survival rate was worse for patients with subcarinal lymph node metastases plus nodes from other sites, than for subgroups of patients with medi-

astinal nodal metastases in other locations. Miller et al[54] analyzed their long-term survival rates in 167 patients who at thoracotomy were found to have N2 nodal metastases not suspected preoperatively. The 5-year survival was worse when there was metastatic disease in the subcarinal or lower lymph nodes (stations 8 or 9). Also, survival was worse when multiple lymph node stations were involved. Finally, Okada et al[55] reviewed their long-term survival rates in 141 patients with N2 nodal metastatic disease and found that the survival rate depended on the location of the lung cancer (upper or lower lobes) in relationship to the location of the nodal metastases. For example, upper-lobe lung cancer patients with metastases limited to upper mediastinal nodal stations did better than when the lower mediastinum (subcarinal nodes) was involved in the upper lobe cancers. The only conclusion that can be realistically drawn from the somewhat conflicting information from these and other studies is that multistation nodal disease has a somewhat worse prognosis that single station disease, but the location of metastatic disease to a single nodal station probably has no significant effect.

There are theoretical advantages of the neoadjuvant approach including decreasing tumor size to allow more ready resection with potential nodal clearance of tumor with down-staging, decreased surgical seeding, *in vivo* chemosensitivity testing of the chemotherapy regimen, and increased patient acceptance and compliance. However, neoadjuvant therapy also has the potential disadvantages of a delay in primary tumor control (resection) and increased surgical morbidity and mortality.

The literature is replete with numerous phase II nonrandomized clinical trials of neoadjuvant chemotherapy with or without radiotherapy followed by lung resection in highly selected patients. As summarized by Rusch,[50] results of these phase II trials suggest that the neoadjuvant approach may offer improved resectability with acceptable surgical morbidity and mortality, and is associated with an improved survival benefit over single modality therapy. Martini et al[56] gave induction chemotherapy with mitomycin C, vindesine or vinblastine, and cisplatin to patients with stage IIIA disease with bulky mediastinal nodal metastases or multilevel nodal disease and found a 65% complete resection rate, 15% treatment-related mortality, and a 28% 3-year survival, which was far better than historical controls (8% 3-year survival). Other phase II induction chemotherapy trials have generally confirmed this trial.

Eight randomized phase III trials of neoadjuvant therapy in stage IIIA patients have been published over the past decade (Table 5) comparing neoadjuvant therapy followed by surgery vs surgery alone. Many concerns have been raised about these phase III as well as the phase II neoadjuvant trials. First, there was no consistent surgical (pathologic) staging of the mediastinal lymph nodes. Second, variable numbers of much better prognosis patients (T3N0 and T3N1) were included in these trials that might have influenced the outcome of the trials. Third, some poorer prognosis patients (stage IIIB) were mixed in with better-prognosis patients, thereby worsening results. Fourth, most trials have small numbers of patients because of poor accrual with resultant low statistical power. With these caveats in mind, the results of the trials from Barcelona[57,58] and MD Anderson[59,60] provide promising results. Both of these trials were closed early to further accrual after the interim analyses

Table 5—*Randomized Controlled Trials of Preoperative Neoadjuvant (Induction) Therapy and Surgery vs Surgery Alone in Stage IIIA NSCLC**

Study	Year	Patients, No.	Induction, Study Arm 1/Study Arm 2	Median Survival, Study Arm 1/Study Arm 2, mo	Survival Rate, Study Arm 1/Study Arm 2, %
Pass et al[61]†	1992	27	Cis, Et/none	29/16 (p = 0.095)	42 (3 yr)/12 (3 yr)
Rosell et al[57,58]‡	1994/1999	60	Ifos, MIC, Cis/none	22/10 (p < 0.005)	29 (2 yr), 17(5 yr)/5(2 yr), 0 (5 yr)
Roth et al[59,60]‡	1994/1998	60	Cis, Et, Cyclo/none	21/14 (p = 0.048)	46 (3 yr), 36 (5 yr)/19 (3 yr), 15 (5 yr)
Wagner et al[62]	1994	57	Mito, Vb, Cis/ XRT 44 Gy	12/12	27% at 4 yr for both arms
Elias et al[63]	1997	57	XRT 40 Gy/ Cis, Et	23/19 (p = 0.64)	NR/NR
DePierre et al[64]§	2002	167 with IIIA	Mito, Cis, Ifos/none	NR	28 (5 yr, chemo)/20 (5 yr, estimated); p = NS
Nagai et al[65]†	2003	62	Cis, Vd none	17/16	10 (5 yr, chemo)/22 (5 yr, estimated); p = 0.5274

*Adapted from Garland et al.[66] > Cis = cisplatin; Cyclo = cyclophosphamide; Ifos = ifosfamide; Mito = mitomycin C; NR = not reported. See Tables 2 and 3 for abbreviation not used in the text.

†Study closed early because of poor accrual.

‡Study closed early due to large, significant differences between treatment arms.

§Study combined patients with stages IB, II, and IIIA disease.

demonstrated significant survival advantages for the induction chemotherapy arm.

Rosell et al[57,58] in Barcelona randomized 60 stage IIIA patients to either surgery alone or three cycles of induction chemotherapy with mitomycin C, ifosfamide, and cisplatin followed by surgery. All patients received postoperative radiation therapy. Lymph nodes were pathologically staged initially by mediastinoscopy in only 73% of patients. Twenty-seven percent of patients had more favorable T3N0 or T3N1 tumors. A significant survival advantage was seen in the induction chemotherapy-surgery arm with a 22-month median survival compared to 10 months in the surgery only arm ($p < 0.005$). The 2- and 5-year survival rates were 29% and 17% for the chemotherapy-surgery arm vs 5% and 0% in the surgery-only arms, respectively. Although encouraging, this study has been criticized not only for the small number of patients but also for the significant imbalance of patients with poor prognosis *K-ras* mutations and aneuploid tumors in the surgery-only arm, which may have adversely biased the outcome in this arm. Also, there were no 5-year survivors in the surgery-only arm, which is surprising because 27% of the patients had more favorable T3N0 or T3N1 tumors.

Roth et al[59,60] at MD Anderson also randomized 60 stage IIIA patients to surgical resection alone or three cycles of induction chemotherapy with cyclophosphamide, etoposide, and cisplatin followed by surgery and then three cycles postoperatively. Postoperative radiation therapy was given only to incompletely resected patients. Only 83% of patients had disease invasively staged before treatment. Also, 26% of patients had more favorable T3N0 or T3N1 tumors. The median survivals were 21 months for the chemotherapy-surgery arm versus 14 months for the surgery-only arm ($p = 0.048$). The 3- and 5-year survival rates likewise favored the chemotherapy-surgery arm at 46% and 36%, compared to 19% and 15% in the surgery-only arms, respectively. This study has also been criticized for its small patient numbers as well as a significant postoperative stage imbalance with 40% stage IIIB and IV patients in the surgery-only arm compared with 11% in the chemotherapy-surgery arm. However, this imbalance potentially could have been the result of down-staging in the chemotherapy-surgery arm because of the induction therapy. Although encouraging, the clinical implications of the results of these small randomized trials are unclear.

The most recent neoadjuvant chemotherapy trial with all stages is from Depierre et al[64] with the French Thoracic Cooperative Group. From 1991 through 1997, they randomized 373 patients with stages IB, II, and IIIA together into two treatment arms: primary surgery vs two cycles preoperative chemotherapy with mitomycin C, ifosfamide, and cisplatin followed by surgical resection and then two cycles postoperatively. Patients in both arms found postoperatively to have pathologic T3 or N2 disease received postoperative radiotherapy. The prerandomization stage was determined clinically based on chest CT, and any lymph node > 1 cm in short-axis diameter was considered positive for purposes of staging. The overall response to preoperative chemotherapy was 64%. The median survival overall with the combined stages was 37 months in the chemotherapy-surgery arm and 26 months in the surgery-only arm ($p = 0.15$). In a subset analysis, patients with N0 and N1 disease had significant improvements in disease-free and overall survival in the chemotherapy-surgery arm compared to surgery only. For the subset of 167 patients with stage IIIA disease (92 patients in chemotherapy-surgery arm; 75 patients in surgery-only arm), there was no significant difference in survival in the two treatment arms, with an estimated 5-year survival of approximately 29% in the chemotherapy-surgery group compared to 20% in the surgery only group (survivals estimated from the published survival curves). Unfortunately, the subset analysis in the published report was not complete. This study may be criticized in a number of aspects, most notably for the lack of preoperative invasive histologic verification of nodal stage before randomization, as well as the combination of diverse stages into the same study arm, thereby making the subset analysis of stages a retrospective exercise with potential imbalance of the patient groups. Despite the obvious deficiencies when evaluating theses results for stage IIIA patients, this study still fails to demonstrate any significant survival benefit for induction chemotherapy followed by surgery compared to surgery alone in locally advanced stage IIIA NSCLC.

The small recent Japanese Clinical Oncology Group 9202 trial[65] randomized 62 histologically proven stage IIIA (N2) patients to either three cycles of induction chemotherapy with cisplatin and vindesine vs surgery alone. Unfortunately, this well-designed study terminated prematurely because of poor accrual lowering the statistical power. After a median 6.2-year follow-up, there were no significant differences in the survival rates of the two arms (median survival, 17 mo in the chemotherapy group, vs 16 mo with surgery alone; $p = 0.5274$).

The 2005 metaanalysis of Berghmans et al[43] evaluating neoadjuvant chemotherapy in the four randomized trials (including the French Cooperative Trial) involving stage III patients found only a very marginal benefit in favor of induction chemotherapy

Table 6—*Randomized Controlled Trials of Preoperative Neoadjuvant (Induction) Therapy and Surgery vs Chemotherapy/Radiotherapy Alone (No Surgery) in Stage IIIA NSCLC

Source	Year	Patients, No.	Chemo/Radiotherapy/Surgery	Chemo-Radiotherapy	Median Survival, mo	Survival, %
Johnstone et al[66]	2002	73	Cis/Vb/Mito, no XRT	Cis/Vb/Mito + 64 Gy XRT	19.4(surgery) vs 17.4 (p = NS)	70 (surgery) vs 66 at 1 yr (p = NS)
Taylor et al[68]	2004	107	Cis-based, 2–4 cycles, no XRT	Cis-based 3 cycles + 69.9 Gy concurrent XRT	31 (surgery) vs 27 (p = NS)	33 (surgery) vs 30 at 5 yr (p = NS)
van Meerbeeck et al[69]	2005	333	Cis-based 3 cycles, no XRT	Cis-based 3 cycles + 60 Gy concurrent XRT	16.4 (surgery) vs 17.5 (p = NS)	16 (surgery) vs 13 at 5 yr (p = NS)
Albain et al[70]	2005	396	Cis/Et 2 cycles + 45 Gy XRT then Surg (26% oper mortality in pneumo)	Cis/Et 2 cycles + 61 Gy concurrent XRT	12.8 (surgery) vs 10.5 (progression-free) [p = 0.017]	27.2 (surgery) vs 20.3 at 5 yr (p = 0.10)

*Oper = operative; Pneumo = pneumonectomy; see other tables for expansion of abbreviations.

(hazard ratio with a random effect, 0.66; 95% confidence interval, 0.48 to 0.93).

The most recent phase III trials (Table 6) of neoadjuvant therapy that were designed specifically for stage IIIA lung cancer took a slightly different approach, comparing induction chemotherapy followed by surgery versus chemoradiotherapy alone (no surgery). This strategy was intended to test which local treatment modality (surgery or radiotherapy) is most efficacious. The Radiation Therapy Oncology Group (RTOG) 8901 trial[67] published in 2002 treated 73 patients with histologically proven N2 disease with cisplatin, vinblastine, and mitomycin C (mitomycin C was eliminated later) then randomized the patients to surgery or 64 Gy radiotherapy, followed by consolidation chemotherapy with cisplatin and vinblastine. Local control and survival rates were essentially equal between the two arms, although low accrual rates to the study lowered the statistical power of the study.

Taylor et al[68] at MD Anderson in 2004 published their trial of 107 patients with "clinical" stage IIIA NSCLC who were randomized to receive either two to four cycles of cisplatin-based chemotherapy followed by surgery and postoperative radiotherapy (64% of patients) vs the concurrent chemotherapy/radiotherapy arm (three cycles of cisplatin-based chemotherapy plus 69.9-Gy radiotherapy). After a mean 20-month follow-up, there was no significant difference in the two treatment groups for local control and survival rates. Of interest, surgical patients whose disease responded to induction chemotherapy had a significantly improved 5-year survival rate over those with stable or progressive disease (50% vs 16%; p = 0.0001).

The large European Organization for Research and Treatment of Cancer 08941 trial[69] presented at the American Society of Clinical Oncology meeting in 2005 treated 333 histologically proven stage IIIA (N2) patients with three cycles of cisplatin-based chemotherapy, then randomized them to surgery (with optional postoperative radiotherapy in 39%) vs sequential 60-Gy thoracic radiotherapy. Complete resection was performed in only 51% patients in the surgical arm, but there was pathologic down-staging in 42%. After a median 72-month follow-up, there was no significant difference in overall survival (35% surgery vs 41% at 2 years; hazard ratio, 0.95) or progression-free survival (2-year progression-free survival 27% surgery vs 24%; p = 0.6).

The more recent of the North American Intergroup 0196 trial[70] presented in 2005 had 396 patients with histologically proven stage IIIA NSCLC that were technically resectable and who were randomized to either chemotherapy (two cycles cisplatin/etoposide) and concurrent 45-Gy radiotherapy followed by surgery (with two cycles postoperative

chemotherapy) vs two cycles cisplatin/etoposide and 61 Gy radiotherapy. Treatment-related mortality was higher in the surgery group (7.9%) vs the nonsurgical arm (2.1%). Surgical mortality was particularly high in pneumonectomies (26%). In the surgical arm, there was a complete pathologic response in 18%, and down-staging with nodal clearance in 46%. Progression-free survival was significantly better in the surgical arm but the overall 5-year survival was similar in the two arms (27.2% surgical vs 20.3%; $p = 0.10$). However the 5-year survival in the surgical arm with complete pathologic clearing of lymph node disease was significantly greater at 41% ($p < 0.0001$).

As is apparent from Tables 5 and 6, the evidence favoring induction chemotherapy followed by surgery in stage IIIA NSCLC is marginal at best, even in the larger trials in which there is pretreatment histologic confirmation of accurate staging. Although the use of induction chemotherapy (with or without radiotherapy with N2 disease) followed by surgery in stage IIIA lung cancer appears feasible, published data do not support this treatment as the standard of care in the community. Ideally, this approach should only be administered in the setting of an investigational protocol. Finally, the older patient or the poor performance status patient should still be approached with caution when considering these aggressive multimodality protocols.

Recommendations

6. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), referral for multidisciplinary evaluation (which includes a thoracic surgeon) is recommended before embarking on definitive treatment. Grade of recommendation, 1C

7. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), induction therapy followed by surgery is not recommended except as part of a clinical trial. Grade of recommendation, 1C

8. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$) who do receive induction chemoradiotherapy as part of a clinical trial, pneumonectomy is not recommended. The subsequent surgical resection in this setting should be limited to a lobectomy. If after induction chemoradiotherapy it appears that a pneumonectomy will be needed, it is recommended that pneumonectomy not be performed and treatment should be continued with full-dose radiotherapy. Grade of recommendation, 1B

9. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), primary surgical resection followed by adjuvant therapy is not recommended except as part of a clinical trial. Grade of recommendation, 1C

10. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), surgery alone is not recommended. Grade of recommendation, 1A

11. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), platinum-based combination chemoradiotherapy is recommended as primary treatment. Grade of recommendation, 1B

Surgical Considerations in Stage $IIIA_3$

Although the use of neoadjuvant chemotherapy with or without radiotherapy may have potential advantages in the treatment of locally advanced lung cancer, concern has been raised in numerous publications about the possible increase in morbidity and mortality of the subsequent lung resections. One of the reports by Roberts et al[71] in 2001 found neoadjuvant chemotherapy increased the perioperative complications in their series of 34 patients. However, other groups such as Sonett et al[72] in 1999 reported safe pulmonary resections after chemotherapy and high-dose thoracic radiation in 19 patients. Siegenthaler et al[73] at MD Anderson in a larger group of 380 patients found no increased surgical morbidity with preoperative chemotherapy in lung cancer when compared to their nonchemotherapy lung resection patients.

There is no doubt that patients with locally advanced lung cancer who undergo neoadjuvant therapy present more intraoperative technical challenges to the thoracic surgeon and require more careful postoperative care. But with certain extra precautions, safe lung resections are indeed possible, especially if the surgeon is experienced with this patient population and is performing a high volume of lung resections. As early as 1992, Romano and Mark[74] reported that hospitals performing a high volume of lung resections experienced significantly better outcomes compared to lower volume hospitals. Using the Surveillance, Epidemiology, and End Results Cancer Registries that are linked to data on Medicare hospitalizations) database, Bach et al[75] in 2001 reviewed 2,118 patients from 76 hospitals sampled from 22 states. They found that patients who undergo lung cancer resections at hospitals that perform large numbers of the procedures are more likely to survive longer than patients who undergo such surgery at hospitals performing a low volume of lung resections. Finally, Silvestri et al[76] reviewed the South Carolina statewide results of lung cancer resections in all nonfederal acute care hospitals from 1991 to 1995.

They found that the mortality for lung cancer resection was lower when the surgery was performed by a thoracic surgeon compared to a general surgeon.

The definition of what is meant by "resectable," "marginally resectable," and "unresectable" is not clear in most published studies. The problem is that this determination is subjective and highly dependent on the experience and expertise of the thoracic surgeon. For the best possible evaluation of an induction therapy candidate, the surgeon who ultimately may operate on the stage IIIA patient needs to be experienced in the handling of these more complex and technically challenging patients. Also, it is critically important that the surgeon is also involved initially in the beginning of the evaluation, such that an informed estimate of the surgical resectability of the tumor can be made initially, so that appropriate candidates for induction therapy are chosen.

The decision to proceed with surgery after induction therapy should not be automatic. While there is evidence that 60 to 75% of patients will respond to induction regimens, nonresponders should not necessarily undergo surgery. Although the data are not conclusive, a combination of anatomic (CT scan) and physiologic (PET scan) imaging may be useful in this decision-making process. In the phase II Southwestern Oncology Group trial[77] of induction chemoradiotherapy followed by surgery in stages IIIA and IIIB disease, there was complete pathologic clearance of tumor in 22% of resection specimens with an overall 27% 3-year survival rate. Of particular interest, the patients with a complete pathologic clearing of residual disease had a 30-month median survival, compared to 10 months for those with residual tumor in the lymph nodes ($p = 0.0005$). A more recent study by Bueno et al[78] emphasized the importance of residual nodal disease after induction therapy in stage IIIA tumors. In their study, the long-term survival stratified by nodal status after induction therapy and lung resection found that 28% of patients down-staged to pathologic N0 had a 35.8% 5-year survival rate, whereas the remainder of patients with residual nodal disease at surgery had only a 9% 5-year survival rate. These and other studies suggest that surgical resection should be avoided after induction therapy in patients who have definite biopsy-proven residual tumor in the mediastinal nodes.

Clinical restaging with standard chest CT scans is not accurate enough to predict pathologic response in the lymph nodes, as recently reported by Margaritora et al.[79] The use of PET after induction therapy to determine response to therapy looks somewhat promising with current studies summarized in Table 7. Early small studies found up to 100% accuracy with PET restaging after induction chemotherapy (100% in one small preliminary trial).[80] In a retrospective review of the accuracy of PET scans after induction chemotherapy, radiotherapy, or both in 56 patients who underwent subsequent surgery, Akhurst et al[81] found that PET had a 98% positive predictive value for detecting residual viable disease in the primary tumor. However, PET overstaged the

Table 7—*Accuracy of ^{18}F Fluorodeoxyglucose-PET for Diagnosis of Residual Tumor or Mediastinal Disease After Induction Chemotherapy or Chemoradiotherapy in Surgically Treated Patients With Stage IIIA NSCLC

Source	Year	Patients, No.	Primary Tumor				Mediastinal Lymph Nodes (Calculated per Nodal Station)				Median Survival
			Se	Sp	PPV	NPV	Se	Sp	PPV	NPV	
Vansteenkiste et al[80]	1998	15 (9 surgical)					100	100	100	100	Better with mediastinal clearance of > 50% decrease in SUV of primary tumor after IC
Akhurst et al[81]	2002	56	90	67	98	29	77	57	63	27	NR
Hellwig et al[82]‖	2004	47	81	64	84	58	50†, 64‡, 64§	88, 79, 96	57, 33, 70	85, 93, 94	After resection > 56 mo with SUV < 4; 19 mo with SUV ≥ 4 ($p < 0.001$)
Cerfolio et al[83]‖	2006	93					68	88	75	80	NR

*IC = induction chemotherapy; NPV = negative predictive value; PPV = positive predictive value; Se = sensitivity; Sp = specificity. See Table 5 for expansion of abbreviation not used in the text.

†Calculated per patient.

‡Quantitative reading.

§Visual (qualitative) reading.

‖Induction chemoradiotherapy used.

nodal status in 33%, understaged it in 15%, and was correct in only 52%. They concluded that after induction therapy, PET accurately detects residual viable primary tumor but not the involvement of mediastinal nodes.

In a subsequent study, Hellwig et al[82] reevaluated 47 patients with FDG-PET after induction chemoradiotherapy in stage IIIA disease, finding unexpected metastases in nine patients. The standardized uptake value (SUV) was higher with viable residual primary tumor than those with no viable tumor, with an SUV > 5.8 indicating viability of the tumor after chemotherapy. Median survival after resection was significantly greater when the tumor SUV was < 4 (56 mo with SUV < 4 vs 19 mo with SUV > 4; $p < 0.001$). The reevaluation of the mediastinal lymph nodes in this study was more accurate. There was a high negative predictive value of PET in mediastinal restaging especially with visual reading of the PET scan, which the authors concluded allows omission of repeat invasive mediastinal restaging.

The most recent trial by Cerfolio et al[83] prospectively evaluated the accuracy of fusion PET/CT and conventional CT in restaging 93 patients after induction chemoradiotherapy. They found that the percentage change in the SUV (MaxSUV) when restaging the primary tumor was an accurate predictor of pathologic response, such that a decrease of $> 75\%$ of MaxSUV suggested no viable malignant cells in the primary tumor. A decrease of $> 50\%$ in the MaxSUV in mediastinal lymph nodes suggested complete tumor clearing. Still, the 20% false-negative rate and 25% false-positive rate in lymph nodes strongly argues for rebiopsy of nodes in question. Although the authors found integrated PET/CT to be more accurate than standard CT in reevaluation of staging after induction therapy especially in stage 0 and I disease, results are not accurate enough to make firm treatment decisions without histologic confirmation.

Therefore, until further refinements in imaging techniques are available, it is premature to routinely use postinduction therapy PET scans for restaging to make decisions about surgical resectability and particularly whether there is residual nodal involvement with viable tumor. Finally, careful reevaluation for surgery after induction therapy is necessary because incomplete resection or thoracotomy with no resection results in a poor survival in the stage IIIA patient.

Recommendations

12. *Surgical Considerations*: In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), surgical debulking procedures are not recommended. Grade of recommendation, 1A

13. *Surgical Considerations*: In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$) who have incomplete resections, postoperative platinum-based chemoradiotherapy is recommended. Grade of recommendation, 1C

Unresectable Bulky N2 Disease (Stage $IIIA_4$)

Many patients with stage IIIA lung cancer have less favorable presentations of their disease because they have bulky nodal involvement and/or unresectable primary tumors. Evaluation of various trials in this subset of patients is complicated by a lack of definition of what constitutes "bulky" nodal disease as well as what is "unresectable." It is generally agreed that mediastinal lymph nodes > 1 cm diameter in short axis are suspicious. We then would define bulky nodal disease as those involving lymph nodes > 2 cm in short-axis diameter measured by chest CT, especially with extranodal involvement, multistation nodal disease, and/or groupings of multiple positive smaller lymph nodes. Nevertheless, this determination is somewhat subjective, much like the definition of resectability, which relies on the experience and judgment of the thoracic surgeon.

However, aside from the relatively few questionable presentations, most experienced lung cancer clinicians can agree on what constitutes unresectable bulky N2 stage IIIA disease that warrants only nonsurgical therapy. Traditionally, these patients with locally advanced disease were treated with conventional radiotherapy alone with relatively poor long-term survivals, but in the past decade combination chemoradiotherapy appears to offer improved results, as discussed in the next sections.

Radiotherapy Alone

Early attempts to use nonsurgical treatment modalities for unresectable locally advanced disease (our stage $IIIA_4$) involved single modality chest radiotherapy, yielding poor survival rates at 5 years of 5 to 10% with traditional dose and fractionation schedules (1.8 to 2.0 Gy per fraction per day to 60 to 70 Gy in 6 to 7 weeks). Patterns of failure for patients treated with radiotherapy alone included both locoregional and distant failures. Attempts to improve on locoregional control tested alternative radiotherapy doses and schedules, applying radiotherapy at escalating doses at shortened intervals (hyperfractionation) that, in theory, would maximize cell killing in lung cancers with relatively short doubling times. A hyperfractionated, higher-dose radiotherapy trial[84] used from 60.0 to 79.2 Gy delivered in smaller-than-standard fractions administered in two fractions per

day rather than one. Hyperfractionation of radiotherapy yielded an improved but still poor 2-year survival rate of 20%, with an apparent benefit for patients treated at 69.6 Gy. There appeared to be acceptable acute or late toxicity using the hyperfractionated schedule.[84]

Further alterations of standard dose and fractionation led to testing accelerated hyperfractionation. In the United Kingdom, three radiotherapy fractions were delivered per day in a continuous schedule (7 days rather than 5 days per week) for > 12 days to a total dose of 50.4 Gy or 54 Gy. This continuous hyperfractionated accelerated radiation therapy (CHART) regimen yielded good radiographic responses in tumors with an acceptable early and late toxicity profile. In a randomized trial[85] comparing CHART with a standard dose and fractionation radiotherapy regimen in locally advanced NSCLC, there was a survival advantage for CHART. American groups have used versions of CHART that eliminate the weekend doses and deliver multiple daily fractions within an 8-hour time period, referred to as hyperfractionated accelerated radiation therapy (HART). A recent Eastern Cooperative Oncology Group (ECOG) pilot study (ECOG 4593) used this schedule and obtained a preliminary median survival of 13 months with acceptable toxicities, primarily esophagitis, at the completion of radiotherapy.[86] In a subsequent companion quality of life assessment of patients undergoing the accelerated HART regimen in EGOG 4593, Auchter et al[87] found that the decrement in physical and functional quality of life during treatment returned to baseline within 4 weeks of completing treatment. However, the emotional well-being of patients improved at all time points.

Recently, the ECOG conducted a multicenter trial for unresectable locally advanced stage IIIA and IIIB NSCLC (ECOG 2597) in which patients were randomized after induction chemotherapy with two cycles carboplatin and paclitaxel to standard fractionation radiotherapy to a total dose of 64 Gy vs HART to a total dose of 57.6 Gy in a randomized design.[88] The trial entered 141 patients into the trial (only 42% of the target), but it closed early because of slow accrual, mucosal toxicity, and logistics of administering HART. Although statistical significance was not reached (possibly because it was underpowered), the median survival rates were 20.3 months for the HART arm vs 14.9 months for standard fractionation radiotherapy ($p = 0.28$). There was a nonsignificant trend for improved 3-year survival with 34% (HART) vs 14% for standard radiotherapy. The findings in this study suggest that this technique of accelerated radiotherapy may work by altering tumor cell kinetics resulting in adverse affects on tumor repopulation and improved patient survival, all arguing for additional future exploration of the HART treatment strategy.

Combined Chemotherapy With Radiotherapy

Although patients have gained symptomatic benefit with radiotherapy for unresectable bulky locally advanced stage IIIA disease, their outcome has generally been poor, usually as a result of systemic not local failure. With the development of more effective platinum-based chemotherapy, attempts to improve outcome of treatment by decreasing relapse from distant disease have prompted the addition of systemic chemotherapy to definitive radiotherapy. Chemotherapy has been combined with radiotherapy in different fashions (chemotherapy followed sequentially by radiotherapy, concurrent chemotherapy/radiotherapy, induction chemotherapy followed by concurrent chemotherapy/radiotherapy, or concurrent chemotherapy/radiotherapy followed by consolidation chemotherapy) in multiple phase II trials involving heterogeneous and often poorly staged groups of patients with locally advanced disease.

In general, trials using platinum-containing chemotherapy regimens in combination with radiotherapy have shown good tumor response rates and have suggested an improvement in survival. One promising pilot trial[89] showed significantly improved median and 2-year survival rates of 16 months and 30%, respectively, using four cycles of etoposide and cisplatin with concurrent radiotherapy to 60 Gy. Looking at collective data from multiple phase II trials, acute and late toxicities associated with combined chemotherapy and radiotherapy have included mild to severe esophagitis, pneumonitis, and also treatment-related deaths. Overall, however, these trials showed the feasibility of combined modality therapy and suggested that chemotherapy plus radiotherapy would yield improved outcomes compared to radiotherapy alone.

Multiple phase III trials using platinum chemotherapy plus radiotherapy have confirmed improved survivals for chemotherapy plus radiotherapy compared to radiotherapy alone. Selected key trials are outlined in Table 8, with some trials discussed in this article. Of note, the earliest trials were negative showing no survival benefit with chemotherapy but the regimens used had either low-dose cisplatin or nonplatinum-based chemotherapy, which might be expected to be ineffective. Later trials using more appropriate dose chemotherapy all had positive results.

A pivotal CALGB randomized trial[98] initially presented in 1990 showed the benefit of adding chemotherapy in a sequential fashion to radiotherapy in the setting of locally advanced disease. The study com-

Table 8—*Randomized Controlled Trials of Sequential or Concurrent Chemoradiotherapy vs Radiotherapy Alone for Unresectable Stage III NSCLC**

Source	Year	Patients, No.	Timing CT/RT	Chemotherapy Radiotherapy Regimens, Gy	Study Result	Acute Toxicity CT+RT/RT, %	2-yr Survival CT+RT/RT, %
Soresi et al[90]	1988	95	Concurrent	Cis, 50	Neg		40/25
Mattson et al[91]	1988	238	Sequential plus concurrent	CAP, 55	Neg		19/17
Ansari et al[92]	1991	183	Concurrent	Cis, 60	Neg		15/9
Morton et al[93]	1991	114	Sequential	MACC, 60	Neg	21/9	21/16
Trovo et al[94]	1992	173	Concurrent	Cis, 45	Neg	15/7	13/13
Schaake-Koning et al[95]	1992	308	Concurrent	Cis, 55 (split course)	Pos	41/11	26/13
Wolf et al[96]	1994	85	Sequential plus concurrent	Vd/Ifos/Cis, 50	Pos	8.2/11	24/12
Le Chevalier et al[97]	1994	353	Sequential	Vd/Lo/Cis/Cyc, 65	Pos		21/14
Dillman et al[98]	1996	155	Sequential	Cis/Vinbl, 60	Pos	14/6	26/13
Jeremic et al[99]	1996	131	Concurrent	Carbo/Et, 69.9 bid	Pos		52/38
Cullen et al[100]	1999	446	Sequential	Mito/Ifos/Cis median, 50	Neg		20/16 (p = 0.14)
Sause et al[101]	2000	490	Sequential	Cis/Vb, + 60 vs standard RT vs Hyper	Pos	Chemo, 3.4; RT, 2.3; Hyper, 2.0	Chemo, 32; RT, 21; Hyper, 24 (p = 0.04)

*Carbo = carboplatin; Hyper = hyperfractionated radiotherapy; Lo = loumustine; MACC = methotrexate-doxorubicin-cyclophosphamide-lomustine; Mito = mitomycin; Neg = negative; Pos = positive. See other Tables for expansion of abbreviations.

pared two cycles of cisplatin and vinblastine added to standard fractionation radiotherapy (60 Gy) versus radiotherapy alone in patients with favorable prognostic characteristics (good performance status and minimal weight loss). Objective tumor response rate was improved for the chemotherapy plus radiotherapy group compared to radiotherapy alone (56% vs 43%; p = 0.012) and survival at 2 years and 5 years was also improved (26% and 13%, vs 13% and 6%, respectively).

A multicenter French study reported by Le Chevalier et al[102] also confirmed improved survival for the chemotherapy plus radiotherapy arm compared to radiotherapy alone (3-year survival rates of 11% vs 5%, respectively) with an improved distant failure rate for chemotherapy plus radiotherapy (22% vs 46% at 1 year, respectively). Unfortunately, both treatment groups showed similarly high locoregional failure with 1-year local control rates of only 15% and 17%, illustrating the vexing problem of obtaining good locoregional control of disease in the locally advanced setting. Three metaanalyses[31,103,104] reviewing > 50 trials have confirmed the survival benefit of combined platinum-based chemotherapy with radiotherapy over radiotherapy alone in locally advanced unresectable NSCLC.

A subsequent large British trial[100] randomized 446 patients with localized unresectable disease to two arms: (1) chemotherapy (mitomycin C, ifosfamide, and cisplatin) followed by radical radiotherapy (median, 50 Gy; range, 40 to 60 Gy); or (2) radical radiotherapy alone (median, 50 Gy; range, 40 to 64 Gy). This trial allowed lower performance status 2 (ECOG performance status 2) patients, and 15% of the chemoradiotherapy arm and 11% of the radiotherapy-only arm were ECOG performance status 2 patients. The median survival and 2-year survival rates were not significantly different (p = 0.14) between the two arms: 11.7 months and 20% in the chemoradiotherapy arm, and 9.7 months and 16% in the radiotherapy arm. The inclusion of the poorer performance status patients in this trial, unlike most other trials, is thought to have influenced the results, particularly in the chemoradiotherapy arm.

However, when patients were selected with a good performance status (Karnofsky ≥ 70) and minimal weight loss (< 5%), the superiority of combined-modality chemotherapy plus radiotherapy in a sequential fashion compared to radiotherapy alone was readily demonstrated in a large randomized trial[101] of 458 patients with unresectable stages II, IIIA, and IIIB, performed by the Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and the Southwest Oncology Group. The final results showed improved 2-year, 5-year, and median survival rates with chemotherapy followed sequentially by conventional radiotherapy, which was significantly better than either conventional radiotherapy or hyperfractionated radiotherapy alone.

Concurrent Chemotherapy and Radiotherapy

With the combination of chemotherapy and radiotherapy demonstrating unequivocal improved survival over radiotherapy alone in locally advanced unresectable stage III NSCLC, this combination has become the standard of care worldwide. The remaining question now is, what is the optimal delivery strategy for treatment?

Concurrent chemotherapy with radiotherapy has been studied in the locally advanced setting through randomized trials that have attempted to capitalize on the radiosensitizing properties of chemotherapy. A European Organization for Research and Treatment of Cancer three-arm trial[95] published in 1992 compared radiotherapy (split course) concurrent with daily or weekly concurrent cisplatin to radiotherapy alone. There were improved 2-year and 3-year survival rates for daily chemotherapy concurrent with radiotherapy compared with radiotherapy alone (26% and 16%, vs 13% and 2%, respectively). There was no significant advantage for the weekly chemotherapy plus radiotherapy arm, with an intermediate survival compared to the other arms.

Whether concurrent chemotherapy plus radiotherapy yields an improvement in survival over sequential chemotherapy plus radiotherapy has been addressed by a few subsequent trials including a large Japanese randomized trial[105] of 320 patients that compared chemotherapy (mitomycin C, vindesine, and cisplatin for two cycles) concurrent with split-course daily radiotherapy to 56 Gy compared to chemotherapy followed by continuous daily radiotherapy to 56 Gy. Esophagitis rates were low with concurrent therapy. At a 5-year median follow-up, 2-year and 5-year survival rates were improved for concurrent chemotherapy over sequential chemotherapy with radiotherapy (34.6% and 15.8%, vs 27.4% and 8.8%, respectively). Myelosuppression was greater among patients in the concurrent arm, but the mortality rate was low ($< 1\%$) and not significantly different in both groups.

A later RTOG trial[106] (RTOG 9410) randomized 610 patients with unresectable stage II and III to one of three arms: (1) sequential chemotherapy with cisplatin and vinblastine followed by 60-Gy radiotherapy; (2) concurrent chemotherapy with cisplatin and vinblastine with daily radiotherapy to 60 Gy; or (3) concurrent chemotherapy with cisplatin and vinblastine with twice-daily radiotherapy. The concurrent chemotherapy with daily radiotherapy significantly improved median and 4-year survival rates over sequential chemotherapy/radiotherapy, and the concurrent chemotherapy with twice-daily radiotherapy had intermediate rates. The 4-year survival rates were 12% sequential vs 21% concurrent chemotherapy/radiotherapy daily vs 17% concurrent chemotherapy/radiotherapy twice daily ($p = 0.46$). As expected, acute toxicity was somewhat higher in the concurrent arms, but late toxicity rates were similar.

Concurrent chemoradiotherapy has several drawbacks, including the difficulty in maintaining full-dose chemotherapy to treat systemic disease, especially with some of the newer agents such as gemcitabine, docetaxel, and paclitaxel, all of which require dose reductions when given concurrently with radiotherapy. Concurrent chemotherapy/radiotherapy also has increased local adverse effects (esophagitis and pneumonitis). Finally, although concurrent is superior to sequential therapy, the long-term survival rates for patients remain low.

Another approach has been induction full-dose chemotherapy, which is intended to address micrometastases, before starting concurrent chemoradiotherapy. Three major randomized trials addressed this approach (CALGB/ECOG,[107] French Lung Cancer Study Group,[108] and CALGB 39801[109]); however, unfortunately, the results did not show any survival benefit for induction chemotherapy followed by concurrent chemotherapy/radiotherapy over concurrent chemoradiation alone.

More recently, interest has focused on the evaluation of concurrent chemoradiotherapy followed by consolidation chemotherapy. The Southwest Oncology Group began with a small phase II trial (Southwest Oncology Group 9019) enrolling 50 patients with stage IIIB NSCLC who received cisplatin/etoposide with concurrent radiotherapy (61 Gy) followed by two additional cycles of cisplatin/etoposide.[110] The 5-year survival rate of 15% was encouraging and led to the Southwest Oncology Group 9504 phase II trial[111,112] of 83 patients receiving concurrent chemotherapy/radiotherapy with cisplatin/etoposide and 61 Gy radiotherapy, but the follow-up consolidation was accomplished by docetaxel. The overall 5-year survival rate was 29% with docetaxel consolidation, which was much improved over the 15% rate with cisplatin/etoposide consolidation in the previous study. These highly encouraging results led to the larger ongoing phase III randomized trial Southwest Oncology Group 0023, which has accrued more than 500 patients. Patients with stage III NSCLC receive concurrent cisplatin/etoposide chemotherapy with radiotherapy followed by docetaxel consolidation chemotherapy, with subsequent randomization to maintenance gefitinib or placebo.[113] Preliminary results show a low incidence of pneumonitis (8%) and a median survival of 29 months (placebo) and 19 months (gefitinib) [$p = 0.09$]. Despite the lack of any favorable effect of gefitinib, this larger trial of concurrent chemotherapy/radiotherapy with docetaxel consolidation shows vary favorable survival rates compared to historical data. This technique of consolidation chemother-

apy is being investigated by the Hoosier Oncology Group LUN 01–24, currently undergoing accrual, which treats stage III patients with concurrent chemotherapy/radiotherapy then with randomization to docetaxel consolidation vs observation.

Although concurrent chemoradiotherapy (with its increased toxicity) in stage III NSCLC looks promising with its superior survival rates over sequential chemotherapy/radiotherapy treatment in good performance status patients, additional positive randomized trials will further cement this regimen in front as the preferred first-line treatment. Adding consolidation chemotherapy promises even greater survival gains, but awaits validation with larger randomized trials. The newer targeted therapies are theoretically attractive either in combination with concurrent therapy (perhaps functioning as radiosensitizers) or in the consolidation setting. Again, further clinical trials are needed to define the optimal role of these novel agents in treatment strategies for unresectable IIIA (N2) disease. The subsequent chapter on treatment of stage IIIB disease reviews chemoradiotherapy for unresectable locally advanced NSCLC in more depth.

Recommendations

14. In patients with NSCLC who have bulky N2 disease ($IIIA_4$) and good performance status, radiotherapy alone is not recommended. Grade of recommendation, 1A

15. In patients with NSCLC who have bulky N2 disease ($IIIA_4$) and good performance status, combination platinum-based chemotherapy and radiotherapy are recommended. Grade of recommendation, 1A

16. In patients with NSCLC who have bulky N2 disease ($IIIA_4$), good performance status and minimal weight loss, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy. Grade of recommendation, 1A

Conclusion

Despite many earlier studies, the optimal treatment recommendations in the various clinical presentations of stage IIIA (N2) disease are still evolving. Hopefully, as the current and future phase III trials accrue and mature and the much needed subsequent randomized trials with newer chemotherapy agents and radiotherapy schemata are started and completed, more definitive treatment guidelines will emerge. Novel new agents including small peptides as well as molecular-directed chemotherapy and immunostimulating techniques may significantly change the future recommendations in stage IIIA disease. Until that time, it is critically important that, whenever possible, clinicians who manage locally advanced NSCLC enroll their patients in every available clinical trial.

Summary of Recommendations

1. *Surgical Considerations:* In patients with NSCLC who have incidental (occult) N2 disease ($IIIA_2$) found at surgical resection and in whom complete resection of the lymph nodes and primary tumor is technically possible, completion of the planned lung resection and mediastinal lymphadenectomy is recommended. Grade of recommendation, 2C

2. *Surgical Considerations:* In patients with NSCLC undergoing surgical resection, systematic mediastinal lymph node sampling or complete mediastinal lymph node dissection is recommended. Grade of recommendation, 1B

3. *Adjuvant Chemotherapy:* In patients with resected NSCLC who were found to have incidental (occult) N2 disease ($IIIA_{1–2}$) and who have good performance status, adjuvant platinum-based chemotherapy is recommended. Grade of recommendation, 1A

4. *Adjuvant Radiotherapy:* In patients with resected NSCLC who were found to have incidental (occult) N2 disease ($IIIA_{1–2}$), adjuvant postoperative radiotherapy should be considered after adjuvant chemotherapy to reduce local recurrence. Grade of recommendation, 2C

5. *Adjuvant Chemoradiotherpy:* In patients with resected NSCLC who were found to have incidental (occult) N2 disease ($IIIA_{1–2}$), combined postoperative concurrent chemotherapy and radiotherapy is not recommended except as part of a clinical trial. Grade of recommendation, 1B

6. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), referral for multidisciplinary evaluation (which includes a thoracic surgeon) is recommended before embarking on definitive treatment. Grade of recommendation, 1C

7. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), induction therapy followed by surgery is not recommended except as part of a clinical trial. Grade of recommendation, 1C

8. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$) who do receive induction chemoradiotherapy as part of a clinical trial, pneumonectomy is not recommended. The subsequent surgical resection in this setting should be limited to a lobectomy. If after induction chemoradiotherapy it appears that a pneumonectomy will be needed, it is recommended that pneumonectomy not be performed and treatment should be continued with full-dose radiotherapy. Grade of recommendation, 1B

9. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), primary surgical resection followed by adjuvant therapy is not recommended except as part of a clinical trial. Grade of recommendation, 1C

10. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), surgery alone is not recommended. Grade of recommendation, 1A

11. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), platinum-based combination chemoradiotherapy is recommended as primary treatment. Grade of recommendation, 1B

12. *Surgical Considerations:* In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), surgical debulking procedures are not recommended. Grade of recommendation, 1A

13. *Surgical Considerations:* In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$) who have incomplete resections, postoperative platinum-based chemoradiotherapy is recommended. Grade of recommendation, 1C

14. In patients with NSCLC who have bulky N2 disease ($IIIA_4$) and good performance status, radiotherapy alone is not recommended. Grade of recommendation, 1A

15. In patients with NSCLC who have bulky N2 disease ($IIIA_4$) and good performance status, combination platinum-based chemotherapy and radiotherapy are recommended. Grade of recommendation, 1A

16. In patients with NSCLC who have bulky N2 disease ($IIIA_4$), good performance status, and minimal weight loss, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy. Grade of recommendation, 1A

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Treatment of Non-small Cell Lung Cancer, Stage IIIB*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Objective: **To develop evidence-based guidelines on best available treatment options for patients with stage IIIB non-small cell lung cancer (NSCLC).**
Methods: **A review was conducted of published English-language (abstract or full text) phase II or phase III trials and guidelines from other organizations that address management of the various categories of stage IIIB disease. The literature search was provided by the Duke University Center for Clinical Health Policy Research and supplemented by any additional studies known by the authors.**
Results: **Surgery may be indicated for carefully selected patients with T4N0-1M0. Patients with N3 nodal involvement are not considered to be surgical candidates. For individuals with unresectable disease, good performance score, and minimal weight loss, treatment with combined chemoradiotherapy results in better survival than radiotherapy (RT) alone. Concurrent chemoradiotherapy seems to be associated with improved survival compared with sequential chemoradiotherapy. Multiple daily fractions of RT when combined with chemotherapy have not been shown to result in improved survival compared with standard once-daily RT combined with chemotherapy. The optimal chemotherapy agents and the number of cycles of treatment to combine with RT are uncertain.**
Conclusion: **Prospective trials are needed to answer important questions, such as the role of induction therapy in patients with potentially resectable stage IIIB disease. Future trials are needed to answer the questions of optimal chemotherapy agents and radiation fractionation schedule. The role of targeted novel agents in combination with chemoradiotherapy is just starting to be investigated.**
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Key words: chemoradiotherapy; hyperfractionated radiotherapy; radiotherapy; treatment stage IIIB

Abbreviations: CHART = continuous hyperfractionated radiotherapy; ECOG = Eastern Cooperative Oncology Group; F2 = 17 Gy in two fractions; F13 = 39 Gy in 13 fractions; MST = median survival time; NSCLC = non-small cell lung cancer; PS = performance score; RM = radiation myelopathy; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; SVC = superior vena cava

Stage IIIB non-small cell lung cancer (NSCLC) includes patients with T4 tumors; any N; M0; and any T, N3, M0.[1] It is estimated that 10 to 15% of all patients are at stage IIIB at the time of diagnosis of their disease.[1] On the basis of the Surveillance, Epidemiology, and End Results registry 2004, Wisnivesky et al[2] evaluated >80,000 cases of NSCLC with adequate documentation of

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tumor size (53% of total Surveillance, Epidemiology, and End Results registry) and reported that 17.6% were stage IIIB. The anticipated 5-year survival for the vast majority of patients who present with clinical stage IIIB NSCLC is 3 to 7%.[1] Data on pathologically staged IIIB disease was not available from the Mountain International Classification but will be included in the revised international staging system that is planned for 2009.

The optimal treatment for stage IIIB NSCLC depends on several variables, including the extent of disease, age, comorbid risk factors, patient performance status (PS), and weight loss. Radiotherapy (RT) alone has been used in the past but should be limited to patients with poor PS. Chemotherapy alone is similarly not a good treatment option, except for patients with malignant pleural effusions (discussed in the "Treatment of Non-small Cell Lung Cancer, Stage IV" chapter). Palliative chemotherapy is not addressed in this article. Surgery can be offered to highly selected patients, either as a single modality or after induction (neoadjuvant) chemotherapy with or without RT. Concurrent chemoradiotherapy is recommended for most cases.

Materials and Methods

This section of the evidence-based guidelines is based on an extensive review of the medical literature from 2002 through mid-2006. A literature search was provided by the Duke University Center for Clinical Health Policy Research and supplemented by additional studies known by the authors. These reports included selected case series and pooled data analysis for rare clinical situations, such as superior vena cava (SVC) resection for T4 tumors. Data from four additional guidelines published since 2002 was reviewed along with 10 phase III trials and numerous phase II treatment trials addressing the more common treatment questions related to stage IIIB disease. Recommendations were developed by the writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), and reviewed by all members of the lung cancer panel before approval by the Thoracic Oncology NetWork, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.

Results

Limited Role of Surgery

Surgery may be indicated for meticulously culled patients with stage IIIB disease[3] (see "Special Treatment Issues in Lung Cancer" chapter). Patients who have T4N0-1 solely on the basis of a satellite tumor nodule(s) within the primary lobe have been reported to have 5-year survival rate of approximately 20%. These reports[4–6] are retrospective case series and pooled data analysis. Carinal resections with lobectomy or pneumonectomy have been performed for T4N0-1 disease.[7–10] Carinal resections carry an appreciable operative mortality of 10 to 15% in experienced centers.[7,8] Sleeve pneumonectomy has been estimated to have an operative mortality two to four times that of standard pneumonectomy.[9] The 5-year survival in these carefully selected retrospective series is approximately 20%. Similarly, surgical resection of the SVC for direct tumor invasion has been performed selectively.[11,12] A review[11] of 109 SVC resections from four international centers included 78 cases of resection for tumor involvement of the SVC and 31 cases for mediastinal lymph nodal involvement of the SVC. Fifty percent of the cases required a pneumonectomy. The operative mortality rate was 12%, and the 5-year survival rate was 21%. Both pneumonectomy and complete resection of the SVC with a prosthetic replacement were associated with a significant increased risk for death.

Trials of neoadjuvant chemotherapy or chemoradiotherapy followed by surgical resection have generally excluded patients with stage IIIB disease. Reports[13–15] of carefully chosen patients with stage IIIB disease have shown a similar survival to patients with stage IIIA disease when treated with induction therapy followed by resection. The overall 5-year survival rate is ≤20%. However, the subset of patients who have stage IIIB disease and demonstrate a complete pathologic response after induction therapy with no residual viable neoplasm identified in the surgical specimen may experience better survival rates. In patients who have stage IIIB NSCLC and are believed to be surgical candidates but are anticipated to require pneumonectomy, surgery with consideration of adjuvant chemotherapy without RT may be a preferable treatment option, because induction chemoradiation therapy followed by pneumonectomy has been shown to be associated with significant mortality risk.[16] For patients with stage IIIB disease and T4 tumors, the presence of N2 disease is considered to be a strong contraindication to surgery, which is consistent with the British Thoracic Society and National Comprehensive Cancer Network guidelines.[3,17] To date, no phase III data demonstrate that neoadjuvant treatment followed by surgery in patients with IIIB disease results in prolonged survival compared with treatment with chemoradiation therapy without surgery. Given the apparent low benefit/risk ratio, any patient who has clinical stage IIIB and is believed potentially to be a surgical candidate would best be evaluated by several disciplines, including a pulmonologist, medical and radiation oncologists, and thoracic surgeon, before treatment.

RECOMMENDATIONS

1. In selected patients with clinical T4N0-1 NSCLC as a result of satellite tumor nodule(s) in the same lobe, carinal involvement, or SVC invasion, it is recommended that evaluation be performed by a multidisciplinary team that includes a thoracic surgeon with lung cancer expertise to determine whether the tumor is operable. Surgery is not recommended when there is N2 involvement. Grade of recommendation, 1C

2. For patients with stage IIIB NSCLC as a result of N3 disease, treatment with neoadjuvant (induction) chemotherapy or chemoradiotherapy followed by surgery is not recommended. Grade of recommendation, 1C

RT Alone vs Combination Chemoradiotherapy

The vast majority of patients with IIIB disease do not benefit from surgery and are best treated with chemoradiotherapy or RT alone, depending on sites of tumor involvement, extent of disease, and PS. Since the American College of Chest Physicians guidelines in 2003, four additional guidelines have been published by the American Society of Clinical Oncology, Cochrane group, National Comprehensive Cancer Network, and Cancer Care Ontario.[17–20] The data for these guidelines were derived from randomized, prospective trials that evaluated patients with both unresectable IIIA and IIIB disease. Results of patients with IIIB disease alone are not independently available. Data in the Cancer Care Ontario guidelines included six metaanalyses and 17 randomized trials of chemotherapy vs RT.[20] The largest metaanalysis was performed by the NonSmall Cell Lung Cancer Collaborative Group as referenced in the last American College of Chest Physicians guidelines[21]; of 22 randomized trials evaluated, only 11 of these trials were with cisplatin-based chemotherapy. The trials with non–cisplatin-based chemotherapy did not demonstrate any survival benefit. The results showed a significant benefit with cisplatin-based chemoradiotherapy. There was a 13% reduction in the risk for death (hazard ratio, 0.87) and an absolute benefit of 4% at 2 years and 2% at 5 years ($p = 0.005$). Results of all four practice guidelines favored cisplatin-based chemoradiotherapy vs RT alone for patients with good PS (0 or 1) and minimal weight loss (≤5%).

RECOMMENDATIONS

3. For patients with stage IIIB disease without malignant pleural effusions, PS of 0 or 1, and minimal weight loss (≤5%), platinum-based combination chemoradiotherapy is recommended. Grade of recommendation, 1A

4. In patients with stage IIIB NSCLC and PS of 2 or those with substantial weight loss (>10%), chemoradiotherapy is recommended only after careful consideration. Grade of recommendation, 1C

Concurrent vs Sequential Therapy

Phase III trials have been performed to compare sequential and concurrent radiation and chemotherapy. The West Japan Lung Cancer Group conducted a randomized phase III trial of concurrent vs sequential thoracic RT and cisplatin-based chemotherapy with >150 patients in each arm.[22] Seventy-two percent had stage IIIB disease. Radiation was begun on day 2 (2 Gy per fraction for 14 days) followed by a 10-day rest and then repeated for a total dose of 56 Gy. In the sequential study arm, the same chemotherapy was administered but RT was initiated after chemotherapy was completed and consisted of 56 Gy (2 Gy per fraction for 14 days) without a break. The median survival time (MST) was superior for patients who were in the concurrent therapy study arm (16.5 months vs 13.3 months), and the 5-year survival difference was 15.8% vs 8.9% ($p = 0.039$; Table 1).

The Radiation Therapy Oncology Group (RTOG) conducted a phase III trial (RTOG-9410) that compared concurrent with sequential chemoradiotherapy.[23] The chemotherapy was vinblastine and cisplatin. Radiation was begun on day 1 with chemotherapy or day 50 after chemotherapy. The total dose was 63 Gy. A third arm in the trial evaluated concurrent bid RT (69.6 Gy in 1.2-Gy bid fractions) with cisplatin and oral etoposide.[23] The median and 4-year survival rates were 17 months and 21%, respectively, on the concurrent therapy arm with once-daily radiation and 14.6 months and 12%, respectively, on the sequential treatment study arm ($p = 0.046$). The twice-daily radiation arm had an intermediate survival rates of 15.2 months and 17%, respectively.

A French phase III trial of concurrent vs sequential chemoradiotherapy randomly assigned 205 patients. RT administered was 66 Gy in 33 fractions.[26] Chemotherapy consisted of vinorelbine and cisplatin for three cycles followed by RT, or concurrent cisplatin and etoposide for two cycles with RT followed by cisplatin and vinorelbine for two additional cycles of consolidative therapy. MSTs were 16.3 months vs 14.5 months in favor of concurrent therapy ($p = 0.24$). The 2-, 3-, and 4-year survival rates were better in the concurrent study arm (39%, 25%, and 21%, respectively) than in the sequential study arm (26%, 19%, and 14%, respectively).

Table 1—*Phase III Trials Comparing Concurrent With Sequential Chemoradiotherapy for Stage III NSCLC: 1995 to Present*

Study/Year	Patients, No.	RT Dose per Fraction/Frequency (Total Dose), Gy	Chemotherapy	MST, mo	Overall Survival at 2 yr, %	Toxicity, %			
						Treatment-Related Deaths	Pneumonitis Grades 3–4	Acute Esophagitis Grades 3–4	Neutropenia Grades 3–4
Curran et al[23]/2003	610	1.8 and 2.0 (63)	Concurrent	17	37	3	4	25	58
			Sequential	14.6*	31	2	7	4	56
Zatloukal et al[24]/2003	102	2.0 qd (60)	Concurrent	16.6	35			17	65
			Sequential	12.9*	14			4	40
Fournel et al[25]/2001	178	2.0 qd (66)	Concurrent	15	35	11		26	75
			Sequential	13.8	23	7		0	88
Furuse et al[22]/1999	314	2.0 qd (56)	Concurrent	16.5	35		1	3	99
			Sequential	13.3*	27		1	2	77

*$p < 0.05$ for comparison of sequential with concurrent chemotherapy.

A trial[27] from the Czech Republic randomly assigned 102 patients (85% with stage IIIB disease) to concurrent (started day 4 of cycle 2) or sequential RT after four cycles of vinorelbine and cisplatin. The concurrent study arm had the superior survival with MST and 3-year survival rates of 16.6 months and 18.6% vs 12.9 months and 9.5%, respectively. The hazard ratio was 0.61 in favor of concurrent therapy.[27]

All of these trials have shown that concurrent chemoradiotherapy is associated with increased toxicity, primarily esophagitis, and some trials showed increased neutropenia and nausea/vomiting (Table 2). Concurrent therapy did not increase the number of treatment-related deaths The most common chemotherapeutic agents used concurrently with RT have been vinorelbine, vinblastine, and etoposide in conjunction with cisplatin or weekly paclitaxel and carboplatin.[28–30] No randomized phase III trials of concurrent chemoradiotherapy have shown the superiority of one chemotherapy regimen over another. The consensus opinion reported in the Cancer Care Ontario Guidelines 2005[20] was that there are insufficient data to determine the most effective chemotherapy.

One phase II trial and one phase III trial[28,29] have evaluated induction chemotherapy followed by concurrent chemoradiotherapy vs initial treatment with concurrent therapy followed by consolidative treatment. In the randomized phase II trial,[27,29] concurrent weekly paclitaxel, carboplatin, and thoracic RT followed by consolidative therapy seemed to have the best outcome vs sequential chemoradiotherapy or induction chemotherapy followed by identical concurrent chemoradiotherapy (MST, 16.3 months vs 13 months or 12.7 months). However, this was a phase II trial, and it was not designed to compare the three study arms directly. A phase III trial was conducted by the Cancer and Acute Leukemia Group B,[28] who compared immediate treatment with weekly paclitaxel/carboplatin and thoracic RT (study arm 1) with two cycles of induction paclitaxel and carboplatin followed by identical concurrent chemoradiotherapy (study arm 2). No consolidative treatment was administered in either study arm.[28] MSTs (11.4 months and 13.7 months [study arm 2]) and 3-year survival rates (18% and 24% [study arm 2]) were similar and not statistically different ($p = 0.14$). The authors[28] concluded that induction chemotherapy followed by concurrent chemoradiotherapy was not superior to initial treatment with concurrent therapy. Because of the poor overall results, they questioned whether the low-dose weekly chemoradiotherapy approach might be inferior to the approach with full-dose chemotherapy and thoracic RT.

Table 2—*Summary of Survival and Toxicity From Trials Comparing Concurrent With Sequential Chemoradiotherapy

Parameters	Comparisons, No.	Rate, % (Total No.)		Ratio (95% CI)†	p Value	
		Concurrent	Sequential		Treatment Effect	Heterogeneity p Value/I^2, %
2-yr survival, summary	3	n = 356	n = 355	0.86 (0.78–0.95)	0.003	0.39/0
Curran et al[23]/2003		37 (201)	31 (201)	0.91 (0.79–1.05)		
Fournel et al[25]/2001		35 (103)	23 (104)	0.85 (0.71–1.01)		
Zatloukal et al[24]/2003		35 (52)	14 (50)	0.76 (0.61–0.95)		
Furuse et al[22]/1999‡		35 (156)	27 (158)	0.90 (0.77–1.00)		
Summary including Furuse et al[22]‡	4	n = 512	n = 513	0.87 (0.80–0.95)	0.001	0.55/0
Toxicity						
Treatment-related deaths	2	n = 290	n = 290	1.60 (0.75–3.40)	0.02	0.90/0
Curran et al[23]/2003		3 (201)	2 (201)	1.50 (0.43–5.20)		
Fournel et al[25]/2001		11 (89)	7 (89)	1.70 (0.63–4.40)		
Acute pneumonitis, grades 3–4	2	n = 253	n = 251	0.66 (0.33–1.45)	0.3	0.34/0
Curran et al[23]/2003		4 (201)	7 (201)	0.57 (0.25–1.30)		
Zatloukal et al[24]/2003		1 (52)	0.5 (50)	1.92 (0.18–20.00)		
Furuse et al[22]/1999‡		1 (156)	1 (158)	1.01 (0.14–7.10)		
Summary including Furuse et al[22]‡	3	n = 409	n = 409	0.70 (0.33–1.50)	0.34	0.59/0
Acute esophagitis, grades 3–4	3	n = 342	n = 340	6.77 (2.90–15.00)	<0.0001	0.28/22
Curran et al[23]/2003		25 (201)	4 (201)	6.20 (3.00–2.80)		
Fournel et al[25]/2001		26 (89)	0 (89)	47.00 (2.90–762.00)		
Zatloukal et al[24]/2003		17 (52)	4 (50)	4.30 (0.98–19.00)		
Furuse et al[22]/1999‡		3 (156)	2 (158)	1.40 (0.31–5.90)		
Summary including Furuse et al[22]‡	4	n = 498	n = 498	5.10 (2.90–9.10)	<0.0001	0.12/49
Neutropenia, grades 3–4	3	n = 342	n = 340	1.07 (0.81–1.43)	0.6	0.003/83
Curran et al[23]/2003		58 (201)	56 (201)	1.04 (0.87–1.20)		
Fournel et al[25]/2001		75 (89)	88 (89)	0.86 (0.75–0.99)		
Zatloukal et al[24]/2003		65 (52)	40 (50)	1.60 (1.10–2.40)		
Furuse et al[22]/1999‡		99 (156)	77 (158)	1.30 (1.20–1.40)		
Summary including Furuse et al[22]‡	4	n = 498	n = 498	1.14 (1.07–1.22)	<0.0001	0.01/89

*Adapted from Rowell and O'Rourke.[19] CI = confidence interval.
†Ratio <1 favors concurrent chemoradiotherapy.
‡No quality-of-life data were reported.

Southwestern Oncology Group investigators[30] have reported some of the best results from a single-arm phase II trial for patients with stage IIIB disease. This trial included concurrent full-dose etoposide and cisplatin and thoracic RT followed by consolidative docetaxel chemotherapy.[30] MST was 26 months, and the 3-year survival rate was 37%. These results are awaiting confirmation in a phase III trial. All patients will receive identical initial treatment with concurrent chemoradiotherapy and are randomly assigned to consolidative docetaxel or no consolidative treatment. It is uncertain how many cycles of chemotherapy are optimal in treatment of patients with stage III disease. The American Society of Clinical Oncology guidelines recommend two to four cycles of platinum-based chemotherapy. Two cycles should be administered concurrently with thoracic RT.[18]

Recommendations

5. For patients with stage IIIB NSCLC and PS 0 or 1 and minimal weight loss (≤5%), concurrent chemoradiotherapy is recommended. Grade of recommendation, 1A

6. The most efficacious chemotherapy drugs to be combined with thoracic RT and the number of cycles of chemotherapy needed to yield the best results are uncertain. No one combination chemotherapy regimen can be recommended. Grade of recommendation, 2C

Radiation Dose Fractionation Studies

Multiple trials have explored the use of altered-dose fractionation schedules as a means of improving the therapeutic index. Two general approaches have been evaluated. Pure hyperfractionated RT uses two or three small doses of RT per day administered over the standard treatment duration. Because smaller radiation fractions result in less damage to normal tissues as compared with rapidly replicating tumor cells, this permits an increase in the total radiation dose administered to the tumor without worsening normal tissue toxicity. Pure accelerated fractionation RT administers the same total dose using standard fraction sizes that are administered multiple times

per day. This results in a decrease in the overall treatment time and provides greater tumor kill because there is less time between treatments for repopulation by rapidly growing cells. Most clinical trials have combined accelerated fractionation and hyperfractionated RT in a hybrid approach, termed *accelerated hyperfractionated RT* (Table 3).

Randomized prospective studies have failed to demonstrate an advantage for twice-daily RT compared with once-daily RT for stage III NSCLC. The RTOG performed a randomized, prospective study[23,34] (RTOG 9410) to compare chemotherapy plus either twice-daily RT or once-daily RT for locally advanced NSCLC. Patients were randomly assigned to three study arms and received sequential therapy with cisplatin plus vinblastine followed by 63 Gy in 34 daily fractions; concurrent therapy with cisplatin, vinblastine, and 63 Gy in 34 daily fractions; or concurrent twice-daily RT (69.6 Gy in 1.2-Gy fractions bid) with cisplatin and oral etoposide. The median and 4-year survival rates were 17 months and 21% in the concurrent once-daily RT study arm, 14.6 months and 12% in the sequential once-daily RT study arm, and 15.2 months and 17% in the concurrent twice-daily RT study arm. The difference in survival between the concurrent once-daily RT study arm and the sequential once-daily RT study arm was significant ($p = 0.046$). In addition to the RTOG 9410 trial, a phase III study[35] was performed by the North Central Cancer Treatment Group (94-24-52) to compare concurrent etoposide plus cisplatin with either standard once-daily RT (60 Gy in 30 daily fractions) or etoposide and cisplatin plus split-course twice-daily RT (60 Gy in 40 fractions bid with a 2-week break in the middle). MST and 5-year survival rates for the once-daily RT study arm were 14 months and 13%, respectively, vs 15 months and 20%, respectively, for the twice-daily RT study arm ($p = 0.4$). There was no advantage to twice daily RT with regard to survival, disease control, or toxicity in either trial.

RT three times daily has shown promise for NSCLC. Saunders et al[33] performed a randomized study that compared once-daily RT (60 Gy in 30 fractions over 6 weeks) with continuous hyperfractionated accelerated RT (CHART) 54 Gy in 36 fractions tid (6 h apart over 12 total days). Sixty-one percent of patients had stage IIIA or IIIB disease. No chemotherapy was administered. Patients who received CHART had a 2-year survival rates of 29%, vs 20% in those who received once-daily ($p = 0.008$). These findings demonstrate the critical importance of the overall treatment time on RT outcome. CHART was delivered in only 12 days, whereas the twice -daily RT programs used in North Central Cancer Treatment Group 94-24-52 and RTOG 9410 were approximately 6 weeks long. Accelerated repopulation of tumor cells during RT occurred to a lesser degree during CHART, yielding more favorable results. However, the CHART trial lacked chemotherapy, which seems to be a critically important addition to RT (Table 3).

The Eastern Cooperative Oncology Group (ECOG) initiated a phase III trial (E-2597) of chemotherapy (two cycles of paclitaxel and carboplatin) followed by either once-daily RT (64 Gy in 32 fractions for 6.5

Table 3—*Phase III Trials Evaluating Multiple Daily Fractions of RT Compared to Once-Daily Fractions of RT for Stage III NSCLC (1995-present)**

Study/Year	Patients, No.	RT	RT Dose per Fraction/Frequency (Total Dose), Gy	CT	MST, mo	Overall Survival, %			
						2 yr	3 yr	4 yr	5 yr
Belani et al[29]/2005	141	HART	1.5 tid (57.6)	Sequential	20.3	44	24		
ECOG 2597		Conv	2 qd (64)	Sequential	14.9	24	18		
Curran et al[23]/2003	610	HF	1.2 bid (69.6)	Concurrent	15.2			17	
RTOG 9410		Conv	1.8 and 2.0 (63)	Concurrent		17†		21†	
		Conv	1.8 and 2.0 (63)	Sequential	14.6†			12†	
Schild et al[31]/2005	234	HF	1.5 bid (60) split course	Concurrent	15	40			20
		Conv	2 qd (60)	Concurrent	14	37			13
Komaki et al[32]/1997	490	HF	1.2 bid (69.6)	None	12.3	24		9	
RTOG 8808/ECOG 4588		Conv	2 qd (60)	None	13.6‡	31‡		4	
		Conv	2 qd (60)	Sequential	11.4‡	20‡		11	
Saunders et al[33]/1999	563	CHART	1.5 tid (54)	None	16.5	30§	20		
CHART		Conv	2 qd (60)	None	13	21§	13		

*HART = hyperfractionated accelerated RT; Conv = conventionally fractionated RT; HF = hyperfractionated RT.
†$p < 0.05$ for comparison of sequential to concurrent chemotherapy.
‡$p < 0.05$ for comparison of none to sequential chemotherapy.
§$p < 0.05$ for comparison of conventionally fractionated RT to CHART.

weeks) or three-times-daily RT (57.6 Gy in 36 fractions for 12 weekdays) for stage III NSCLC.[36] Unfortunately, accrual was slow and the study was closed before completion. MSTs were 14.9 months with once-daily RT vs 20.3 months with three-times-daily RT (p = not significant).

Very few patients have been treated with concurrent chemotherapy and three-times-daily RT. Oral et al[37] reported a 20-patient trial that included concurrent CHART and paclitaxel. Unfortunately, this resulted in excessive toxicity, with 50% of patients having grade 3 or greater pneumonitis. Mayo Clinic investigators[31] performed a trial with 20 patients who were treated with escalating doses of daily cisplatin administered concurrently with the same regimen of three-times-daily RT used in the ECOG trial. The maximum tolerated dose of daily cisplatin was 7.5 mg/d. The median survival was 22 months, and 5-year survival was 25%.[31]

For patients with stage IIIB NSCLC, there are convincing data that RT three times daily (CHART) alone is better than standard once-daily RT alone. However, there are problems that preclude this type of RT from being recommended for use. First, CHART is logistically difficult and has not been embraced by most radiation oncology facilities worldwide. Second, there is definitive proof that systemic chemotherapy improves survival when added to RT, especially when the two therapies are administered concurrently. Integrating chemotherapy with RT three times daily has posed difficult challenges. There has been some use of sequential therapy and a very small experience with concurrent therapy. No phase III trials have proved that chemotherapy plus multiple daily fraction RT yields significantly better survival than chemotherapy plus once-daily RT (Table 3). Although ECOG 2597 was provocative, it was never completed, leaving unanswered the question as to whether RT three times daily would be better than once-daily RT when used as part of a combined modality program.

Recommendation

7. For patients with stage IIIB NSCLC, once-daily thoracic RT plus chemotherapy is recommended. Grade of recommendation, 1B

Palliation of Lung Cancer With RT

A patient can be treated with curative intent when the disease can be contained within a reasonable RT field. In addition, the patient should be physically fit enough to withstand the effects of therapy. Usually, patients are considered able to withstand potentially curative therapy when they have Zubrod PS of 0 to 2 and adequate pulmonary function (spirometry with $FEV_1 \geq 1$ L/s).

The most common symptoms that are considered for palliative thoracic RT include dyspnea, cough, hemoptysis, and pain. These symptoms occur as a result of tumor-related obstruction and irritation of the normal intrathoracic structures. In addition, RT is frequently used for the palliation of metastases to other normal structures, such as the brain, spine, or bones (palliation of sites outside the chest are covered elsewhere).

Many studies[38–52] have been performed to identify the optimal thoracic RT regimen for the palliation of NSCLC. The perfect regimen would rid the patients of all symptoms permanently, cause no adverse effects, extend survival, and require little time. Clearly, these goals are not 100% attainable, but one should strive to maximize palliation and minimize adverse effects. Several phase III trials have compared various RT dose-fractionation regimens. Most of these trials detected no significant benefit for the study of RT regimens. Of the phase III trials performed, the trials that had positive findings are reviewed here. There is heterogeneity among the trials in intent and design, which makes them difficult to compare directly with one another.

Nestle et al[47] and Macbeth et al[50] performed a trial that included 509 patients with nonmetastatic inoperable NSCLC that was too extensive for radical RT. Patients received either 17 Gy in two fractions (F2) 1 week apart or 39 Gy in 13 fractions (F13) 5 d/wk. Survival was better in the F13 group; MST was 7 months in the F2 group, compared with 9 months in the F13 group (p = 0.03). The most common symptoms were cough, shortness of breath, fatigue, worrying, and chest pain. These were more rapidly palliated by the F2 regimen. Three patients (two F13, one F2) exhibited evidence of myelopathy. Nestle et al[47] and Macbeth et al[50] concluded that the F2 regimen had a more rapid palliative effect, but survival was longer in the F13 group.

Teo et al[39] performed a trial that included 291 patients who had inoperable advanced NSCLC and were randomly assigned to 45 Gy in 18 fractions for 4.5 weeks administered in study arm 1 or 31.2 Gy in four fractions for 4 weeks administered in study arm 2. MST was 20 weeks and was similar in both study arms. Study arm 1 was superior to study arm 2 in achieving symptom palliation (71% vs 54%; p < 0.02). Both study arms were equally well tolerated. Toxicity was mild and included radiation esophagitis, pneumonitis, and pulmonary fibrosis.

Reinfuss et al[44] included 240 patients with stage III, unresectable, asymptomatic NSCLC and were randomly assigned to one of the three treatment

arms: conventional RT, hypofractionated RT, and a control group treated with delayed RT when symptoms required treatment. In the conventional irradiation treatment arm (79 patients), a dose of 50 Gy in 25 fractions in 5 weeks was delivered to the primary tumor and the mediastinum. In the hypofractionated irradiation treatment arm (81 patients), two courses of irradiation were separated by an interval of 4 weeks. Each of the two courses included 20 Gy in five fractions in 5 days to the same treatment volume as the conventional irradiation group. The delayed RT arm included 80 patients who received a single course of palliative hypofractionated irradiation (20 to 25 Gy in four to five fractions in 4 to 5 days) administered to the primary tumor. The 2-year actuarial survival rates for patients in the conventional irradiation, hypofractionated irradiation, and control group arms were 18%, 6%, and 0%, with MSTs of 12 months, 9 months, and 6 months, respectively. The differences between survival rates were statistically significant. The comparison of conventional and hypofractionated irradiation shows a survival advantage for the conventional schedule.

Bezjak et al[48] randomly assigned 230 patients to either 10 Gy in one fraction or 20 Gy in five fractions. The changes in the scores on the Lung Cancer Symptom Scale indicated that the fractionated RT (five fractions) group had greater improvement in symptoms related to lung cancer ($p = 0.009$), pain ($p = 0.0008$), ability to carry out normal activities ($p = 0.037$), and better global quality of life ($p = 0.039$). The European Organization for Research and Treatment of Cancer QLQ-C30 scores showed that patients who received five fractions had a greater improvement in scores with respect to pain ($p = 0.04$). No significant difference was found in treatment-related toxicity. Patients who received five fractions survived on average 2 months longer ($p = 0.0305$) than patients who received one fraction. They concluded that the fractionated regimen was preferable.

Erridge et al[46] performed a phase III trial to determine whether palliation of chest symptoms from a 10-Gy single fraction was equivalent to that from 30 Gy in 10 fractions. They randomly assigned 149 patients and analyzed 74 patients in each treatment arm. The total symptom score improved in 49 patients (77%) with 10 Gy and in 57 patients (92%) with 30 Gy, a difference of 15%, which was not significantly different. However, complete resolution of all symptoms was achieved in 3 patients (5%) with 10 Gy and in 14 patients (23%) with 30 Gy ($p < 0.001$). Although this trial met the predetermined criteria for equivalence between the two palliative regimens, significantly more patients achieved complete resolution of symptoms and palliation of chest pain and dyspnea with the fractionated regimen.

Kramer et al[49] compared the efficacy of 2×8 Gy vs 10×3 Gy in 297 patients with inoperable stage IIIA/B (with an ECOG PS of 3 to 4 and/or substantial weight loss) and stage IV NSCLC. The primary end point was a patient-assessed score of treatment effect on seven thoracic symptoms. Palliation in the 10×3-Gy treatment arm was more prolonged (until week 22) with fewer worsening symptoms than in the 2×8-Gy treatment arm. Survival in the 10×3-Gy treatment arm was significantly ($p = 0.03$) better than in the 2×8-Gy treatment arm, with 1-year survival rates of 19.6% vs 10.9%. They concluded that the 10×3-Gy RT schedule was preferred over the 2×8-Gy schedule for palliative treatment because it improved survival and resulted in a longer duration of the palliation.

Senkus-Konefka et al[51] compared two palliative RT schedules for inoperable symptomatic NSCLC. One hundred patients were randomly assigned to 20 Gy in five fractions for 5 days (treatment arm A) or 16 Gy in two fractions for 1 and 8 days (treatment arm B). Treatment tolerance was good and did not differ between study arms. No significant differences between study arms were observed in the degree of relief of symptoms. Overall survival time differed significantly in favor of treatment arm B (median, 8.0 months vs 5.3 months; $p = 0.016$). Both irradiation schedules provided comparable, effective palliation of tumor-related symptoms. The improved overall survival and treatment convenience of a two-fraction schedule suggest its usefulness in the routine management of symptomatic inoperable NSCLC.

Radiation myelopathy (RM) is one of the most serious and feared complications of RT. Macbeth et al[52] described the Medical Research Council Lung Cancer Working Party experience. Five cases of RM occurred among 1,048 patients who had inoperable NSCLC and were treated with palliative RT in three randomized trials. Seven RT regimens were used in these trials: 10 Gy in a single fraction on 1 day (114 patients); 17 Gy in two fractions over 8 days (524 patients); 27 Gy in six fractions over 11 days (47 patients); 30 Gy in six fractions over 11 days (36 patients); 30 Gy in 10 fractions over 12 days (88 patients); 36 Gy in 13 fractions over 16 days (86 patients); and 39 Gy in 13 fractions over 17 days (153 patients). Of the five instances of RM, three occurred in the 524 patients who were treated with 17 Gy in 2 fractions and two in the 153 patients who were treated with 39 Gy in 13 fractions. The estimated cumulative

risks of RM by 2 years were 2.2% for the 17-Gy group, 2.5% for the 39-Gy group, and 0% for the remainder. This suggests that one might consider avoiding the regimens of 17 Gy in 2 fractions over 8 days and 39 Gy in 13 fractions over 12 days to avoid this potential devastating complication.

The general trend in studies with positive findings were that higher dose, more fractionated regimens resulted in better palliation and longer survival. This is not a particular surprise because palliation of tumor-related symptoms requires the death of enough tumor cells to relieve pressure and irritation of normal structures. As is true of all treatment, there seems to be dose dependence in achieving the desired outcome, symptomatic relief. The most commonly used palliative RT regimen is 30 Gy in 10 fractions, which would be a reasonable choice for a patient who requires palliative RT for thoracic symptoms. However, the use of common sense in customizing therapy to the needs of the patient is still the best approach. A patient with good PS could be treated with a longer fractionated regimen as opposed to a very ill-appearing patient who has poor PS and may be better served with a short regimen, such as 10 Gy in one fraction or 16 Gy in two fractions (days 1 and 8). Because of the Medical Research Council findings of RM in some patients, one might consider avoiding the regimens of F2 for 8 days and F13 for 12 days.

For patients who have stage IIIB disease and poor PS or disease that is too extensive to treat with curative intent and symptoms as a result of chest disease, palliative RT is recommended. The fractionation pattern should be chosen on the basis of the physician's judgment and the patient's needs. Patients who seem to be more vigorous should be treated with a longer RT program because this will likely palliate symptoms for a greater period and may increase survival. Representative RT regimens were already presented. Patients with very tenuous health and very short estimated survival should be treated with a short course of RT because it is likely that this will help the symptoms without using up a great amount of their limited lifespan.

Recommendation

8. For patients with stage IIIB disease, either poor PS or disease that is too extensive to treat with curative intent, and symptoms as a result of chest disease, palliative RT is recommended. The fractionation pattern should be chosen on the basis of the physician's judgment and the patient's needs. Grade of recommendation, 1A

Summary of Recommendations

1. In selected patients with clinical T4N0-1 NSCLC as a result of satellite tumor nodule(s) in the same lobe, carinal involvement, or SVC invasion, it is recommended that evaluation be performed by a multidisciplinary team that includes a thoracic surgeon with lung cancer expertise to determine whether the tumor is operable. Surgery is not recommended when there is N2 involvement. Grade of recommendation, 1C

2. For patients with stage IIIB NSCLC as a result of N3 disease, treatment with neoadjuvant (induction) chemotherapy or chemoradiotherapy followed by surgery is not recommended. Grade of recommendation, 1C

3. For patients with stage IIIB disease without malignant pleural effusions, PS of 0 or 1, and minimal weight loss (≤5%), platinum-based combination chemoradiotherapy is recommended. Grade of recommendation, 1A

4. In patients with stage IIIB NSCLC and PS of 2 or those with substantial weight loss (>10%), chemoradiotherapy is recommended only after careful consideration. Grade of recommendation, 1C

5. For patients with stage IIIB NSCLC and PS of 0 or 1 and minimal weight loss (≤5%), concurrent chemoradiotherapy is recommended. Grade of recommendation, 1A

6. The most efficacious chemotherapy drugs to be combined with thoracic RT and the number of cycles of chemotherapy needed to yield the best results are uncertain. No one combination chemotherapy regimen can be recommended. Grade of recommendation, 2C

7. For patients with stage IIIB NSCLC, once-daily thoracic RT plus chemotherapy is recommended. Grade of recommendation, 1B

8. For patients with stage IIIB disease, either poor PS or disease that is too extensive to treat with curative intent, and symptoms as a result of chest disease, palliative RT is recommended. The fractionation pattern should be chosen on the basis of the physician's judgment and the patient's needs. Grade of recommendation, 1A

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Treatment of Non-small Cell Lung Cancer, Stage IV*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **Stage IV non-small cell lung cancer (NSCLC) remains a treatable but incurable disease.**

Methods: **A MEDLINE search was performed to identify pertinent peer-reviewed articles that addressed the questions posed for this section. The writing committee developed and graded recommendations, which were subsequently approved by the American College of Chest Physicians.**

Results: **Platinum-based doublets remain the standard of care in patients with good performance status (PS); there is no evidence that the addition of a third cytotoxic agent improves survival. Likewise, with only one exception, the addition of a new targeted or biological agent to platinum-based doublets does not improve survival. The one exception is the addition of bevacizumab, an antiangiogenic agent, to carboplatin/paclitaxel in patients with stage IV disease and good PS. Patients for whom bevacizumab is recommended must also be selected on the basis of histology (nonsquamous), absence of brain metastases and hemoptysis, and no indication for therapeutic anticoagulation. In patients with stage IV NSCLC and PS of 2, chemotherapy is recommended, but the optimal approach has not been defined. Elderly patients, defined as ≥ 70 years old, also derive benefit from chemotherapy. Most elderly patients should receive single-agent chemotherapy, but elderly patients with good PS and without significant comorbidities seem to derive a similar benefit from platinum-based doublets compared with their younger counterparts without a prohibitive difference in treatment toxicities. Because stage IV NSCLC is incurable, quality-of-life issues are important, and tools exist to monitor a patient's quality of life during therapy. Last, patients need to be informed of the implication of the diagnosis of stage IV NSCLC and be educated about treatment options that are available to them.**

Conclusions: **Advances have been made in stage IV NSCLC, and the appropriate use of chemotherapy continues to evolve on the basis of well-designed clinical trials that address critical issues in this population.** ***(CHEST 2007; 132:277S–289S)***

Key words: chemotherapy; non-small cell lung cancer; quality of life; targeted therapy

Abbreviations: ACCP = American College of Chest Physicians; BSC = best supportive care; CALGB = Cancer and Leukemia Group B; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C3 = European Organization for Research and Cancer Treatment Quality of Life Questionnaire; FACT-L = Functional Assessment of Cancer Therapy-Lung; FLIC = Functional Living Index-Cancer; HRQOL = health-related quality of life; NSCLC = non-small cell lung cancer; PS = performance status; QOL = quality of life

Lung cancer remains the leading cause of cancer-related mortality in the United States. In 2006, there will be approximately 170,000 new cases of lung cancer diagnosed and roughly 158,000 deaths from lung cancer.[1] The majority (85%) of patients who receive a diagnosis of lung cancer will have non-small cell lung cancer (NSCLC).[2] It is estimated that 40% of patients with newly diagnosed NSCLC will have stage IV disease. In 2003, the American College of Chest Physicians (ACCP) issued its first guidelines that

included recommendations for chemotherapeutic management of stage IV NSCLC.[3] Table 1 summarizes the recommendations endorsed by the ACCP in 2003. In brief, these recommendations supported the use of chemotherapy on the basis of the performance status (PS) of the patient; in patients with stage IV NSCLC and good PS, chemotherapy clearly improves survival and palliates disease-related symptoms. The role of chemotherapy in patients with poor PS was less certain. Second-line chemotherapy also had a survival and palliative effect in patients with good PS. The duration of first-line chemotherapy should be brief (three to four cycles), and there was no clearly superior regimen in the first-line setting. Patient preferences should be respected, and educating patients about the advantages and disadvantages of chemotherapy was advocated.

The purpose of the stage IV guideline update is to address additional questions raised by the ACCP having pertinence to the everyday management and evaluation of advanced stage IV NSCLC. Although this chapter concerns stage IV, the recommendations also apply to certain subsets of patients with stage IIIB, as did the 2003 recommendations. The subsets of patients who have stage IIIB and are treated as though they have stage IV disease include patients with malignant pleural or pericardial effusions, with advanced ipsilateral supraclavicular adenopathy, and whose intrathoracic disease is not amenable to combined modality approaches.

Materials and Methods

In light of the recommendations made in 2003, additional questions that were believed to be pertinent to patients with advanced stage IIIB/IV NSCLC were asked. A systematic review of the literature was undertaken by the multidisciplinary writing committee to identify published materials, including both original articles and guidelines, that address lung cancer diagnosis, management, and treatment. Materials that are appropriate to this topic were obtained by literature search of a computerized database (MEDLINE) to identify relevant articles for review. Recommendations were developed by the writing committee and graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guidelines Development" chapter). These recommendations were then approved by the Thoracic Oncology NetWork, Health and Science Policy Committee, and the Board of Regents of the ACCP.

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Results

Is There an Advantage to Using Three Chemotherapeutic Agents Compared With Two in Patients With Stage IV NSCLC and Good PS?

The 2003 ACCP recommendations defined platinum-based doublets as the standard of care for patients with stage IV NSCLC and good PS.[3] Delbaldo et al[4] reported a metaanalysis that included 13,601 patients in 65 trials and showed that two chemotherapeutic agents led to superior response and survival rates in patients with stage IV NSCLC compared with single agents (Table 2). Since the report of that metaanalysis, platinum-based doublets were shown to be superior to single-agent therapy in three randomized trials.[5–7] Although overall survival was statistically superior in only one of the three trials, the overall therapeutic efficacy, including response rate and progression-free survival, improved with the doublets with no significant cost in toxicity or quality of life (QOL).

Several large, randomized trials[3] have compared various platinum doublets (both cisplatin based and carboplatin based) and failed to identify a superior regimen. The only potential exception was the TAX 326 trial,[8] which demonstrated improved QOL and a trend toward improved survival (statistically, it was "noninferior") for cisplatin-docetaxel compared with cisplatin-vinorelbine. This experience, although valid, remains an exception, and cisplatin-docetaxel has not been widely adopted as the "preferred regimen." There is general agreement that either cisplatin or carboplatin combined with a taxane (paclitaxel or docetaxel), gemcitabine, vinorelbine, or irinotecan can be used in the first-line treatment of patients with advanced NSCLC and good PS.

A number of randomized trials[4] have tested the addition of a third chemotherapeutic agent to existing doublets. As shown in Tables 2, 3, these "triplets" consistently failed to show superiority over established two-drug combinations with regard to survival, although response rates were improved. In most trials, these efficacy parameters were at best comparable, whereas toxicity was substantially more pronounced with the triplets. Only one trial[9] showed better results for a triplet compared with a doublet, but the result seen in this trial stands alone and has not been reproduced by other investigators.[10]

Table 1—*Summary of 2003 Recommendations in Treatment of Stage IV NSCLC

Level of Evidence	Benefit	Grade	Recommendation
PS 0–1, good	Substantial	A	†
PS 2, poor	Small/weak	B	†
PS 3–4, fair	Moderate	B	†
Good	Substantial	A	Platinum-based therapy improves survival over BSC in patients with good PS (0–1).
Poor	Small/weak	I	New single agents alone are equivalent to platinum-based combinations.
Fair	Moderate	B	Combination regimens that incorporate the new single agents with a platinum should be used.
Good	Substantial	A	There is not one clearly superior platinum-based combination regimen.
Good	Substantial	A	Duration of first-line therapy should be 3–4 cycles.
Good	Moderate	B	Second-line treatment should be offered to patients with a good PS at the time of disease progression.
Good	Moderate	B	Chemotherapy has a palliative effect on disease-related symptoms and can improve QOL.
Fair	Moderate	B	Patient preferences need to be considered and respected with regard to the decision to treat with chemotherapy.
Poor	Substantial	C	Patients with stage IV NSCLC should be referred to a physician with specialized training in oncology.
Good	Substantial	A	Combination platinum-based chemotherapy can be administered safely with acceptable and manageable toxicity.

*From Socinski et al.[3]
†PS should be used to select patients for therapy because it is a consistent prognostic factor for survival.

The advent of molecular-targeted agents has raised expectations that these agents, which are different from traditional chemotherapeutic drugs, could be added to standard doublets with enhanced efficacy and no additional toxicity. Large, randomized trials tested the two available tyrosine kinase inhibitors, gefitinib and erlotinib, in combination with cisplatin-gemcitabine[11] and carboplatin-paclitaxel.[12,13] Unfortunately, no significant difference in survival was observed with the addition of the two novel agents when used concomitant with chemotherapy in any of the four trials, which together accrued nearly 4,000 patients worldwide. However, in a subset analysis of one of the trials,[12] patients with no history of smoking experienced a significant benefit when treated with erlotinib plus chemotherapy compared with chemotherapy alone. This observation is being tested in a prospective manner. Other promising agents, including but not limited to metalloproteinase inhibitors (prinomastat), antisense therapy (ISIS 3521), farnesyl transferase inhibitors (lonafarnib), and retinoid derivatives (bexarotene), all failed to improve outcomes when added to standard chemotherapy in patients with advanced NSCLC.

Bevacizumab, an anti-vascular endothelial growth factor humanized monoclonal antibody, already approved for the treatment of advanced colorectal cancer, was evaluated in a large, randomized, phase III trial conducted by the Eastern Cooperative Oncology Group (ECOG) and referred to as ECOG 4599.[14] This trial randomly assigned patients with advanced NSCLC, except squamous histology, to carboplatin-paclitaxel with or without bevacizumab. Other exclusion criteria were history of hemoptysis, history of brain metastases, history of bleeding or thrombotic disorders, or need for full anticoagulation. The primary reason for the more selected patient population was the risk for hemoptysis, sometimes fatal, observed in the initial phase II trial of chemotherapy plus bevacizumab.[15]

The ECOG 4599 trial enrolled 855 eligible patients with PS of 0 to 1. All efficacy end points, including response rate and progression-free and overall survival, were significantly better in the bevacizumab arm. Among 420 patients who were treated with bevacizumab, toxicity was in general tolerable, except for five deaths secondary to hemoptysis. This trial is

Table 2—*Metaanalysis Addressing the Number of Cytotoxic Agents in Advanced NSCLC

	Ratio (95% CI)		
Regimen	Response Rate†	Median Survival	1-yr Survival‡
Two agents vs one agent	0.42 (0.37–0.47)	0.83 (0.79–0.89)	0.80 (0.70–0.91)
Three agents vs two agents	0.66 (0.58–0.75)	1.00 (0.94–1.06)	1.01 (0.85–1.21)

*From Delbaldo et al.[4] CI = confidence interval.
†Absolute benefit: 13% for two-agent vs one-agent regimens; 8% for three-agent vs two-agent regimens.
‡Although there was a 5% absolute benefit for two-agent vs one-agent regimens, there was no benefit for three-agent vs two-agent regimens.

Table 3—*Randomized Trials Evaluating Three-Drug vs Two-Drug Combinations in Advanced NSCLC

Study	Patients Analyzed/Randomly Assigned, No.	Treatment Regimen		Response Rate		1-yr Survival	
		Doublet	Triplet	Ratio (95% CI)	p Value	Ratio (95% CI)	p Value
Sandler et al[14]/ 2006	878/878	Paclitaxel plus carboplatin	Paclitaxel plus carboplatin plus bevacizumab	0.32 (0.22–0.47)	< 0.0001	0.77 (0.65–0.93)	0.07
Bissett et al[74]/ 2005	333/362	Cisplatin plus gemcitabine	Cisplatin plus gemcitabine plus prinomastat	0.95 (0.58–1.5)	0.81	0.92 (NR)	0.45
Douillard et al[75]/ 2004	75/75	Paclitaxel plus carboplatin	Paclitaxel plus carboplatin plus BMS-275291	2.0 (0.69–5.7)	NR		
Gatzemeier et al[76]/ 2004	101/103	Cisplatin plus gemcitabine	Cisplatin plus gemcitabine plus trastuzumab	1.24 (0.56–1.40)	NR		
Giaccone et al[11]/ 2004	1,093/1,093	Cisplatin plus gemcitabine	Cisplatin plus gemcitabine plus gefitinib	0.87 (0.67–1.13)	NS	0.97 (NR)	0.456
Herbst et al[13]/ 2004	1,037/1,037	Paclitaxel plus carboplatin	Paclitaxel plus carboplatin plus gefitinib	0.91 (0.69–1.2)	NR	0.93 (NR)	NS
Herbst et al[12]/ 2005	1,059/1,078	Paclitaxel plus carboplatin	Paclitaxel plus carboplatin plus erlotinib	0.87 (0.65–1.2)	0.36	NR	NR
Johnson et al[15]/ 2004 (NR)	99/99	Paclitaxel plus carboplatin	Paclitaxel plus carboplatin plus bevacizumab	0.56 (0.22–1.4)	"trend"		
Leighl et al[77]/ 2005	774/774	Paclitaxel plus carboplatin	Paclitaxel plus carboplatin plus BMS-275291	1.45 (1.1–2.0)	0.10		
Danson et al[78]/ 2003	361/372	Gemcitabine plus carboplatin	MIC/MVC	0.91 (0.59–1.4)	NR	0.97 (NR)	NR
Gebbia et al[79]/ 2002	247/247	Cisplatin plus vinorelbine	Cisplatin plus vindesine plus mitomycin C	0.91 (0.55–1.5)	0.13	0.97 (NR)	NS
Rudd et al[80]/ 2005	422/422	Gemcitabine plus carboplatin	MIC	1.03 (0.64–1.7)	0.84	1.17 (1.05–1.3)	NR

*NR = not reported; NS = not significant; MIC = mitomycin, ifosfamide, cisplatin; MVC = mitomycin, vinblastine, cisplatin; BMS = Bristol Myers Squibb. See Table 2 for expansion of abbreviation.

the first to demonstrate a superiority for a triplet over a doublet, with the understanding that bevacizumab is not a conventional chemotherapeutic agent. It is also the first trial to show a survival benefit for the use of an angioinhibiting agent in the treatment of advanced NSCLC.

Recommendations

1. In patients with stage IV NSCLC and good PS, two-drug combination chemotherapy is recommended. The addition of a third cytotoxic chemotherapeutic agent is not recommended because it provides no survival benefit and may be harmful. Grade of recommendation, 1A

2. Bevacizumab improves survival combined with carboplatin and paclitaxel in a clinically selected subset of patients with stage IV NSCLC and good PS (nonsquamous histology, lack of brain metastases, and no hemoptysis). In these patients, addition of bevacizumab to carboplatin and paclitaxel should be considered a therapeutic option. Grade of recommendation, 1A

Should Elderly Patients Be Treated Differently From Younger Patients?

Approximately two thirds of patients with NSCLC are ≥ 65 years old, and approximately 40% are ≥ 70 years old.[16] Surveillance, Epidemiology, and End Results data[17] suggest that the percentage of patients who are > 70 years old is closer to 50%, yet elderly patients are generally underrepresented on clinical trials; participation of elderly patients with advanced disease in national clinical trials has ranged from 15% in the early 1990s to 29% in more recent studies.[18] Although the trend in enrollment is en-

couraging, it demonstrates a residual bias against treating elderly patients with advanced NSCLC. Indeed, Ramsey et al[17] reviewed the Surveillance, Epidemiology, and End Results Medicare data from 1994 to 1999 and found a much lower rate of chemotherapy use than expected for the overall population. It also suggests that the elderly may have more comorbidities or a higher rate of functional compromise that would make study participation difficult, if not contraindicated. There is general agreement that the elderly fall into two categories: the "fit" and the "unfit." Having said this, there is not general agreement as to how to define these two groups accurately or how the increasing incidence of comorbidities in elderly patients influences treatment choices or recommendations.

The notion that chemotherapy was too toxic or provided only marginal benefit for elderly patients was first challenged by the Elderly Lung Cancer Vinorelbine Italian Study[19] (Table 4). The study randomly assigned 154 patients who were > 70 years old to vinorelbine vs supportive care. Patients who were treated with vinorelbine had a 1-year survival rate of 32%, compared with 14% for those who were treated with supportive care alone. QOL parameters were also significantly improved in the chemotherapy arm, and toxicity was acceptable. A more recent trial[20] from Japan compared single-agent docetaxel with vinorelbine in 180 elderly patients with good PS. Response rates and progression-free survival were significantly better with docetaxel (22% vs 10%; 5.4 months vs 3.1 months, respectively), whereas median and 1-year survival rates did not reach statistical significance (14.3 months vs 9.9 months; 59% vs 37%, respectively), despite an obvious trend.

These trials confirm the benefits of single-agent chemotherapy in elderly patients with advanced NSCLC. A more difficult issue is whether combination chemotherapy is superior in the elderly subset as already demonstrated for younger patients. Although there was a suggestion that the combination of gemcitabine plus vinorelbine was superior to vinorelbine alone in one trial,[21] the Multicenter Italian Lung Cancer in the Elderly Study[22] was a much larger comparison of combination gemcitabine and vinorelbine with the constituent single agents (Table 4). Nearly 700 elderly patients were enrolled. There were no differences in outcome between the single agents and the combination arm, which led the Italian investigators to recommend single-agent therapy as standard for elderly patients.

The experience in the United States is based almost exclusively on retrospective data analyzing and comparing younger (< 70 years old) with older (≥ 70 years old) patients who participated in large, randomized trials that were not necessarily designed to address the elderly issue (Table 5). Because the majority of these trials evaluated platinum-based doublets, it is generally assumed that older patients who entered these trials were considered fit and met the eligibility criteria for enrollment onto the trials. Langer et al[23] analyzed the outcomes of elderly patients in a randomized trial of cisplatin-etoposide vs cisplatin-paclitaxel (ECOG 5592). Approximately 15% of 584 eligible patients were ≥ 70 years. Elderly patients had more leukopenia and neuropsychiatric complications, but efficacy results, including response and survival, were not significantly different compared with the younger cohort. A similar retrospective analysis[24,25] was conducted of the more recent ECOG trial 1594, which randomly assigned 1,139 eligible patients, 20% of whom were ≥ 70 years old, to four different platinum-based regimens. Response rates, survival, and toxicity were similar between the groups. Only nine patients (1%) who entered in this trial were ≥ 80 years old. This subgroup had a much poorer outcome. A similar retrospective analysis was conducted in TAX 326,[26] a phase III trial comparing docetaxel, in combination with either cisplatin or carboplatin, with a reference regimen of cisplatin-vinorelbine. Among > 1,200 patients enrolled, 390 were ≥ 65 years old, the cutoff used for this analysis. Again, elderly patients did as well as younger patients, with no significant difference observed in the efficacy parameters or toxicity end points. Overall, carboplatin-docetaxel had a more favorable therapeutic index. Among the elderly evaluated in this subanalysis, cisplatin-docetaxel, compared with the reference regimen, yielded a statistically significant 3-month improvement in median survival and a consistent benefit in 1-year and 2-year survival rates.

Table 4—*Chemotherapy in Elderly Patients With Advanced NSCLC

Study/Year	No.	Response Rate, %	MS, mo	1-yr Survival, %
ELVIS[19]/1999				
Vinorelbine	78	20	6.5	32†
BSC	76		4.9	14
Frasci et al[21]/2000				
Gemcitabine plus vinorelbine	76	22	7	30†
Vinorelbine	76	15	4.5	13
Gridelli et al[22]/2003				
Vinorelbine	233	18.4	8.8	41
Gemcitabine	233	17.3	6.6	26
Gemcitabine plus vinorelbine	237	20	7.6	31

*ELVIS = Elderly Lung Cancer Vinorelbine Italian Study Group; MS = median survival time.
†$p < 0.05$.

Table 5—*Treatment Outcomes for Elderly Patients With Advanced Stage IIIB/IV NSCLC*

Study/Year	Patients, No.	Subgroups by Age, yr	Survival From Start of Treatment by Age Group			Comments
			Median, mo	1 yr, %	p Value for Effect of Age	
Hensing et al[27]/2003	230	≥ 70	7.1	33	0.65	By treatment arm
		< 70	7.8	30		
Belani et al[26]/2005	1,218	≥ 65	12.6/9.0/9.9	53/39/41	NS	
		< 65	11.0/9.7/10.1	44/37/41		
Langer et al[23]/2002	574	≥ 70	8.5/9.1	29.1	0.29	
		< 70		37.7		
Rocha Lima et al[81]/2002	265	≥ 70	5.7	30	0.63	CALGB 8931 only
		60–69	7.7	26		
		50–59	9.3	28		
Sederholm et al[7]/2005	334	≥ 70	9.4/11	NR	0.2	By treatment arm
		Overall	8.6/10	32/40		
Lilenbaum et al[5]/2005	561	≥ 70	5.8/8.0	1/35	0.546	By treatment arm
		< 70	6.8/9.0	38/33		

*See Table 3 for expansion of abbreviations.

The Cancer and Leukemia Group B (CALGB) performed a randomized trial[5] of carboplatin-paclitaxel vs paclitaxel alone (CALGB 9730). Stratification factors included stage, age, and PS. A total of 155 elderly patients were enrolled, accounting for 27% of the study population. There was no significant difference in response or survival between the elderly and the younger patients. Toxicity was also similar between the two groups, except for a higher incidence of leucopenia in the elderly, but there was no increase in febrile or septic episodes. When results in the elderly subset were analyzed by treatment arm, the nonsignificant difference in survival observed in the general study population was also observed in the elderly subset.

Hensing et al[27] reported an age-based retrospective analysis of a prospective trial that evaluated the optimal duration of therapy in the first-line setting using carboplatin and paclitaxel. In that trial, 29% of patients were ≥ 70 years old. There was no difference in response or survival outcomes or any differences in the rates of hematologic or nonhematologic toxicities seen in the older vs younger patients.

Very little information is available regarding the treatment of patients who have advanced disease and are > 80 years old. Accrual of octogenarians to national trials has been negligible. In the subset analysis[24,25] from ECOG 1594, octogenarians fared substantially worse than patients aged 70 to 79 years when treated with platinum-based combinations (but those who were ≥ 80 years old constituted < 1% of enrollees).

In summary, age alone, at least up to 79 years, should not dictate treatment-related decisions in patients with advanced NSCLC. Elderly patients with a good PS enjoy longer survival and a better QOL when treated with chemotherapy compared with supportive care alone. The single agents vinorelbine, gemcitabine, and docetaxel all are viable options. Elderly patients with good PS and no major comorbid conditions ("fit elderly") seem to benefit from carboplatin-based combination chemotherapy with acceptable toxicity. To date, however, no elderly-specific trial has demonstrated a survival advantage for a doublet compared with a single agent in this setting. Caution should be exercised when extrapolating data for elderly patients (70 to 79 years old) to patients who are ≥ 80 years old. Until more information becomes available, platinum-based chemotherapy cannot be routinely recommended to patients who have advanced NSCLC and are ≥ 80 years old.

Recommendations

3. In patients who have stage IV NSCLC and are elderly (≥ 70 to 79 years old), single-agent chemotherapy is recommended for most. Grade of recommendation, 1A

4. However, in patients who have stage IV NSCLC, are elderly (≥ 70 to 79 years old), have good PS, and lack significant comorbidities, two-drug combination chemotherapy is recommended as an option. Grade of recommendation, 1B

5. In patients who have stage IV NSCLC and are ≥ 80 years old, the benefit of chemotherapy is unclear and should be decided on the basis of individual circumstances. Grade of recommendation, 2C

Is There Evidence That Chemotherapy Benefits Patients With Poor PS?

PS is the most important prognostic factor in advanced NSCLC.[3] Prospective clinical trials and

retrospective analyses[28,29] in the 1980s suggested that patients with stage IV NSCLC and compromised PS experienced substantial toxicity and derived no benefit from systemic chemotherapy. This observation led to the exclusion of patients with a PS of 2 from subsequent cooperative group research. Trials conducted in the late 1990s resumed inclusion of patients with PS of 2 as a subgroup of the overall study population. Arguably as a result of more effective and less toxic chemotherapy, the results demonstrated better tolerability and a trend toward improvement in disease-related symptoms.

CALGB trial 9730,[5] discussed previously, enrolled 99 patients with PS of 2 (18% of the study population). When compared with patients with PS of 0 to 1, who had a median survival of 8.8 months and a 1-year survival of 38%, the corresponding figures for patients with PS of 2 were 3.0 months and 14%, respectively, demonstrating once more the poor prognosis conferred by a lower PS. These differences were statistically significant. However, of importance, when patients with PS of 2 were analyzed by treatment arm, those who received combination chemotherapy had a significantly higher response rate (24% vs 10%), longer median survival (4.7 months vs 2.4 months), and superior 1-year survival (18% vs 10%) compared with those who were treated with single-agent paclitaxel.

ECOG investigators[30] reported a subset analysis of 68 patients with PS of 2 from trial 1594, which randomly assigned > 1,200 patients to four platinum-based regimens. Despite a high incidence of adverse events, including five deaths, the final analysis showed that the overall toxicity experienced by patients with PS of 2 was not significantly different from that experienced by patients with PS of 0 to 1. Efficacy analysis demonstrated an overall response rate of 14%, median survival time of 4.1 months, and a 1-year survival rate of 19%, all substantially inferior to the patients with PS of 0 to 1. The same group of investigators[31] subsequently conducted a phase II randomized trial of attenuated dosages of cisplatin-gemcitabine and carboplatin-paclitaxel in 102 patients with PS of 2. Response rates were 25% and 16%, median survival times were 6.8 months and 6.1 months, and 1-year survival rates were 25% and 19%, respectively. None of these differences was statistically significant, but the survival figures were longer than expected on the basis of historical controls.

Some investigators reported on symptom improvement experienced by patients with PS of 2. Vansteenkiste et al[32] from Belgium compared single-agent gemcitabine with the combination of cisplatin and vindesine in a phase III trial whose primary end point was clinical benefit. Gemcitabine compared favorably to cisplatin and vindesine with longer lasting clinical benefit (16 weeks vs 10 weeks) and no major differences in survival (6.7 months vs 5.5 months). A substantial percentage (20 to 40%) of patients with PS of 2 reported improvement in disease-related symptoms. These findings were similar to those reported by Hickish et al,[33] who concluded that patients with poor PS experienced symptom relief from chemotherapy.

In summary, patients with advanced NSCLC and poor PS represent a sizable component of our practice, yet they have been largely excluded from clinical trials until recently. Although it is unlikely that chemotherapy will eliminate the gap in outcome between patients with PS of 0 to 1 and patients with PS of 2, evidence now suggests that patients with PS of 2 should be offered active treatment. The results of the CALGB subset analysis showed a significant benefit for combination chemotherapy over single-agent therapy in patients with PS of 2. Future trials will need to ascertain the reason for compromised PS and carefully distinguish outcome in those whose functional decline is due to comorbidities vs rapidly advancing malignancy.

Recommendations

6. In patients with stage IV NSCLC and a PS of 2, chemotherapy is recommended on the basis of defined response rates and symptom palliation. Grade of recommendation, 1B

7. In patients with stage IV NSCLC and a PS of 2, no specific recommendation can be given with regard to the optimal chemotherapeutic strategy. A single phase III trial showed a survival benefit to a carboplatin-based doublet compared with a single agent in a prospectively planned subset analysis. Grade of recommendation, 2C

Are There Health-Related QOL Measures That Can Be Used To Predict Outcomes?

Several trials[34–53] have identified patient-reported QOL as a significant prognostic factor for response to therapy, time to progression, and overall survival in patients with NSCLC. A variety of health-related QOL (HRQOL) tools have been used in these trials, although the European Organization for Research and Cancer Treatment Quality of Life Questionnaire (EORTC QLQ-C30), Functional Assessment of Cancer Therapy-Lung (FACT-L), and Functional Living Index-Cancer (FLIC) questionnaires have been the most common. Many of the trials studied heterogeneous patient populations that included patients with other malignancies,[41,49] small cell histology,[43,50] and varying stages of NSCLC.[40,42,43,47,50]

For patients with NSCLC disease, baseline patient-reported QOL has been shown to have prognostic significance for overall survival in patients with early stage disease that was treated with surgery,[47] locally advanced disease that was treated with definitive radiation[48] or combined chemotherapy and radiation,[46] and advanced disease that was treated with chemotherapy alone.[35,36,44,45,53]

Two of these trials[44,47] used the FLIC questionnaire to establish baseline QOL. The first trial[44] studied 40 patients who had advanced NSCLC and were part of a randomized trial to compare best supportive care (BSC) with BSC plus vinblastine and cisplatin. Patients were put into two groups, including those with high baseline FLIC scores ($\geq$ 106.5) and low baseline FLIC scores ($<$ 106.5). The median survival for the high-score group was 24 weeks, compared with 11.9 weeks for the low-score group ($p = 0.03$). In a two-step Cox regression model, baseline FLIC score and marital status were significantly associated with survival ($p = 0.01$ and $p = 0.03$, FLIC score and marital status, respectively). The prognostic significance of the baseline FLIC score was confirmed in a second trial[47] that included a larger patient population (438 patients) enrolled into one of seven trials that were conducted by the Lung Cancer Study Group. Patients with localized and advanced-stage NSCLC, as well as a limited number of patients with small cell disease and mesothelioma, were included in this data set. In a multivariate proportional hazards model, baseline QOL, T status, N status, PS, and small cell histologic features were significantly associated with survival.

Six randomized trials[34–39,52–55] that have compared various treatment regimens for patients with advanced disease have included an analysis of HRQOL measurements and treatment outcomes Two of these trials[52,53] used the FACT-L questionnaire, and both confirmed the prognostic significance of the baseline FACT-L for overall survival. In the ECOG 5592 trial,[53] high baseline scores on the physical well-being and trial outcome index subscales of the FACT-L questionnaire were also significant predictors of both response to treatment and time to disease progression and overall survival. Likewise, in the SWOG 9509 trial,[52] patients with a total FACT-L score of $\leq$ 98 (median FACT-L score) had a significantly worse survival compared with those with higher scores ($p = 0.003$), and the baseline total FACT-L score remained a significant prognostic factor in the multivariate model even when treatment arm, PS, weight loss ($< 5\%/\geq 5\%$), stage (IIIB/IV), and lactate dehydrogenase were considered. Of the three trials[35,39,52] that used the EORTC QLQ-C30 questionnaire, two trials[35,52] confirmed the prognostic significance of the baseline QOL for survival in multivariate models. In the Multicenter Italian Lung Cancer in the Elderly Study,[52] overall QOL was the most significant prognostic factor for survival in the multivariate analysis ($p = 0.0003$), followed by PS ($p = 0.006$), number of disease sites ($p = 0.02$), and instrumental activities of daily living ($p = 0.04$). Similarly, in the Big Lung Trial,[35] global QOL was a significant prognostic factor in the multivariate model ($p = 0.009$), but other subscales and symptoms were also identified, including role functioning ($p = 0.026$), fatigue ($p = 0.013$), appetite loss ($p = 0.023$), and constipation ($p = 0.0003$). In the third trial[56] that used the EORTC QLQ-C30 questionnaire, QOL subscales including pain ($p < 0.0001$), appetite loss ($p = 0.048$), fatigue ($p = 0.020$), lung cancer symptoms ($p = 0.049$), level of physical functioning ($p = 0.051$), and overall QOL ($p = 0.026$) were significant predictors of survival in the univariate analysis. However, in the multivariate model, only the European Organization for Research and Cancer Treatment pain subscale ($p = 0.020$) added any prognostic information to the clinical factors that were identified (nonadenocarcinoma histology, albumin $<$ 3.5 mg/dL).

Although a number of different questionnaires have been used to establish baseline HRQOL, the results from these larger, randomized trials suggest that patient-reported HRQOL as established by either the FACT-L (physical well-being, trial outcome index, or total FACT-L score) or EORTC QLQ-C30 (global QOL) questionnaire can be used to predict clinical outcomes after treatment with chemotherapy. Furthermore, the data from these trials suggest that HRQOL can provide prognostic information that remains significant when other known prognostic factors are considered, including PS.

Recommendation

8. It is recommended that patient-reported HRQOL be measured using the FACT-L or EORTC QLQ-C30 questionnaire because it is a significant prognostic factor for survival. Grade of recommendation, 1A

Which Factors Should Patients Consider in Choosing Active Treatment Over BSC?

Although it is now clear that survival and QOL of many patients with advanced lung cancer are improved by chemotherapeutic intervention, this treatment course may not be the best choice for all patients. Average survival benefits are modest, with more extended survival occurring in a minority of patients. Survival benefits are also often associated with treatment toxicity. Benefits of chemotherapy in

certain patient groups, such as patients with poor PS or significant comorbid diseases, are less well established. In addition, survival of patients who have advanced disease and do not undergo active treatment seems to have improved in the past decade, further supporting a role for this option in some patients.[57] Studies[58,59] that have investigated patient preferences for active therapy have demonstrated a broad spectrum of individual patient choices regarding active therapy vs BSC that seems unrelated to age, gender, or educational background. Individual preferences not only are based on potential survival benefits but also likely depend on patient attitudes regarding the chances of treatment success, toxicities related to therapy, and short- and long-term effects on overall QOL. Physicians and patients need to understand these factors so that a range of treatment options that are best suited for the patient can be offered.

Most patients want detailed information about their disease. This not only includes disease stage, extent, and expected survival, but also expected disease-related impact on QOL factors that are important to the individual patient. Patient assessments of their own survival time play a large role in their choices regarding treatment planning.[60] However, patients often misunderstand the extent of their disease, which results in inaccurate perceptions regarding treatment goals and survival that are unrecognized or unappreciated by their physicians.[61,62] This phenomenon may be related to physician difficulties explaining a lung cancer diagnosis and prognosis as well as unintended alternative patient perceptions of the information being provided.[60,62,63]

Once armed with individualized knowledge about their cancer, patients should expect a choice of treatment options, understand why their physician has offered these choices, and understand what the goals of each treatment option are. Epidemiologic studies[64,65] of chemotherapy for advanced lung cancer in the United States demonstrate wide variations in treatment patterns that are related to both nonmedical and medical factors. Among medical factors, attitudes of physicians toward various treatment regimens and who should or should not be treated actively are broadly varied and may be influenced by age, PS, associated comorbidities, or knowledge or acceptance of established guidelines.[66,67] Understanding why their physician has chosen these options can help the patient feel more comfortable about the treatments that they will eventually choose.

In addition, careful discussion of the tradeoffs of active treatment to improve survival and overall QOL with the more short-term impact of treatment adverse effects on symptoms and daily activities provides clearer choices for the patient. Retrospective studies[58] in patients who have already received chemotherapy suggest that patient reticence about active chemotherapy may be related to inadequate information regarding therapeutic choices. Specific information related to short- and long-term toxicities, expected beneficial effects of therapy, and treatment risks with regard to the patient's physical and emotional status, in addition to a straightforward explanation of the chances of significant survival improvement, have been welcomed by patients when presented in a structured and understandable manner.[59,68,69] Most patients strongly support receiving a broad array of information about therapeutic choices, and the majority of patients want to participate in decisions regarding therapy to some extent.[58,59,70,71]

Ultimately, decisions regarding active vs supportive treatment are as strongly influenced by personal values, perceived goals for remaining life, social circumstances (*eg*, available support during treatment and illness progression), religious or other spiritual beliefs, and emotional or psychological responses to disease and specific treatment modalities as by potential survival benefits from active treatment. Patients should consider the broad range of information regarding their disease and treatment options in the context of these individualized expectations. One study[72] indicated that patients reported that a majority of physicians provide patients with a general overview of toxicities associated with chemotherapy, although a smaller proportion reported discussion comparing specific toxicities of alternative regimens. However, although a majority of patients are concerned about specific adverse effects, a recent study[73] suggest that the overall effect of changes in QOL on daily physical and social activities may play a larger role in patient perceptions of their sense of well-being rather than specific disease-related symptoms or treatment-related toxicities, suggesting that encouraging a clear understanding of the effects of therapy or BSC on this area by patients and physicians should be emphasized.

Recommendation

9. It is recommended that patients with stage IV NSCLC receive adequate education about the risks and benefits of chemotherapy to enable active participation in the decision-making process regarding treatment selection. Grade of recommendation, 1C

Conclusions

The standard of care for the treatment of the patient with stage IV NSCLC and good PS remains doublet-based therapy, with the exception of patients who are eligible to receive bevacizumab, which has been shown in a large, randomized, phase III trial to improve survival over chemotherapy alone. Elderly patients (≥ 70 to 79 years old) also benefit from therapy, as do patients with poor PS. These populations are heterogeneous, and the optimal approach in these patients remains controversial and should be individualized. The impact of treatment on the extreme elderly (> 80 years old) has not been well documented and requires further study in well-designed clinical trials. Because stage IV NSCLC is not curable, QOL measures should be used to assess treatment benefit because they are patient based and can predict therapeutic benefit. Last, patients should be educated about the nature of their incurable disease and the potential benefit of chemotherapeutic approaches.

Summary of Recommendations

1. In patients with stage IV NSCLC and a good PS, two-drug combination chemotherapy is recommended. The addition of a third cytotoxic chemotherapeutic agent is not recommended because it provides no survival benefit and may be harmful. Grade of recommendation, 1A

2. Bevacizumab improves survival combined with carboplatin and paclitaxel in a clinically selected subset of patients with stage IV NSCLC and good PS (nonsquamous histology, lack of brain metastases, and no hemoptysis). In these patients, addition of bevacizumab to carboplatin and paclitaxel should be considered a therapeutic option. Grade of recommendation, 1A

3. In patients who have stage IV NSCLC and are elderly (≥ 70 years old), single-agent chemotherapy is recommended for most. Grade of recommendation, 1A

4. However, in patients who have stage IV NSCLC, are elderly (≥ 70 years old), have a good PS, and lack significant comorbidities, two-drug combination chemotherapy is recommended as an option. Grade of recommendation, 1B

5. In patients who have stage IV NSCLC and are ≥ 80 years old, the benefit of chemotherapy is unclear and should be decided on the basis of individual circumstances. Grade of recommendation, 2C

6. In patients with stage IV NSCLC and a PS of 2, chemotherapy is recommended on the basis of defined response rates and symptom palliation. Grade of recommendation, 1B

7. In patients with stage IV NSCLC and a PS of 2, no specific recommendation can be given with regard to the optimal chemotherapeutic strategy. A single phase III trial showed a survival benefit to a carboplatin-based doublet compared with a single agent in a prospectively planned subset analysis. Grade of recommendation, 2C

8. It is recommended that patient-reported health-related quality of life be measured using the FACT-L or EORTC QLQ-C30 questionnaire because it is a significant prognostic factor for survival. Grade of recommendation, 1A

9. It is recommended that patients with stage IV NSCLC receive adequate education about the risks and benefits of chemotherapy to enable active participation in the decision-making process regarding treatment selection. Grade of recommendation, 1C

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Special Treatment Issues in Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **This chapter of the guidelines addresses patients who have particular forms of non-small cell lung cancer that require special considerations. This includes patients with Pancoast tumors, T4N0,1M0 tumors, satellite nodules in the same lobe, synchronous and metachronous multiple primary lung cancers (MPLCs), solitary brain and adrenal metastases, and chest wall involvement.**

Methods: **The nature of these special clinical cases is such that in most cases, metaanalyses or large prospective studies of patients are not available. For ensuring that these guidelines were supported by the most current data available, publications that were appropriate to the topics covered in this chapter were obtained by performance of a literature search of the MEDLINE computerized database. When possible, we also referenced other consensus opinion statements. Recommendations were developed by the writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), and reviewed by all members of the lung cancer panel before approval by the Thoracic Oncology NetWork, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.**

Results: **In patients with a Pancoast tumor, a multimodality approach seems to be optimal, involving chemoradiotherapy and surgical resection, provided appropriate staging has been conducted. Patients with central T4 tumors that do not have mediastinal node involvement are uncommon. Such patients, however, seem to benefit from resection as part of the treatment as opposed to chemoradiotherapy alone when carefully staged and selected. Patients with a satellite lesion in the same lobe as the primary tumor have a good prognosis and require no modification of the approach to evaluation and treatment than what would be dictated by the primary tumor alone. However, it is difficult to know how best to treat patients with a focus of the same type of cancer in a different lobe. Although MPLCs do occur, the survival results after resection for either a synchronous presentation or a metachronous presentation with an interval of < 4 years between tumors are variable and generally poor, suggesting that many of these patients may have had a pulmonary metastasis rather than a second primary lung cancer. A thorough and careful evaluation of these patients is warranted to try to differentiate between patients with a metastasis and a second primary lung cancer, although criteria to distinguish them have not been defined. Selected patients with a solitary focus of metastatic disease in the brain or adrenal gland seem to benefit substantially from resection. This is particularly true in patients with a long disease-free interval. Finally, in patients with chest wall involvement, as long as tumors can be completely resected and there is absence of N2 nodal involvement, primary surgical treatment should be considered.**

Conclusions: **Carefully selected patients may benefit from an aggressive surgical approach.**

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Key words: adrenal metastasis; brain metastasis; carina; metachronous primary lung cancers; multiple primary lung cancer; Pancoast tumor; satellite nodules; superior sulcus tumor; superior vena cava; synchronous primary lung cancers; T4N0,1M0 tumor

Abbreviations: ACCP = American College of Chest Physicians; MPLC = multiple primary lung cancer; NSCLC = non-small cell lung cancer; PET = positron emission tomography; WBRT = whole-brain radiotherapy

In general, patients with an early stage non-small cell lung cancer (NSCLC) without mediastinal nodal involvement (stage I and II) are treated primarily with surgery, whereas those with a locally advanced lung cancer with mediastinal nodal involvement (stages IIIA and IIIB) are treated with chemotherapy and radiation. However, there are several relatively unusual presentations of NSCLC in which the anatomic and biological issues seem to dictate a different approach. In addition, the presence of an isolated, second focus of cancer in a patient with lung cancer presents a situation in which the biology of this phenomenon is often not clear and, therefore, the approach to treatment is difficult.

This section addresses patients with particular forms of NSCLC that require special considerations. This includes patients with Pancoast tumors, T4N0,1M0 tumors, satellite nodules in the same lobe, synchronous and metachronous multiple primary lung cancers (MPLCs), and solitary metastases.

Materials and Methods

A formal metaanalysis was not available for any of the particular forms of NSCLC that are the subject of this chapter, and resources did not permit the American College of Chest Physicians (ACCP) to conduct such an analysis independently. Clinical guidelines from other organizations were available only with regard to Pancoast tumors. These involve primarily consensus opinion statements and are discussed in the "Pancoast Tumors" section.[1–6] However, a systematic review of the most recent literature in each of these areas was performed. The recommendations in this section rely heavily on the data from this review.

The data regarding the approach to these special situations were reviewed, summarized, and used to define management recommendations by the writing committee. This document was then reviewed by three independent reviewers, and further changes were made. The revised document and recommendations were further reviewed by the entire ACCP Guidelines Committee to ensure that it met the requirements of a balanced, accurate, and generally acceptable representation of the issues with regard to these particular forms of NSCLC.

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Results

Pancoast Tumors

Definitions: Lung cancers that occur in the apex of the chest and invade apical chest wall structures are called superior sulcus tumors, or Pancoast tumors. The classic description of such patients involves a syndrome of pain radiating down the arm as a manifestation of brachial plexus involvement. With improvements in radiographic techniques, earlier diagnosis, and a more detailed understanding of the anatomy, a tumor can be classified as a Pancoast tumor when it invades any of the structures at the apex of the chest, including the most superior ribs or periosteum, the lower nerve roots of the brachial plexus, the sympathetic chain near the apex of the chest, or the subclavian vessels. These tumors are now divided into anterior, middle, and posterior compartment tumors depending on the location of the chest wall involvement in relation to the insertions of the anterior and middle scalene muscles on the first rib.[7] A syndrome of pain radiating down the arm is no longer a prerequisite for an apical tumor to be designated a Pancoast tumor.

Workup: No data specifically address the reliability of the clinical examination in patients with Pancoast tumors with regard to the presence of distant metastases. Given that benign lesions such as granulomas, fungal infections, and small cell lung cancer can masquerade as NSCLC in the superior sulcus region, it is recommended that a histologic diagnosis of the mass be obtained before initiation of any treatment. In the absence of data to the contrary, the panel thought that Pancoast tumors should be treated like most other resectable lung cancers, meaning that imaging tests for distant metastases are not routinely necessary in the presence of a negative clinical evaluation. There are also no data regarding the reliability of CT or positron emission tomography (PET) scans for mediastinal node involvement specifically in patients with Pancoast tumors. The reader is referred to the "Noninvasive Staging of Non-small Cell Lung Cancer" chapter for additional discussion regarding the sensitivity and specificity of CT and PET scans in lung cancer staging. The consensus of the panel is that mediastinoscopy should be performed in all patients who are being considered for an attempt at a curative resection, regardless of whether the CT or PET scan suggests involvement of the mediastinal lymph nodes. The argument for this approach to surgically staging the mediastinum in all patients with a Pancoast tumor is that it is consistent with the general recommendation for accurate staging before initiation of a major intervention such as resection and consistent with data demonstrating

that N2,3 node involvement is a major negative prognostic factor. No firm recommendation can be made about whether mediastinoscopy should be done before or after preoperative therapy. An MRI demonstrates involvement of apical chest wall structures better than a CT scan,[8] but CT provides more information about the presence of nodal enlargement and pulmonary, hepatic, and adrenal metastases; therefore, both chest CT and MRI are indicated to assess the resectability of a Pancoast tumor.

Treatment: The classic approach to curative treatment of Pancoast tumors has been preoperative radiotherapy followed by surgical resection. This dates back to an experience published in 1961 by Shaw et al,[9] in which 12 of 18 patients who were treated with this approach were still alive at the time the article was written. However, the follow-up was < 2 years in 90% of the patients.[9] Alternatives are treatment with radiation alone, preoperative chemoradiotherapy and resection, or chemoradiotherapy without resection.

Treatment with radiation alone has achieved good palliation of pain in approximately 75% of patients.[10] In general, very few patients who are treated with radiation alone are long-term survivors (approximately 5%).[11] However, many of these series have included patients with advanced-stage tumors. Among studies[10,12–14] that have involved primarily patients who had a reasonable chance of cure, the average median survival time was 16 months and the average 5-year survival was 20% (range, 15 to 23%).

Treatment with preoperative radiation and resection has resulted in an average median survival time of 22 months and a 5-year survival of 27%.[11] In these series, approximately one third of patients underwent an incomplete (R1 or R2) resection, and approximately one third of the resections involved only a limited resection of the affected lobe of the lung.[11] Retrospective analysis[15] found that a complete resection with negative margins (R0) and a pulmonary resection involving at least a lobectomy are major factors associated with better survival. Furthermore, N2,3 lymph node involvement is a major negative prognostic factor and should generally be considered a contraindication to surgery.[11] Patients with vertebral body or subclavian vessel involvement have traditionally not been consider for resection, but it seems that with improved surgical approaches to these structures, a few experienced centers[16,17] have been able to achieve reasonable survival in such patients. The presence of Horner syndrome is also associated with poor survival.[11]

A large phase II study[18] of preoperative chemoradiotherapy in patients with Pancoast tumors showed a complete resection rate of 92% and a good 2-year survival rate compared with historical controls of radiotherapy followed by surgery. Furthermore, local recurrences were seen in only 33% of patients with a recurrence, whereas in series[18] involving preoperative radiotherapy alone, the majority of recurrences involved the tumor bed. These data, in combination with the data for non-Pancoast stage III NSCLC, suggest that preoperative chemoradiotherapy is a significant improvement over preoperative radiotherapy, particularly in light of the fact that there are insufficient numbers of patients with a Pancoast tumor to be able to complete a randomized comparison. The Southwest Oncology Group is accruing patients with Pancoast tumors into a phase II study of induction chemotherapy with cisplatin/etoposide and concurrent radiation followed by surgical resection, followed by consolidation docetaxel (S0220).

A single-institution, retrospective report[19] using high-dose three-dimensional radiation as part of induction chemotherapy and radiation therapy followed by surgery strategy showed that doses up to 60 Gy could be tolerated by most patients without any significant increase in postoperative complications. In 37 patients with pretreatment Pancoast tumors stages IIB to IV, the authors[19] reported a complete resection rate of 97.3%, with a complete response rate of 40.5%. Overall median survival time was 2.6 years, and 7.8 years in the group with a pathologic complete response. The overall recurrence rate was higher than most other series at 50%, with 50% of those being in the brain.

Other published guidelines[3] have recommended that patients with Pancoast tumors be evaluated by a thoracic surgeon. If there is no evidence of mediastinal node involvement[1] or extensive local invasion,[5] then patients should undergo resection in combination with radiotherapy or chemoradiotherapy.[1,4,5] Patients with inoperable, painful Pancoast tumors should be treated with radiotherapy with or without chemotherapy for palliation of their pain.[2] The last two recommendations were rated grade B, whereas the strength of the other statements was rated grade C. Other guidelines have reached the same conclusions as this ACCP document, although the recommendations in those other documents were less detailed and more vaguely worded.

In summary, the available data suggest that the best survival is achieved by preoperative chemoradiotherapy followed by surgical resection in carefully selected patients. Preoperative radiotherapy followed by surgical resection is a reasonable alternative. Involvement of subclavian vessels or the vertebral column is associated with poor survival after resection. However, a few centers have gained experience with improved surgical approaches to these

structures and have reported reasonable survival rates after resection. Involvement of mediastinal nodes is associated with poor survival after resection. At the time of resection, it is important to carry out a complete resection that should involve at least a lobectomy. There are no data on how unresectable yet still potentially curable Pancoast tumors should be managed. However, extrapolation from the data for non-Pancoast stage III NSCLC suggests that chemoradiotherapy is the best approach. For patients in whom cure is not believed to be possible, radiotherapy offers good palliation of pain.

Recommendations

1. In patients with a Pancoast tumor, it is recommended that a tissue diagnosis be obtained before initiation of therapy. Grade of recommendation, 1C

2. In patients who have a Pancoast tumor and are being considered for curative intent surgical resection, an MRI of the thoracic inlet and brachial plexus is recommended to rule out tumor invasion of unresectable vascular structures or the extradural space. Grade of recommendation, 1C

3. In patients with a Pancoast tumor involving the subclavian vessels or vertebral column, it is suggested that resection be undertaken only at a specialized center. Grade of recommendation, 2C

4. In patients who have a Pancoast tumor and are being considered for curative resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

5. In patients with a potentially resectable, nonmetastatic Pancoast tumor (and good performance status), it is recommended that preoperative concurrent chemoradiotherapy be administered before resection. Grade of recommendation, 1B

6. In patients who undergo resection of a Pancoast tumor, it is recommended that every effort be made to achieve a complete resection. Grade of recommendation, 1A

7. It is recommended that resection of a Pancoast tumor consist of a lobectomy (instead of a nonanatomic wedge resection) as well as the involved chest wall structures. Grade of recommendation, 1C

8. In patients with either a completely or incompletely resected Pancoast tumor, postoperative radiotherapy is not recommended because of lack of demonstrated survival benefit. Grade of recommendation, 2C

9. In patients who have an unresectable but nonmetastatic Pancoast tumor and good performance status, definitive concurrent chemotherapy and radiotherapy is recommended. Grade of recommendation, 1C

10. In patients who have Pancoast tumors and are not candidates for curative intent treatment, palliative radiotherapy is recommended. Grade of recommendation, 1B

T4N0,1M0 Tumors

Patient Selection and Workup: Most patients with involvement of T4 structures have mediastinal node involvement as well. These patients should be treated with chemoradiotherapy, as is generally recommended for patients with stage IIIB NSCLC. However, very selected patients with T4 involvement but without mediastinal node involvement can be viewed as candidates for surgery. Although many reports have demonstrated the technical feasibility of resection of T4 structures, fewer series have provided long-term survival data. The largest experience of resection for T4 involvement involves carinal resections, usually together with a right pneumonectomy. Since 1980, there have been 12 published series of carinal resections for lung cancer. Four of the largest series[20–24] have been published since 2000 and provide long-term survival data on 395 patients. A moderate experience is available with left atrial involvement (88 patients)[25–29] and involvement of the superior vena cava (189 patients),[30–33] and a smaller experience has been reported with tumors invading the aorta (60 patients)[34–37] and vertebral bodies (48 patients).[38–41] That so few patients have been reported with long-term survival statistics underscores that patients who are candidates for a surgical approach are extremely rare and highly selected.

Mediastinoscopy should be performed even if a CT suggests no N2,3 involvement in patients who have T4 tumors and are being considered for a surgical approach. This argument is based on the fact that CT evaluation of the mediastinum in central tumors has a high false-negative rate. Furthermore, a consistent finding is that survival for patients with T4N2,3 disease is so poor that the presence of positive N2 disease should be considered a contraindication to aggressive surgical therapy. In patients who are being considered for carinal resection, it may be best to perform mediastinoscopy at the same

time as resection to prevent scarring and therefore lack of mobility of the airways at the time of reconstruction.

Outcomes After Surgery: In a fairly large series[25] involving an aggressive approach to T4 tumors from Japan, approximately one third of patients were able to undergo complete (R0) resection, one third a microscopically incomplete resection (R1), and one third a grossly incomplete resection (R2). The 5-year survival rates for these groups were 22%, 18%, and 0%, respectively.[25] Two small series from Japan on highly selected patients who had T4 tumors invading the aorta and underwent *en bloc* aortic resection reported complete resection rates of 50%[22] and 75%.[21] The 5-year survival rates were significantly better in patients who underwent complete resection and in those who had no N2 or N3 mediastinal lymph node disease.

The data regarding the outcome after resection in patients with carinal involvement show an average 5-year survival of 28%. However, the survival comes at a price of an average operative mortality of 17% (range, 7 to 29%). It should be noted, however, that the survival statistics have included all operative deaths as well. That the best reported 5-year survival (44%) comes from the largest series[24]—which also reported an operative mortality of only 7%—can be interpreted to suggest that such resections should be undertaken only in experienced centers. Survival data for resections involving other T4 structures have involved fewer patients, making interpretation of the data difficult (Table 1). The survival of patients with left atrial involvement has been less favorable. In general, however, the survival of patients with involvement of other T4 structures has been similar to that reported for patients with carinal involvement.

Patients with involvement of T4 structures should be very carefully selected before surgical resection is undertaken because of the limited survival and the high mortality. This means that these patients should have a high likelihood of being able to tolerate a major operation from a general medical standpoint. This also means that the evaluations to rule out either mediastinal or extrathoracic metastases should be especially thorough and that the threshold for pursuing subtle abnormalities seen on imaging tests should be low.

Preoperative chemotherapy or chemoradiotherapy in patients with T4 tumors has been reported in several trials. A 5-year survival of 20% was reported among all patients in the largest trial[34] (57 patients; 62% of whom underwent complete resection). These results are encouraging, however, given that 60% of the patients entered in the study had T4N2M0 tumors by careful surgical staging. By comparison, 5-year survival results for chemoradiotherapy without surgery in patients with stage IIIA and IIIB tumors have been approximately 9 and 14% in large, randomized trials involving sequential or concurrent chemoradiotherapy trials, respectively.[38] However, these latter series included patients both with stage IIIA and IIIB disease and did not report data separately or report any data specifically in patients with T4N0,1 tumors. A retrospective analysis[42] of the Southwest Oncology Group experience suggested that patients with T4N0,1M0 tumors benefited from preoperative chemoradiotherapy and surgery compared with chemoradiotherapy alone (2-year survival, 64% vs 33%).

Recommendations

11. In patients who have a clinical T4N0,1M0 NSCLC and are being considered for curative resection, it is recommend that invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) be undertaken. Involve-

Table 1—*Results of Resection of Patients With T4 Involvement From NSCLC**

Structure	Studies, No.	Patients, No.	Hospital Mortality, %	5-yr Survival, %		
				Average	Highest	Lowest
Any	1	101	13	13	23 (R0)	0 (R2)
Carina	12	722	17	28	44	13
Left atrium	4	88	3.5	15	22	10
Superior vena cava	4	189	12	25	31	21
Vertebral bodies	3	48	0	50†		
Aorta	3	60	13	27	37	17
Esophagus	1	7		14		
Main pulmonary artery	1	7		0		

*R0 = complete resection; R2 = incomplete resection with gross residual disease.
†Two-year survival.

ment of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

12. In patients with a T4N0,1M0 NSCLC, it is recommended that resection be undertaken only at a specialized center. Grade of recommendation, 1C

Satellite Nodules and MPLCs

Occasionally, patients present with more than one focus of cancer within the lung. The American Joint Committee on Cancer staging system classifies a second focus of cancer within the same lobe as T4, whereas a second focus in another lobe is classified as M1. However, the classification does not help in grouping tumors according to similar biological situations. Although the secondary focus may represent a hematogenously spread metastasis, it may also be a second primary lung cancer or a second focus that is a manifestation of local spread. Distinguishing these situations is difficult. In this section, these tumors are classified according to clinical presentation, which is a method that at least has practical relevance in defining an approach to these patients. This section distinguishes a synchronous lesion within the same lobe as the primary tumor, two synchronous foci of cancer in different lobes, and two metachronous foci of cancer in the lung. Circumstances can be identified for each of these clinical presentations to allow them to be defined reasonably as satellite lesions and synchronous and metachronous MPLCs. In this document, as well as in the published literature, a satellite lesion is any additional focus of lung cancer of the same histologic type within the same lobe, regardless of the relative size or location in different segments and regardless of whether it is discovered by the radiologist, the surgeon, or the pathologist.

Definitions for satellite lesions within the same lobe as the primary tumor, synchronous second primary lung cancers, and metachronous second primary lung cancers are given in Table 2. In general, these criteria are relatively well accepted, but some authors have varied slightly in some details (*eg*, the minimum interval between metachronous MPLCs). Many data are available regarding the incidence of a second primary lung cancer and the recurrence rates and patterns of resected lung cancer. Therefore, the incidence of a second primary cancer and the incidence of a solitary pulmonary metastasis can be estimated for different stages of the primary lung cancer and by location of the second focus of cancer, as is shown in Figure 1. Although such estimates are based on extrapolations from known data, the resulting incidences and distributions between synchronous and metachronous presentations or same histology and different histologic types both are internally consistent and very close to what is actually observed. Analysis of these rates suggests that the biological situation (*ie*, new primary vs locally or hematogenously spread metastasis) can be defined clearly in some clinical presentations (*eg*, satellite lesions, MPLCs of different histologic types, metachronous tumors with a ≥ 4-year interval). In other clinical presentations, the biological situation is very unclear.

Table 2—*Definition of Satellite Nodules, MPLCs, and Pulmonary Metastases*

Satellite nodules from primary tumor
Same histology
And same lobe as primary cancer
And no systemic metastases
MPLCs
Same histology, anatomically separated
Cancers in different lobes
And no N2,3 involvement
And no systemic metastases
Same histology, temporally separated
≥ 4-yr interval between cancers
And no systemic metastases from either cancer
Different histology
Different histologic type
Or different molecular genetic characteristics
Or arising separately from foci of carcinoma *in situ*
Hematogenously spread pulmonary metastases
Same histology and multiple systemic metastases
Same histology, in different lobes
And presence of N2,3 involvement
Or < 2-yr interval

Small pulmonary lesions are frequently seen in addition to the primary tumor on the chest CT. This occurred in 16% of patients with potentially operable clinical stages I to IIIA NSCLC in one large study.[43] The lesions were not calcified and ranged from 4 to 12 mm. A definitive diagnosis (biopsy or follow-up of > 24 months) was established in only 20% of the patients, the remainder being unavailable for follow-up or having unavailable pathology reports. Of the lesions for which a definitive diagnosis was available, 86% were found to be benign. In another study,[44] 10% of patients had a second lesion detected preoperatively, nearly 60% of which were found to be benign. Therefore, a patient should not be denied a curative approach on the basis of a second pulmonary nodule without a definitive tissue diagnosis.

In this section, a prospective approach is formulated for patients with cI to III NSCLC in whom a second intraparenchymal focus of cancer not only is identified radiographically but also is proved to be malignant by cytologic studies. Patients with disseminated disease (extrathoracic metastases) are ex-

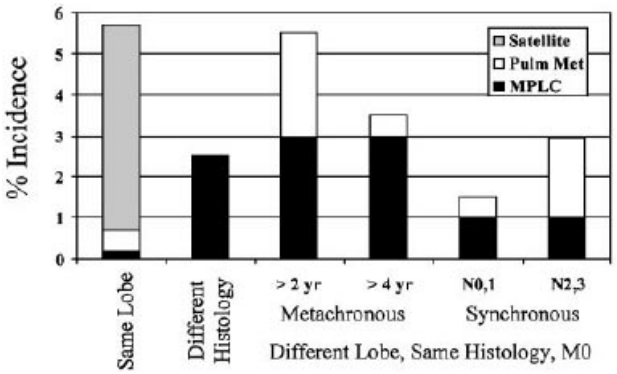

FIGURE 1. Estimated incidence of MPLCs, solitary pulmonary metastases (Pulm Met), and satellite lesions in different clinical presentations. These estimates are based on data concerning recurrence rates by stage and time interval, location of metastases, and the observed incidence of MPLCs and satellite lesions for each clinical presentation. Adapted from Detterbeck et al.[45]

cluded. In addition, the 30% of patients who had synchronous MPLCs and in whom the second cancer was found incidentally at thoracotomy are excluded for obvious reasons. Patients with bronchioloalveolar carcinoma should also be considered separately. Finally, it must be emphasized that the majority (57 to 86%) of additional nodules seen radiographically in patients with cI to III NSCLC are benign lesions.[43,44] Therefore, the considerations noted in the following discussion are relevant only when a histologic diagnosis of an MPLC has been made.

Satellite Nodules of Cancer in the Same Lobe:

Studies that have reported on long-term survival specifically of patients with satellite nodules in the same lobe as the primary tumor have generally reported good survival. The overall 5-year survival rate of all patients, approximately 60% of whom have N1 or N2 involvement, is 34%.[45] The 5-year survival for patients with satellite nodules and no node involvement is 64% (range, 54 to 70%), which is similar to the survival for patients with stage I NSCLC without satellite nodules.[45] Direct comparisons have generally demonstrated a slightly inferior survival in patients with satellite nodules, stage for stage, compared with patients without satellite nodules.[46] Nevertheless, the survival of patients with satellite nodules in the same lobe is consistently higher than that reported for patients with a second cancer nodule in a separate lobe (5-year survival, approximately 10%; range, 0 to 23% for all patients).[45]

In general, no additional diagnostic workup is necessary in patients with a secondary lesion in the same lobe. The available data indicate that most secondary lesions in the same lobe as the primary tumor were found to be benign. Furthermore, the prognosis in patients who are found to have a satellite nodule of cancer is only slightly inferior to those without a satellite focus, which argues that resection should be undertaken even in patients who do, in fact, have a satellite focus of cancer. Therefore, there is little reason to attempt to diagnose definitively a second lesion preoperatively in patients who have cI and II tumors and a second radiographic nodule in the same lobe. Furthermore, there is little reason to perform any additional preoperative staging investigations (*eg*, mediastinoscopy, CT of the head, bone scan) in patients with a second nodule in the same lobe as the primary tumor, other than what is dictated by the patient's clinical status and the primary tumor.

RECOMMENDATIONS

13. In patients with suspected or proven lung cancer and a satellite nodule within the same lobe, it is recommend that no further diagnostic workup of a satellite nodule be undertaken. Grade of recommendation, 1B

14. In patients with a satellite lesion within the same lobe as a suspected or proven primary lung cancer, evaluation of extrathoracic metastases and confirmation of the mediastinal node status should be performed as dictated by the primary lung cancer alone and not modified because of the presence of the satellite lesion. Grade of recommendation, 1C

15. In patients with NSCLC and a satellite focus of cancer within the same lobe (and no mediastinal or distant metastases), resection via a lobectomy is the recommended treatment. Grade of recommendation, 1B

Synchronous Second Primary Lung Cancer

Definition: A synchronous second focus of lung cancer in a different lobe is easily defined as a second primary lung cancer when the two sites are of different histologic types. Cancers may also be distinguished on the basis of different molecular genetic characteristics. In the absence of molecular analysis, it is difficult to distinguish two synchronous cancers that are of the same histologic type as separate primary lung cancers. One proposed requirement for classification as synchronous second primary lung cancers is that there be no mediastinal node involvement and no sites of distant metastases when the two cancers are of the same histologic type.[45] It can be estimated that the incidence of a second primary cancer using this definition is slightly

higher than the incidence of an isolated pulmonary metastasis, given what is known about the incidence of MPLCs and the rate and sites of spread of lung cancer.[45] Conversely, when mediastinal node involvement is present, the incidence of an isolated pulmonary metastasis is higher than that of a second primary cancer.[45] Although the exact incidence of multiple primary cancers and isolated pulmonary metastasis may not be fully defined by these estimates, at the very least it is clear that the identification of two synchronous foci of cancer of the same histologic type is difficult.

Patient Selection and Treatment Results: The survival of patients with synchronous (different lobe) MPLCs (either same or different histologic types) is highly variable, consistent with the difficulty of reliably classifying these tumors.[45] The 5-year survival for all patients ranges from 0 to 70%, and the survival of patients in whom both tumors are classified as stage I ranges from 0 to 79%.[47–50] These data suggest that a great deal of caution is necessary in classifying two synchronous foci of cancer as two separate primary lung cancers. Approximately one third of the second foci of cancer are found incidentally at the time of resection.[45] Approximately 60% of synchronous second primary lung cancers are squamous cell cancers; in approximately 60% of the cases, the tumors are of the same histologic type.[45]

The first issue to consider in approaching patients with a synchronous second focus of lung cancer in a different lobe is the accuracy of the diagnosis. If two histologic types of primary NSCLC are diagnosed preoperatively, then it must be remembered that the accuracy of determining lung cancer cell type by cytologic studies is only 60 to 80%.[51–54] A histologic or core needle diagnosis should be obtained, especially when there is evidence of mediastinal lymph node involvement. Mediastinal lymph node involvement increases the probability that a second focus of tumor is an isolated pulmonary metastasis. Even when a diagnosis of synchronous second primary lung cancers is secure, careful staging with distant organ scanning and mediastinoscopy should be carried out because the survival of patients with synchronous MPLC is poor, even in patients who have cancers of different histologic types.[55]

Patients with a synchronous second cancer of similar histologic type present a conundrum. These patients should undergo an extensive search for mediastinal involvement, distant metastases, or an extrapulmonary primary cancer. Genetic marker analysis may be useful in distinguishing between MPLC and a metastasis. In the absence of distant metastases, lymph node involvement, or evidence that the second focus of cancer is a metastasis, resection is reasonable, although the reported long-term survival is generally poor.

Occasionally, patients who are not suspected of having a second primary cancer are found intraoperatively to have a second cancer. It is usually difficult to determine whether the histologic type of the two cancers is the same or different on frozen-section examination. No published data specifically address this situation. The panel believes that it is reasonable to proceed with a resection of each lesion when each seems to be a resectable primary lung cancer, given that the patient has already been exposed to the morbidity of a thoracotomy. However, this can be recommended only when the patient has adequate pulmonary reserve to tolerate the resection, when there is no mediastinal nodal involvement, and when there is no clinical evidence of distant metastases. Concerns about the adequacy of pulmonary reserve may make it necessary to perform a limited resection (segmentectomy or wedge) of one or both of the lesions. Nevertheless, the resection must be a complete resection; if this cannot be achieved, then nothing more than a biopsy of the lesions for diagnosis is indicated. The prognosis after resection in such situations has not been defined but is likely to be poor, similar to the survival of patients with synchronous primary lung cancers that are recognized or at least suspected preoperatively.

Recommendations

16. In patients who have two synchronous primary NSCLCs and are being considered for curative surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

17. In patients suspected of having two synchronous primary NSCLCs, a thorough search for an extrathoracic primary cancer to rule out the possibility that both of the lung lesions represent metastases is recommended. Grade of recommendation, 1C

18. In patients (not suspected of having a second focus of cancer) who are found intraoperatively to have a second cancer in a different lobe, resection of each lesion is recommended, provided that the patient has adequate pulmonary reserve and there is no N2 nodal involvement. Grade of recommendation, 1C

Metachronous Second Primary Lung Cancer

Definition: A metachronous second focus of lung cancer is easily defined as a second primary lung

cancer when the two tumors are of different histologic types. When they are of the same type, the second focus can be reliably defined as a second primary when there is no evidence of systemic metastases and at least a 4-year interval between the two.[45] Some authors[56] have included patients with > 2-year interval, but the estimated incidence of a solitary pulmonary metastasis from the previous lung cancer is practically the same as the estimated incidence of a new primary lung cancer.[45] Therefore, an interval of 2 to 4 years represents a gray area, where it is difficult to determine whether a new lesion is a second primary. If the interval is < 2 years, then it is much more likely that the lesion is a metastasis from the original cancer than a second primary lung cancer.

Patient Selection and Treatment Results: Among studies that have reported on metachronous second primary lung cancers, approximately two thirds of these have been tumors of the same histologic type (most often squamous cell).[45] The average time interval between tumors in these studies is 48 months. Approximately 80% of second primary lung cancers are found on a routine chest radiograph, and approximately 75% are stage I.[45–47] Approximately 65% of second primary lung cancers are able to be resected, with approximately one third of the resections involving a limited resection. The operative mortality for the resection has been reported to average 7%.[45] The 5-year survival of all patients who present with a second primary is approximately 20%.[48,50,57,58] The survival of patients who are able to undergo resection of the second primary is 36%.[48–50,55,59–62] The survival of patients who are found to have a second primary lung cancer that is stage pI is also only 36% (range, 20 to 50%).[48,49,55,58,59,61]

A careful search for sites of recurrence should be conducted in patients who present with a nodule that is suspected of being a metachronous second primary lung cancer. This is particularly important when the histologic type is the same as the primary cancer and when the interval between cancers has been < 4 years. A new cancer that appears in < 2 years should be assumed to be a metastasis unless it is clearly of different histologic type. Although some cancers that appear between 2 and 4 years after the first primary lung cancer are probably MPLC, a fair amount of doubt about this exists until the interval has been > 4 years. Resection of a second primary lung cancer that is early stage should be undertaken, although the prognosis is not as good as that of an early stage single primary lung cancer.

RECOMMENDATION

19. In patients who have a metachronous NSCLC and are being considered for curative surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

Isolated Brain Metastasis

Patient Selection and Workup: Approximately 25% of patients with stage IV NSCLC have a brain metastasis as well as other sites of metastatic disease.[63] The median survival of patients with a brain metastasis is approximately 2 months when treated with steroids alone and 3 to 6 months when treated with whole-brain radiotherapy (WBRT).[63] Because the survival of patients with a brain metastasis is so short, there is reason to consider aggressive treatment of the brain metastasis with either surgical resection or radiosurgery as a palliative treatment to prolong survival. However, a subset of patients with stage IV disease have a brain metastasis as the only site of metastatic disease. In this group, it is reasonable to consider aggressive therapy of both the primary lesion and the isolated metastatic site as a potentially curative therapy. This latter group is the focus of this section. Patients who have a brain metastasis and are treated with surgery or radiosurgery of the brain metastasis as a palliative treatment are discussed in the "Palliative Care in Lung Cancer" chapter.

Aggressive treatment of a brain metastasis may involve either surgical resection of the metastasis or ablation of the metastasis by radiosurgery. This latter technique involves a precisely focused beam of radiation with a steep fall-off of the dose outside the target area, hence the name radiosurgery. Although no randomized trial of surgery vs radiosurgery has ever been completed, comparison of the results of these techniques in patients who have been treated palliatively suggests that they are similar with regard to survival, local control, morbidity, and mortality.[64,65] A number of technical issues often favor one of these treatments over the other; therefore, they are best viewed as complementary modalities. In the discussion in this section, they are considered together as similar methods of aggressive treatment of a brain metastasis.

Patients with a brain metastasis should be selected for curative treatment only after a thorough search for other sites of disease has been negative. Furthermore, it is fairly obvious that only patients in whom

both the brain metastasis and the primary tumor can be completely resected can be considered candidates for curative treatment (synchronous presentation). It seems reasonable to assume that patients with N2,3 involvement and a brain metastasis are not good candidates for curative therapy, although data demonstrating this are lacking.[65] Therefore, it seems reasonable to perform mediastinoscopy in selecting patients for resection of the brain metastasis and the primary lesion. The histologic subtype does not play a role.[65] The number of brain metastases may not play a role as long as the number is small (≤ 3) and they all can be completely resected (as has been demonstrated by several retrospective studies in patients who were treated for palliation).[66–69]

The outlook is likely to be more optimistic for patients who are younger or female or have a metachronous presentation.[65] The outlook may also be better in patients with supratentorial lesions and those with a brain metastasis < 3 cm in diameter. However, these considerations are relative and should not necessarily exclude patients who are otherwise fit and in whom a complete resection is likely to be achieved.

Treatment Outcomes: Survival statistics of patients who have a brain metastasis and were treated with curative intent have been reported by a number of studies.[65] The overall survival for all patients is fairly consistent and averages 14% (range, 8 to 21%). The 5-year survival for patients in whom complete resection has been achieved averages 21% (range, 16 to 30%).[65] The operative mortality in these studies has been low, averaging 2%.[65] Approximately two thirds of the cases involved a metachronous presentation.[65]

There are conflicting data regarding the role of adjuvant WBRT after resection of an isolated brain metastasis. Retrospective analyses of patients who were primarily treated with curative intent have suggested either no survival benefit[70] or a significant benefit.[71] The rate of intracranial recurrence among patients who were treated primarily with palliative intent was lower after WBRT in a randomized study,[72] whereas retrospective analyses[65] in such patients have shown conflicting results. It is likely that a benefit might be seen only in patients without other sites of metastases, given the experience with prophylactic cranial irradiation in patients with small cell lung cancer. There are no data regarding the role of adjuvant chemotherapy in patients who have undergone curative resection of a brain metastasis.

Recommendations

20. In patients who have an isolated brain metastasis from NSCLC and are being considered for curative resection of a stage I or II lung primary tumor, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

21. In patients with no other sites of metastases and a synchronous resectable N0,1 primary NSCLC, resection or radiosurgical ablation of an isolated brain metastasis is recommended (as well as resection of the primary tumor). Grade of recommendation, 1C

22. In patients with no other sites of metastases and a previously completely resected primary NSCLC (metachronous presentation), resection or radiosurgical ablation of an isolated brain metastasis is recommended. Grade of recommendation, 1B

23. In patients who have undergone a curative resection of an isolated brain metastasis, adjuvant WBRT is suggested, although there are conflicting and insufficient data regarding a benefit with respect to survival or the rate of recurrent brain metastases. Grade of recommendation, 2B

24. In patients who have undergone curative resections of both the isolated brain metastasis and the primary tumor, adjuvant chemotherapy may be considered. Grade of recommendation, 2C

Isolated Adrenal Metastasis

Highly selected patients who have undergone resection of an adrenal metastasis from NSCLC with intent to cure have been reported.[65,73,74] The overall 5-year survival for these patients has been 10 to 23%. Survival after resection of the primary and the adrenal metastasis seems to be good primarily in patients without nodal involvement.[65,74] Other factors such as the histologic type, synchronous vs metachronous presentation, and ipsilateral vs contralateral location do not have prognostic value in the limited number of reported patients who underwent this treatment.[65,73,74]

One report[75] from a single institution suggested that a disease-free interval > 6 months is an independent and significant predictor of increased survival in patients who undergo resection of an isolated solitary adrenal metastasis from NSCLC. The overall 5-year survival was 23.3% in the 23 patients treated but was 38% after resection of an isolated adrenal metastasis that occurred > 6 months after lung resection. All patients with a disease-free interval of

< 6 months died within 2 years of the operation, most commonly from progression of their disease.

Recommendations

25. In patients who have an isolated adrenal metastasis from NSCLC and are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

26. In patients with a synchronous resectable N0,1 primary NSCLC and no other sites of metastases, resection of the primary tumor and an isolated adrenal metastasis is recommended. Grade of recommendation, 1C

27. In patients with no other sites of metastases and a previously completely resected primary NSCLC (metachronous presentation), resection of an isolated adrenal metastasis is the recommended treatment when the disease-free interval is > 6 months and complete resection of the primary NSCLC has been achieved. Grade of recommendation, 1C

Tumors That Invade the Chest Wall

Patient Selection and Workup: Lung cancers that invade the chest wall are usually peripheral in location, and hilar and mediastinal lymph nodes are less likely to be involved in this group of patients. Tumors that extend to invade the parietal pleura, muscles, and ribs of the chest wall and can be completely resected with *en bloc* resection techniques are classified as T3. Significant numbers of these patients are amenable to treatment by resection, and because of their favorable survival after resection, their disease has been recategorized as stage IIB as long as no lymph nodes are involved. Factors that influence survival in this group of patients include the following: (1) the extent of invasion of the chest wall, (2) completeness of resection of the tumor, and (3) the presence or absence of regional lymph node metastases.

Once lymph node involvement is present, the overall survival after resection of tumors that invade the chest wall is worse and survival is comparable to patients with stage IIIA disease. In patients who are being considered for extensive chest wall resections, it is essential to identify nodal involvement by noninvasive imaging or minimally invasive biopsy techniques before subjecting patients to extensive chest wall resections. Hilar and mediastinal lymph nodes can be assessed before surgery using CT, MRI, and PET scans. Mediastinoscopy remains the most sensitive and specific test for evaluating mediastinal nodes and should be considered before undertaking a major chest wall resection.

The use of spirometry, xenon scanning, and exercise oxygen testing are helpful in identifying patients who are not suitable for surgery on the basis of their pulmonary function. No studies, however, have accurately predicted the increased postoperative pulmonary compromise of patients who have T3 lesions and require chest wall resections. The overall effect on chest wall mechanics can be significant and must be taken into account when evaluating the medical condition of the patient and the extent of the pulmonary resection.

Treatment Outcomes: Overall 5-year survival rates for patients with complete resection range from 18 to 61%.[76–79] Long-term results are affected most importantly by complete resection to microscopically negative margins and by absence of N2 nodal involvement. In those in whom resection was incomplete or not possible, the 5-year survival in the two largest series[77,79] was virtually zero. The addition of postoperative radiation therapy in these patients does not seem to have an impact on their ultimate survival. In most series, depth of invasion of the tumor affects survival rates, with invasion limited to the pleura being an independent factor favoring long-term survival only when compared with deeper invasion.

Recommendations

28. In patients who have an NSCLC invading the chest wall and are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection, and definitive chemoradiotherapy is recommended for these patients. Grade of recommendation, 2C

29. At the time of resection of a tumor invading the chest wall, we recommend that every effort be made to achieve a complete resection. Grade of recommendation, 1B

Conclusions

The available data for patients with Pancoast tumors suggest that the best survival is achieved by

preoperative chemoradiotherapy followed by surgical resection in carefully selected patients. Preoperative radiotherapy followed by surgical resection is a reasonable alternative. Involvement of subclavian vessels, vertebral column, or mediastinal lymph nodes is associated with poor survival after resection. At the time of resection, it is important to perform a complete resection that should involve at least a lobectomy. There are no data on how unresectable yet still potentially curable Pancoast tumors should be managed. However, extrapolation from the data for non-Pancoast stage III NSCLC suggests that chemoradiotherapy is the best approach. For patients in whom cure is not believed to be possible, radiotherapy offers good palliation of pain.

Although most patients with T4 NSCLC have N2,3 or M1 involvement, surgical resection should be pursued in highly selected patients with T4N0,1M0 tumors. The survival of such patients in whom a complete resection is achieved seems to be better than after treatment with chemoradiotherapy alone. However, the operative mortality is relatively high, and patients must be carefully staged and selected. In patients with complete resection and an absence of N2 mediastinal lymph nodes, long-term survival is possible. Preoperative chemoradiotherapy may also be beneficial.

An additional small pulmonary nodule is not an infrequent finding on a CT scan in patients with an NSCLC. Most of these lesions are benign. If the lesion is within the same lobe as the lung cancer, then no special workup is necessary other than what would usually be done because lobectomy is associated with good survival even when a second focus of cancer is present (satellite lesion). When a second lesion in another lobe is suspected of being malignant, it is difficult to define whether this represents a synchronous second primary lung cancer vs a manifestation of systemic disease. The patient should undergo a thorough investigation for evidence of metastatic disease before making a decision regarding treatment. The prognosis and whether resection should be undertaken are difficult to define when two lesions of the same histologic type are present in different lobes. Resection of both lesions may be appropriate, but the prognosis is likely to be much worse than for similarly staged isolated primary lung cancers.

A careful search for sites of recurrence should be conducted in patients who present with a nodule that is suspected to be a metachronous second primary lung cancer. This is particularly important when the histologic type is the same as the primary cancer and when the interval between cancers has been < 4 years. A new cancer that appears in < 2 years should be assumed to be a metastasis unless it is clearly of a different histologic type. Although some cancers that appear between 2 and 4 years after the first primary lung cancer may be MPLC, a fair amount of doubt about this exists until the interval has been > 4 years. Resection of an early stage second primary lung cancer should be undertaken, although the prognosis is not as good as that for an early stage single primary lung cancer.

Patients who have previously undergone complete resection of the primary tumor but are subsequently found to have a solitary cranial or adrenal metastasis should be evaluated for resection of the metastasis with curative intent. In addition, patients who present with a resectable primary lung cancer and a solitary metastasis to the brain and possibly also the adrenal gland should be evaluated for possible resection of both lesions with curative intent. It is necessary to perform a careful search for other sites of metastases, and patients with mediastinal node involvement should be excluded from such an approach. Five-year survival rates of 15 to 20% have consistently been reported in patients who have undergone resection of a solitary metastasis (as well as resection of the primary tumor).

Summary of Recommendations

1. In patients with a Pancoast tumor, it is recommended that a tissue diagnosis be obtained before initiation of therapy. Grade of recommendation, 1C

2. In patients who have a Pancoast tumor and are being considered for curative intent surgical resection, an MRI of the thoracic inlet and brachial plexus is recommended to rule out tumor invasion of unresectable vascular structures or the extradural space. Grade of recommendation, 1C

3. In patients with a Pancoast tumor involving the subclavian vessels or vertebral column, it is suggested that resection be undertaken only at a specialized center. Grade of recommendation, 2C

4. In patients who have a Pancoast tumor and are being considered for curative resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

5. In patients with a potentially resectable, nonmetastatic Pancoast tumor (and good performance status), it is recommended that preoperative concurrent chemoradiotherapy be given before resection. Grade of recommendation, 1B

6. In patients who undergo resection of a Pancoast tumor, it is recommended that every effort be made to achieve a complete resection. Grade of recommendation, 1A

7. It is recommended that resection of a Pancoast tumor consist of a lobectomy (instead of a nonanatomic wedge resection) as well as the involved chest wall structures. Grade of recommendation, 1C

8. In patients with either a completely or incompletely resected Pancoast tumor, postoperative radiotherapy is not recommended because of lack of demonstrated survival benefit. Grade of recommendation, 2C

9. In patients who have an unresectable but nonmetastatic Pancoast tumor and good performance status, definitive concurrent chemotherapy and radiotherapy is recommended. Grade of recommendation, 1C

10. In patients who have Pancoast tumors and are not candidates for curative intent treatment, palliative radiotherapy is recommended. Grade of recommendation, 1B

11. In patients who have a clinical T4N0,1M0 NSCLC and are being considered for curative resection, it is recommend that invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) be undertaken. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

12. In patients with a T4N0,1M0 NSCLC, it is recommended that resection be undertaken only at a specialized center. Grade of recommendation, 1C

13. In patients with suspected or proven lung cancer and a satellite nodule within the same lobe, it is recommend that no further diagnostic workup of a satellite nodule be undertaken. Grade of recommendation, 1B

14. In patients with a satellite lesion within the same lobe as a suspected or proven primary lung cancer, evaluation of extrathoracic metastases and confirmation of the mediastinal node status should be performed as dictated by the primary lung cancer alone and not modified because of the presence of the satellite lesion. Grade of recommendation, 1C

15. In patients with NSCLC and a satellite focus of cancer within the same lobe (and no mediastinal or distant metastases), resection via a lobectomy is the recommended treatment. Grade of recommendation, 1B

16. In patients who have two synchronous primary NSCLCs and are being considered for curative surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

17. In patients suspected of having two synchronous primary NSCLCs, a thorough search for an extrathoracic primary cancer is recommended to rule out the possibility that both of the lung lesions represent metastases. Grade of recommendation, 1C

18. In patients (not suspected of having a second focus of cancer) who are found intraoperatively to have a second cancer in a different lobe, resection of each lesion is recommended, provided that the patient has adequate pulmonary reserve and there is no N2 nodal involvement. Grade of recommendation, 1C

19. In patients who have a metachronous NSCLC and are being considered for curative surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

20. In patients who have an isolated brain metastasis from NSCLC and are being considered for curative resection of a stage I or II lung primary tumor, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

21. In patients with no other sites of metastases and a synchronous resectable N0,1 primary NSCLC, resection or radiosurgical ablation of an isolated brain metastasis is recommended (as well as resection of the primary tumor). Grade of recommendation, 1C

22. In patients with no other sites of metastases and a previously completely resected primary NSCLC (metachronous presentation), resection or radiosurgical ablation of an isolated brain metastasis are recommended. Grade of recommendation, 1B

23. In patients who have undergone a curative resection of an isolated brain metastasis, adjuvant WBRT is suggested, although there are conflicting and insufficient data regarding a benefit with respect to survival or the rate of recurrent brain metastases. Grade of recommendation, 2B

24. In patients who have undergone curative resections of both the isolated brain metastasis and the primary tumor, adjuvant chemotherapy may be considered. Grade of recommendation, 2C

25. In patients who have an isolated adrenal metastasis from NSCLC and are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

26. In patients with a synchronous resectable N0,1 primary NSCLC and no other sites of metastases, resection of the primary tumor and an isolated adrenal metastasis is recommended. Grade of recommendation, 1C

27. In patients with no other sites of metastases and a previously completely resected primary NSCLC (metachronous presentation), resection of an isolated adrenal metastasis is the recommended treatment when the disease-free interval is > 6 months and complete resection of the primary NSCLC has been achieved. Grade of recommendation, 1C

28. In patients who have an NSCLC invading the chest wall and are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection, and definitive chemoradiotherapy is recommended for these patients. Grade of recommendation, 2C

29. At the time of resection of a tumor invading the chest wall, we recommend that every effort be made to achieve a complete resection. Grade of recommendation, 1B

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Bronchioloalveolar Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Objectives: **To review the current evidence on special issues relating to the diagnosis, imaging, prognosis, and treatment of bronchioloalveolar carcinoma (BAC).**
Methods: **This guideline focuses on aspects of BAC that are unique and ways in which BAC differs importantly from other forms of non-small cell lung cancer (NSCLC). The author reviewed published literature reporting on BAC using key words "histology," "CT scans," "fluorodeoxyglucose positron emission tomography scan," "sensitivity," "specificity," "surgical resection," "sublobar resection," and "epidermal growth factor receptor tyrosine kinase inhibitor" and selected references from published review articles. Also included was a review of the 1999 World Health Organization (WHO) revised classification system for lung tumors, which established a more restrictive definition of BAC to tumors with a pure lepidic spreading pattern and no evidence of stromal, vascular, or pleural invasion.**
Results: **With the notable exception of a lower likelihood of a positive positron emission tomography finding in the presence of BAC, staging, diagnosis, and treatment are the same as for other histologic subtypes of NSCLC, but additional treatment options that may prove to be equivalent, if not more effective, for more patients exist (*eg*, epidermal growth factor receptor tyrosine kinase inhibitor therapy, sublobar resection).**
Conclusions: **BAC is a form of adenocarcinoma with unique clinical, radiologic, and epidemiologic features. The diagnosis of BAC should be reserved for tumors that meet the WHO criteria. Additional clinical trials are needed on this population of patients, using strict definitions and enrollment criteria to allow the results to be applied to appropriate patient populations.**
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Key words: adenocarcinoma; bronchioloalveolar; cancer; epidemiology; guidelines; therapy

Abbreviations: BAC = bronchioloalveolar carcinoma; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; FDG = 18-F-deoxyglucose; NSCLC = non-small cell lung cancer; PET = positron emission tomography; PS = performance status; TKI = tyrosine kinase inhibitor; WHO = World Health Organization

Although descriptions of disease consistent with bronchioloalveolar carcinoma (BAC) appeared in the medical literature > 125 years ago,[1] the term *bronchioloalveolar carcinoma* was first applied by Liebow[2] in 1960 to describe peripheral, well-differentiated lung tumors that grew in a lepidic manner without distortion of the lung architecture. Subsequently, many pathologists and clinicians applied the BAC label in cases of adenocarcinoma with the presence of any significant degree of lepidic growth pattern within the tumor. Perhaps because of this, the apparent incidence of BAC increased dramatically, and some authors[3,4] cited a prevalence of BAC among cases of non-small

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cell lung cancer (NSCLC) as high as 20 to 24%. Some reports attributed the increased prevalence of adenocarcinomas among all NSCLCs in part to the apparent increased rate of diagnosis of BAC. In 1999, the World Health Organization (WHO) published a revised classification system for lung tumors that established the more restrictive definition of BAC to tumors with a pure lepidic spreading pattern and no evidence of stromal, vascular, or pleural invasion. With this revised criteria, the prevalence of pure BAC among NSCLC case series using the revised classification is $< 5\%$. Despite this lower prevalence, the unique pathologic and radiologic characteristics and unique response profile to targeted therapies make a separate consideration of BAC appropriate for this guidelines update.

Materials and Methods

The diagnosis, staging, physiologic evaluation, and treatment of NSCLC are thoroughly covered in other guideline chapters. Therefore, the clinical questions in this guideline were chosen to focus on areas in which there are important differences between BAC and other forms of NSCLC.

These guidelines are restricted to patients with known or suspected "pure BAC" as defined in the 1999 WHO revised classification for lung tumors. This classification system requires that the term *bronchioloalveolar carcinoma* be reserved for a more narrowly defined histologic appearance of cells growing in a lepidic pattern with no stromal, vascular, or pleural invasion. Articles dealing with the prognosis, treatment, and positron emission tomography (PET) characteristics of BAC were chosen from literature searches. Many articles were selected for review on the basis of their presence in the bibliographies of initially selected papers. Meeting abstracts were searched from the last 5 years of meetings of the American Society of Clinical Oncology. Except when needed to illustrate differences over time, articles were chosen preferably when published after 1999 to reflect data using the most current WHO definition of BAC.

Results

Are There Distinctive Clinical and Epidemiologic Features of Patients With BAC? Are There Prognostic Differences Between BAC and Other NSCLC Histologic Subtypes?

Compared with patients who have other forms of lung cancer, patients with BAC are more likely to be nonsmokers (although smokers are at increased risk for all forms of lung cancer, regardless of histology) or have a minimal smoking history. The proportion of patients who have BAC and are female is closer to 50% and is higher than in other histologic types of lung cancer, and the occurrence of nodal spread and extrathoracic metastasis is much less than in other forms of NSCLC.[5]

The pathologic features that distinguish BAC from adenocarcinoma are discussed in the "Diagnostic Surgical Pathology in Lung Cancer" chapter and are not reiterated in detail here. Perhaps because of the recent history of the use of CT screening, particularly in Japan, there is a large body of literature emerging on small peripheral adenocarcinomas. One especially important report[6] in 1995 subclassified 236 patients with small-diameter (< 2 cm) peripheral adenocarcinomas on the basis of the degree of stromal response or invasiveness associated with the proliferating carcinoma cells. As in most pathologic descriptions of adenocarcinoma since then, the majority of tumors were of a mixed subtype, with areas of lepidic (or bronchioloalveolar) patterns of growth mixed with areas of more solid, invasive tumors and/or a stromal fibrotic response. They found that patients with no or only minimal stromal response and no invasion (Noguchi type A or B, what would now be commonly referred to as *pure BAC*) had the most favorable prognosis, with a 100% 5-year survival rate among the 34 patients who met these criteria.[6] Since this report, numerous studies[7–21] have confirmed a more favorable prognosis for patients whose tumors have more prominent, or purely BAC, growth patterns relative to those with tumors that display a prominent stromal reaction or invasive components. While all these studies have found improved stage-specific survival in patients with BAC as compared with more invasive adenocarcinomas, not all have found a correlation between the percentage of tumor occupied by BAC histology and prognosis.[22] Partly as a result of observations such as these, the WHO revised its classification system for lung tumors in 1999 and again in 2004, in each case reserving the BAC classification for tumors that demonstrate only lepidic growth patterns and have no evidence of stromal, vascular, or pleural invasion. Tumors that have a "solid" component but possess some areas of lepidic growth are considered adenocarcinomas with focal bronchoalveolar features and should not be included in series of pure BAC.[23,24]

Subsequent to the revised classification, Zell et al[25] examined the survival of patients with BAC diagnosed before and after the revision (1985 through 2003) and demonstrated that the median survival of patients whose BAC was diagnosed after 1999 (53 months) was significantly greater than those whose BAC was diagnosed before 1999 (32 months). The authors[25] concluded that the improved survival reflected the more restrictive definition of BAC, suggesting that the current definition selects patients with a more favorable prognosis compared with stage-matched patients with other histologic types of NSCLC. This same group[26] subsequently confirmed the improved stage-specific survival of patients with BAC relative to "non-BAC" adenocarcinomas. These[26] and other authors[27] have advocated for a revised staging system for patients with BAC, revised criteria for surgical resection, or both.

It is important to note that the pattern of growth that characterizes BAC can be appreciated accurately only in large biopsy specimens. In fact, the 1999 WHO classification of lung tumors advocates that a final diagnosis of BAC can be rendered only on the basis of a surgical specimen.[23,24] In patients with unresectable BAC, this presents pathologists and clinicians with a dilemma because the diagnosis of BAC may have implications for treatment choice (see recommendation 3). In such cases, the diagnosis should be made with caution or not at all on small biopsy specimens such as those obtained during bronchoscopy. This is especially true when the radiologic pattern of disease on CT scan is not consistent with pure BAC because many invasive adenocarcinomas have a leading edge of lepidic growth pattern that might suggest BAC.[9] That this diagnosis has prognostic implications underscores the importance of patients' being evaluated in a multidisciplinary setting that includes pathologists, radiologists, oncologists, thoracic surgeons, and chest physicians.

Recommendations

1. We recommend that the use of the term *bronchioloalveolar carcinoma* be reserved for lung cancers that meet the criteria established in the revised WHO classification system for lung tumors. Grade of recommendation, 1B

2. For patients with suspected BAC, we recommend that a surgical biopsy be used to establish a histopathologic diagnosis. Grade of recommendation, 1C

In the Absence of a Surgical Biopsy, Are There Characteristic Radiologic Patterns of Disease That Suggest the Presence of BAC?

Because many patients with lung cancer are not candidates for surgery and the diagnosis of BAC may have prognostic implications, it is important to determine whether there are radiologic correlates that predict the histologic pattern. In the original description of BAC by Liebow,[2] the characteristic patterns of radiologic disease noted in association with BAC were separated into one of three patterns: (1) a single focus of disease on a CT scan with ground-glass appearance or a nodule/mass containing prominent air-bronchograms, (2) multifocal lesions with the same appearance, or (3) dense pneumonic consolidation. In the context of trials examining low-dose helical CT scans for lung cancer screening and with the increased use of CT scans for diagnosing nonpulmonary disease, a field of literature examining the management of small, peripheral pulmonary nodules is newly emerging, and the Fleischner Society[28] issued recommended guidelines for managing very small pulmonary nodules. One concept that is emerging from this body of literature is that of the nonsolid, "ground-glass" nodule, defined as a focal area of increased lung opacity that does not distort or obscure the underlying lung markings. Yang et al[29] found a strong correlation between ground-glass attenuation in a nodule and the presence of BAC in the corresponding histology. They examined high-resolution CT morphologic features of 59 small (diameter, 6 to 20 mm), surgically resected peripheral lung adenocarcinomas to determine the correlation between CT features and tumor growth pattern. Sixteen of 17 pure BAC tumors (94%) appeared as ground-glass attenuation. Ten of 14 tumors with a focal solid/invasive component appeared as heterogeneous nodules having both ground-glass and solid components on CT. All four of four entirely solid tumors appeared on CT as homogeneous nodules of soft-tissue attenuation. These authors[29] concluded that CT patterns corresponded to the histopathologic findings of different tumor growth patterns. Two studies[30,31] examined the prognostic significance of pure ground-glass attenuation in CT scans of a combined 179 patients and found that the presence of a significant ground-glass component is associated with reduced likelihood of lymph node metastasis and increased long-term survival. A second appearance that can be seen is the presence of a pneumonic consolidation. Many times, patients with the latter presentation are treated for presumed pneumonia, and the initial suspicion for BAC is not raised until radiologic follow-up fails to show any resolution. In most series, patients with a pneumonic pattern have a worse prognosis than single-focal or multifocal nodular patterns of BAC and frequently have complaints of bronchorrhea.[22,32] Given that the current criteria for BAC mandate that the diagnosis be made only on examination of large (surgical) biopsy specimen, the appearance of a CT scan characteristic of BAC has important implications when patients are not surgical candidates. In the absence of a surgical biopsy, the diagnosis of BAC should be made only in patients with a compatible CT radiologic pattern, accompanied by a compatible histopathologic pattern on biopsy.

Recommendation

3. For patients who are unable to undergo surgical biopsy, the diagnosis of BAC should be made only with compatible histopathologic pattern on transbronchial or core needle biopsy and a CT demonstrating a pure ground-glass or pneumonic appearance. Grade of recommendation, 1C

Are There Important Differences in the Performance Characteristics (Sensitivity, Specificity, and Positive and Negative Predictive Values) of PET Scans Among Patients With BAC?

Whereas many studies have addressed the performance characteristics (sensitivity, specificity, and positive and negative predictive values) of 18-F-deoxyglucose (FDG) PET scanning for patients with known or suspected lung cancer, none has prospectively identified patients with BAC to determine separately the accuracy of FDG-PET for this subtype of NSCLC. Nevertheless, available data permit drawing some important conclusions about the utility of FDG-PET in the diagnosis and staging of BAC. In the most widely cited metaanalysis of PET scanning in NSCLC, Gould et al[33] found a sensitivity of 96.8% and a specificity of 77.8% of FDG-PET for lung cancer. Higashi et al[34] reported on 29 patients with 30 adenocarcinomas of the lung (7 BAC) using a semiquantitative measure of FDG uptake relative to the mediastinal blood pool. Of the 7 BACs, 4 showed negative results on FDG-PET, whereas only 1 of 23 non-BAC tumors showed a negative result. These authors[34] also reported on quantitative measures of FDG uptake (standardized uptake value) and showed that the mean standardized uptake value of the patients with BAC (1.36 ± 0.821) was lower than that of well-differentiated adenocarcinomas (2.92 ± 1.28) and moderately differentiated adenocarcinomas (4.63 ± 1.86). Kim et al[35] performed PET scans in 48 patients with lung cancer, 9 with BAC. The mean peak standardized uptake value for patients with BAC was again significantly lower than for other histologic subtypes ($p < 0.001$). The authors noted that BAC is a potential cause of false-negative findings of malignancy on FDG-PET scans and cautioned that FDG-PET scans should be interpreted in combination with high-resolution CT findings. Lowe et al[36] prospectively enrolled 89 patients with solitary pulmonary nodules, 60 of which turned out to be malignant. Of five false-negative PET scan results in their study, one was BAC, three were squamous cell carcinoma, and one was a malignant melanoma.

One more retrospective review of a tumor registry by Heyneman et al[37] during a 6-year period revealed 15 patients who had pathologically documented BAC and had PET scans. Nine of 15 patients in their study had positive PET scan results. The majority of false-negative results were in patients with focal BAC, as opposed to those with pneumonic pattern of disease, who, in this small study, were more likely to have positive PET scan results. Marom et al[38] reported on FDG-PET findings of 192 patients with lung cancer ranging in size from 3 to 25 mm in diameter, 9 of whom had negative results on PET scan (*ie*, demonstrated low FDG uptake). Patients with small tumors, as well as those with carcinoid tumors and BAC, were more likely to have negative PET scan results. This and other studies[34–36,39,40] confirm that BAC tumors are disproportionately represented in that group of lung cancers in which FDG-PET scan results are negative.

Recommendation

4. For patients whose CT scans show ground-glass attenuation or pneumonic consolidation (suggesting BAC), PET scans often show false-negative results, and therefore we recommend that a PET scan with negative results be followed by additional diagnostic testing to exclude the presence of cancer. Grade of recommendation, 1C

Is Lobectomy Necessary for All Patients With BAC?

As with other forms of NSCLC, surgery represents the "gold standard" of treatment in early stage disease. Patients with resected BAC have prolonged survival and a lower recurrence rate after surgical resection than those with other subtypes of NSCLC.[41,42] The recognition of lower rates of regional lymph node spread in patients with small BAC tumors has led several groups of investigators[20,43–46] to study the possibility that lesser resection could provide equivalent oncologic outcome in patients with pure BAC (Table 1[44–46,48,49,63]). Ishiwa et al[47] examined the presence of lymph node micrometastasis (by cytokeratin immunohistochemistry) in 54 patients with small peripheral carcinomas (< 2 cm). Of the 13 patients with pure BAC tumors, none had micrometastasis, as compared with 11 of 30 patients with non-BAC histology.

Several investigators have explored the use of wedge resection vs lobectomy in stage I disease. Koike et al[48] reported on results of 233 patients with small (< 2 cm) peripheral lesions. All patients were believed to be suitable candidates for lobectomy but were offered limited resection (in a nonrandom manner); 159 patients opted for lobectomy, and 74 patients consented to more limited resection. Sixty patients underwent segmentectomy, and 14 patients underwent a wedge resection. After a mean follow-up of 52 months, there was no difference between the two groups in overall 3-year or 5-year survival rates or in the recurrence of tumor. No information was provided on histologic subtypes. Sakurai et al[20] retrospectively examined the pathology of 108 patients with T1 adenocarcinomas resected between 1985 and 2002, using the revised WHO classification, and found 25 patients with pure BAC. The remaining patients had invasive adenocarci-

Table 1—*Summary of Studies of Sublobar Resections for Patients With Pure BAC

Study/Year	Patients, No.	Selection Criteria	Survival	Comments
Yamato et al[43]/2001	42	BAC < 20 mm, confirmed by intraoperative histology	No recurrence after mean follow-up of 30 mo	
Watanabe et al[45]/2002	17	Focal ground-glass opacities	No recurrence after mean follow-up of 32 mo	Mean tumor size, 7.9 mm
Koike et al[48]/2003	74 limited, 159 lobectomy	All with nodules < 2 cm offered option of limited resection	No difference in tumor-free or overall survival, mean follow-up of 52 mo	Nonrandomized, but patients allowed to choose lesser resection
Nakata et al[46]/2003	33	Pure ground-glass lesions < 1 cm	No recurrence, period of follow-up not reported (< 2 yr)	
Sakurai et al[20]/2004	25 BAC, 83 adenocarcinoma	Retrospective series of patients with tumors < 3 cm	100% 5-yr survival among patients with BAC, 63.5% for patients with adenocarcinoma	1985–2002, pathology reexamined using WHO criteria from 1999
Yamada and Kohno[63]/2004	39	Pure ground-glass lesions < 2 cm	No recurrence, mean follow-up of 29 mo	
Watanabe et al[49]/2005	68	Nonrandom, < 2-cm lesions, resection depended on suspected histology	No difference on 5-yr survival in lobectomy and limited resection	Wedge vs segmentectomy vs "extended" segmentectomy depended on histology

noma. None of the patients with pure BAC and 30 of 83 patients with adenocarcinoma had lymph node involvement at the time of surgery. The 5-year survival rates of the groups with BAC and adenocarcinoma were 100% and 63.5%, respectively. On the basis of these studies, there seems to be no disadvantage for a more limited resection when compared with lobectomy for patients with stage I BAC (particularly tumors < 2 cm in size by CT).

As radiologic imaging continues to improve and gains wider use, detection of incidental BACs will increase. Wedge resection provides an ability to remove these lesions while maximally preserving lung function. Watanabe et al[45,49] studied the role of wedge resection for patients with ground-glass opacities < 2 cm in diameter. When preoperative CT scans demonstrated a pure ground-glass nodule < 2 cm and intraoperative histology demonstrated pure BAC without evidence of stromal invasion, the patient underwent wedge resection (n = 48). Patients without pure BAC received "extended segmentectomy" with lymph node dissection (n = 20). During the same period, they performed lobectomy on 57 patients with stage IA NSCLC and tumors < 2 cm. There was no difference in clinical outcomes after a mean follow-up period of > 3 years.[49]

Although these studies all were well done and provide a compelling rationale for sublobar resections of small peripheral ground-glass lesions, there are important limitations to the routine application of this practice. First, none of these studies reported on a prospectively randomized series of patients. Second, many (although not all) of these studies were conducted in the context of a systematic program of screening using low-dose helical CT, something that is yet to be proved effective in randomized studies and that is still controversial in most health systems. Finally, most of these data come from literature from a single country. Studies[50] of the use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have raised the possibility of ethnic differences in the biology of lung cancer. These potential differences suggest the need to prove these results in more ethnically diverse populations before accepting lesser resections as a global standard of care.

Recommendation

5. In patients who have suspected BAC and are good surgical candidates, a sublobar resection may be appropriate, provided that the CT scan shows a pure ground-glass appearance, intraoperative pathologic consultation confirms pure BAC without evidence of invasion, and surgical margins are free of disease. Grade of recommendation, 1B

Is First-Line Therapy With EGFR-Targeted Agents Appropriate for Patients With Confirmed BAC?

The widely held view that BAC is less responsive to traditional cytotoxic chemotherapy derives largely from anecdotal experience. Although this may be true, it is not well documented in prospective series, partly because of the differing criteria used to define BAC in older series of patients. Older studies[51,52] that examined the response rates of patients with

BAC to standard chemotherapy suggested similar response rates but longer overall survival, comparing BAC with other histologic subtypes. These studies[51,52] predated both modern chemotherapy regimens and the revised WHO classification, raising questions about the applicability of these studies to present-day lung cancer management. Breathnach et al[52] reported on 52 patients with stage IIIB and IV NSCLC, 28 of whom were designated as having BAC (by pre-1999 criteria) and reported longer survival times for patients with BAC as compared with non-BAC histologic types of NSCLC. However, they did not report chemotherapy response rates by histologic pattern, so no conclusions can be drawn about the relative response rates from this study.

More recently,[53,54] agents that target the EGFR have entered clinical practice, and the results of these trials have improved our knowledge of the biology of lung cancer. One consistent feature of studies[55–57] that use small-molecule TKI-targeting EGFR is that patients with BAC are disproportionately represented among those who respond to these agents, with some patients demonstrating profound and rapid responses.[58] Therefore, an appropriate question is whether patients with unresectable BAC should be treated primarily with an EGFR-TKI as first-line therapy. One study[59] examined gefitinib in the first-line setting for 37 nonsmokers with stage IIIB or IV adenocarcinomas (7 with pure BAC) and performance status (PS) of 0 to 2 (Eastern Cooperative Oncology Group [ECOG]). They observed a partial response in 25 patients (69%) and stable disease in 4 more (11%) but did not report on response by subtype. Another small study[60] that examined gefitinib as first-line therapy for advanced NSCLC found repose rates that varied by PS regardless of histology. Two of the 4 responders (of 22 total patients) had BAC, and the other 2 had adenocarcinoma. This study also found that the response rates were greater in patients with better ECOG PS. The largest study, by Shepherd et al,[61,62] enrolled 731 patients with stage IIIB or IV NSCLC and ECOG PS from 0 to 3. These patients had received one or two previous chemotherapy regimens and were randomly assigned to receive either erlotinib or placebo. The response rates were 8.9% in the erlotinib group and $< 1\%$ in the placebo group ($p < 0.001$). Only nonsmoking status, adenocarcinoma histology, and EGFR expression were independent predictors of survival. There was no separate report of BAC subtype.[61,62] Overall, although the high response rate of patients with BAC to EGFR-targeted TKIs raises the hope that this is an appropriate alternative to standard chemotherapy, there is little experimental proof of its superiority in patients with good PS. In addition, although it is tempting to conclude that patients with poorer PS should be treated with first-line EGFR-TKIs, we must recognize that these patients also have a lesser response to these agents.

Recommendation

6. For patients with good PS and unresectable BAC, we recommend the use of standard chemotherapy. The use of first-line EGFR-targeted agents should be reserved for patients with poor PS or those who are enrolled in clinical trials. Grade of recommendation, 2C

Gaps in Research

Is Primary Treatment With an EGFR Inhibitor More Effective and Less Toxic Than Standard Chemotherapy or Chemoradiation for Patients With Unresectable Disease? Randomized trials to compare first-line standard chemotherapy with first-line EGFR inhibitors for patients with good PS are needed.

Is Wedge Resection Sufficient for Patients With Small Peripheral BAC? Preliminary data from nonrandomized studies in Japan are very encouraging. However, to be generalized, these should be the rationale for prospective studies that enroll highly selected patients who have pure ground-glass opacities of small size and are randomly assigned to lobectomy vs lesser resections if intraoperative pathology documents a pure BAC pattern.

Conclusions

BAC is a form of adenocarcinoma with unique clinical, radiologic, and epidemiologic features. Hints that the presence of BAC should be considered frequently come from findings of a pure ground-glass nodule or nodules on a CT scan. Alternatively, the presence of a pneumonic consolidation that does not respond to pneumonia therapy should raise BAC in the differential diagnosis. With the notable exception of a lower likelihood of positive PET scan results in the presence of BAC, staging, diagnosis, and treatment are the same as for other histologic subtypes of NSCLC, but some additional options that may prove to be equivalent, if not more effective, for more patients exist. Additional clinical trials that use strict definitions and enrollment criteria to allow the results to be applied to appropriate patient populations are needed.

Summary of Recommendations

1. We recommend that the use of the term *bronchioloalveolar carcinoma* be reserved for lung cancers that meet the criteria established in the revised WHO classification system for lung tumors. Grade of recommendation, 1B

2. For patients with suspected BAC, we recommend that a surgical biopsy be used to establish a histopathologic diagnosis. Grade of recommendation, 1C

3. For patients who are unable to undergo surgical biopsy, the diagnosis of BAC should be made only with compatible histopathologic pattern on transbronchial or core needle biopsy and a CT demonstrating a pure ground-glass or pneumonic appearance. Grade of recommendation, 1C

4. For patients whose CT scans show ground-glass attenuation or pneumonic consolidation (suggesting BAC), PET scans often have false-negative results, and therefore we recommend that a PET scan with negative results be followed by additional diagnostic testing to exclude the presence of cancer. Grade of recommendation, 1C

5. In patients who have suspected BAC and are good surgical candidates, a sublobar resection may be appropriate, provided that the CT scan shows a pure ground-glass appearance, intraoperative pathologic consultation confirms pure BAC without evidence of invasion, and surgical margins are free of disease. Grade of recommendation, 1B

6. For patients with good PS and unresectable BAC, we recommend the use of standard chemotherapy. The use of first-line EGFR-targeted agents should be reserved for patients with poor PS or those who are enrolled in clinical trials. Grade of recommendation, 2C

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Evidence for Management of Small Cell Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Purpose: **This systematic review addressed the following key questions on managing small cell lung cancer (SCLC): the sequence, timing, and dosing characteristics of primary thoracic radiotherapy (TRTx) for limited-stage disease; primary TRTx for extensive-stage disease; effect of prophylactic cranial irradiation (PCI); positron emission tomography (PET) for staging; treatment of mixed histology tumors; surgery; and second-line and subsequent-line treatment for relapsed/progressive disease.**

Methods: **The review methods were defined prospectively in a written protocol. We primarily sought randomized controlled trials that compared the interventions of interest.**

Results: **Robust evidence was lacking for all questions except PCI, for which a patient-level metaanalysis showed that PCI improves survival of SCLC patients who achieved complete response after primary therapy from 15.3 to 20.7% (p = 0.01). The case for concurrent over sequential radiation delivery rests largely on a single multicenter trial. Support for early concurrent therapy comes from one multicenter trial, but two other multicenter trials found no advantage. Metaanalysis did not find significant reductions in 2-year and 3-year mortality rates for early TRTx. Favorable results from a single-center trial on TRTx for extensive stage disease need replication in a multicenter setting. Relevant comparative studies were nonexistent for management of mixed histology disease and surgery for early limited SCLC. PET may be more sensitive in detecting extracranial disease than conventional staging modalities, but studies were of poor quality.**

Conclusions: **PCI improves survival among those with a complete remission to primary therapy. A research agenda is needed to optimize the effectiveness of TRTx and its components.** ***(CHEST 2007; 132:314S–323S)***

Key words: carboplatin; chemotherapy; cisplatin; etoposide; irinotecan; meta-analysis; paclitaxel; prophylactic cranial irradiation; radiation therapy; small cell lung cancer; systematic review

Abbreviations: ACCP = American College of Chest Physicians; CR = complete remission; PCI = prophylactic cranial irradiation; PET = positron emission tomography; RCT = randomized, controlled trial; RR = relative risk; SCLC = small cell lung cancer; TRTx = thoracic radiotherapy

Small cell lung cancer (SCLC) accounts for 13 to 20% of the 172,570 new cases and 163,510 deaths from lung cancer expected in the United States in 2005.[1–8] Untreated SCLC is aggressive, with a median survival of 2 to 4 months after diagnosis.[4] Most clinicians use a simplified dichotomous staging scheme developed by the Veterans Administration Lung Cancer Study Group.[3,4,8] Limited-stage SCLC (approximately 30% of patients at diagnosis) includes those with tumor confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes.[3,4,8] In extensive-stage SCLC, tumor has spread outside these limits.[4,8]

Diagnostic procedures commonly used to establish the presence of distant metastases include bone marrow aspiration, brain scans using CT or

MRI, chest and abdomen scans using CT, and radionuclide bone scans.[2,4,8] Whether positron emission tomography (PET) metabolic scanning using 18-fluorodeoxyglucose provides any additional information to current staging techniques is uncertain.[2,3]

Chemotherapy is used for most patients, either as adjuvant therapy for the few patients eligible for surgery, or as primary therapy for patients with inoperable tumors. Current guidelines[3,8,9] recommend platinum-etoposide combinations in patients with limited-stage disease and platinum-based regimens in patients with extensive-stage disease. According to the 2003 American College of Chest Physicians (ACCP) guidelines, there is no evidence on the benefit of maintenance chemotherapy in any patient achieving a partial or complete remission (CR), and maintenance therapy is not recommended outside of a clinical trial.[3] The 2007 guideline from the National Comprehensive Cancer Network essentially agrees with this position, noting that maintenance yields a minor prolongation of response duration without improving survival, yet increases the risk of toxicity.[8]

Surgery is usually limited to patients with smaller tumors (T1 or T2) and no evidence of nodal involvement or spread outside the hemithorax of origin.[4,8] Whether surgery added to chemotherapy for patients with limited-stage disease improves survival is currently uncertain.

Metaanalyses published in the 1990s demonstrated the benefit of adding thoracic radiotherapy (TRTx) to chemotherapy in patients with limited-stage disease.[10,11] Uncertainties remain with respect to optimal timing, sequencing, and radiation regimens (*ie*, dosages and fractionation schemes).[9,12] Metaanalyses using different study inclusion criteria have addressed the timing of TRTx administered with chemotherapy for limited-stage SCLC.[13–16] These metaanalyses included varying numbers of studies and did not consistently demonstrate a significant advantage of early TRTx over late TRTx.

The role of radiation therapy in extensive disease is less established than in patients with limited-stage disease.[2] Several large studies[2,17,18] reported in the 1980s by the Southwest Oncology Group and that did not randomize patients to TRTx vs no TRTx suggested that, although thoracic radiation reduced initial relapse at the primary tumor site, there was no effect on overall survival.

Clinicians often add prophylactic cranial irradiation (PCI), particularly for patients achieving a CR after primary therapy. Without PCI, patients who achieve an extracranial CR have a 50 to 80% actuarial risk for CNS metastases within 2 to 3 years.[3,19] In addition, among patients who achieve a CR with chemotherapy, approximately 15% have brain metastases as the initial or only manifestation of recurrence.[19]

Most patients respond to primary therapy but relapse after remissions of varying duration.[2] Second-line therapy is offered to most patients if the first remission has lasted 3 to 6 months; relapse after ≥3 months is also known as *sensitive relapse*.[2] Evidence of benefit is lacking from second-line therapy for refractory SCLC (*ie*, no remission after primary therapy). Response to second-line therapy appears to be related to the chemotherapy agents administered in both the induction and second-line regimens.[2] It is also unknown whether third-line or subsequent lines of therapy for relapsed or progressive SCLC improve outcomes compared with best supportive care.

The ACCP nominated SCLC as a topic for an evidence report to support updating of its 2003 guideline. Consultation with technical experts, some nominated by ACCP, identified nine key issues in need of systematic review.

Key Questions

1. For limited-stage SCLC, what are the relative benefits and harms (survival, toxicity, and quality of life) of TRTx combined with chemotherapy in alternating fashion, concurrently, or sequentially?

2. For limited-stage SCLC, do outcomes (survival, toxicity, or quality of life) differ if concurrent TRTx is administered in early vs late chemotherapy cycles?

3. For limited-stage SCLC, do outcomes (survival, toxicity, quality of life) of primary therapy differ if one varies dose rate, treatment interval, or fractionation scheme for delivering TRTx? Comparisons of interest include:

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a. Accelerated regimens (>10 Gy/wk completed over a short interval) vs standard duration regimens (<10 Gy/wk) vs split courses delivered over the standard interval; and

b. Single daily fractions vs hyperfractionated (two or more daily fractions or concomitant boost).

4. What are the relative benefits and harms (survival, toxicity, and quality of life) of adding TRTx to chemotherapy for primary treatment of extensive-stage SCLC?

5. What are the benefits and harms (survival, toxicity and quality of life) of PCI?

6. Does the addition of PET scanning improve the accuracy of staging for patients with SCLC over the use of other techniques, including CT and MRI, without PET?

7. What are the outcomes (survival, toxicity, and quality of life) of treatments used to manage patients with mixed SCLC/non-small cell lung cancers?

8. What is the role of surgery, and what is its impact on survival in patients with early stage SCLC? How do available studies define early stage SCLC?

9. What are the outcomes of second-line or subsequent-line therapy in patients with relapsed or progressive SCLC? Where available data permit, patients with limited-stage and extensive-stage disease will be addressed separately, as will those with refractory disease (relapse or progression within 3 months of primary treatment).

Materials and Methods

The review methods were defined prospectively in a written protocol. A technical expert group provided consultation. The draft report was also reviewed by other experts and stakeholders.

Primary outcomes include duration of survival, disease-free or progression-free survival, quality of life, brain metastasis, and adverse events. Secondary outcomes include response rates, response duration, and recurrence. For key question 6 (PET staging), additional outcomes are diagnostic accuracy and changes in patient management.

Electronic database searches of MEDLINE (through December 21, 2004), EMBASE (through March 4, 2005), and the Cochrane Controlled Trials Register (through March 11, 2005) were conducted. The search was not limited to the English language, but foreign-language references without abstracts were excluded. Relevant conference proceedings were searched electronically.

We sought randomized, controlled trials (RCTs) that compared the interventions of interest. Where randomized trials were limited or nonexistent, we sought additional studies. For question 8 (surgery), we also sought nonrandomized comparative trials, prospective or retrospective. For question 9 (second-line or subsequent-line therapy), we also sought phase II multicenter studies reporting on at least 25 patients. For question 6 (PET staging), we sought single-arm trials that permitted computation of specificity and sensitivity in relation to an appropriate reference standard.

A single reviewer screened titles and abstracts for full-text retrieval; a second reviewer reviewed citations marked as uncertain. Review of full-text articles was conducted in the same fashion to determine inclusion in the systematic review. One reviewer performed primary data abstraction and a second reviewer reviewed the evidence tables for accuracy. All disagreements were resolved by consensus.

The general approach to assessing quality of evidence from studies of therapeutic interventions developed by the US Preventive Services Task Force[20] was applied. For diagnostic studies, we used the Quality Assessment of Diagnostic Accuracy Studies tool.[21]

We performed a metaanalysis that combined studies included in key questions 1 and 2. The metrics used were 2-year and 3-year mortality relative risks (RRs). Publication bias and heterogeneity of treatment effects were assessed. Pooled RR estimates were made with the inverse variance weighted method. Influence analysis, subgroup/sensitivity analyses, and random effects metaregression were performed. Additional details on the methods and findings of this systematic review can be obtained from the full Agency for Healthcare Research and Quality Evidence Report.[22]

Results

Key Question 1: For limited-stage SCLC, what are the relative benefits and harms (survival, toxicity, and quality of life) of TRTx combined with chemotherapy in alternating fashion, concurrently, or sequentially?

Table 1 summarizes RCTs concerning this key question. One multicenter trial[23] and one single-center trial[24] (n = 307) compared concurrent and sequential TRTx. Results are not conclusive but suggest better outcomes for concurrent TRTx. Overall survival adjusted for confounders significantly favored concurrent TRTx in the trial by Takada et al[23] (n = 228), although unadjusted results were not significant. Additionally, the trial by Park et al[24] found significantly longer response duration for concurrent TRTx. Of 11 types of adverse events reported, only leukopenia occurred significantly more frequently in the concurrent TRTx group in both studies.

No conclusions could be drawn on alternating TRTx. No significant differences in overall or progression-free survival were found in any of five trials: two comparisons to sequential TRTx (n = 458),[25,26] two comparisons with concurrent TRTx (n = 266),[27,28] and one comparison of early and late alternating TRTx (n = 199).[29,30]

Key Question 2: For limited-stage SCLC, do outcomes differ if concurrent TRTx is administered in early vs late chemotherapy cycles?

The evidence is equivocal, finding no difference or small advantage for early concurrent TRTx.[31–40] Among studies summarized in Table 2, one large multicenter trial of good quality significantly favored

Table 1—*Summary of Trials Comparing Alternating, Concurrent, and Sequential TRTx

Source	Treatment Arm (Patients, No.)	Control Arm (Patients, No.)	CTx	TRTx Dose, Gy; Fractions/d	Timing of TRTx, wk		PCI	Quality Rating	Treatment/Control Survival, %		p Value
					Treatment	Control			2 yr	3 yr	
Takada et al[23] (multicenter)	Concurrent (114)	Sequential (114)	PE	45; 2/d	1–3	13–15	Yes	Good	54.4/35.1	29.8/20.2	0.02
Park et al[24] (single center)	Concurrent (32)	Sequential (47)	CAV-CbPE	40–50; 2/d, 1/d	1–3	19–24	Yes	Poor	29.0/27.7	13.8/8.8	0.11
Sun et al[25] (multicenter)	Alternating (64)	Sequential (59)	COME, CAP	30–60; 1/d	4–9	13–18	UK	Poor	28.0/13.6	16.0/12.0	UK
Gregor et al[26] (multicenter)	Alternating (170)	Sequential (165)	CAE	50; 1/d	7, 11, 15, 19	15–18	UK	Good	26/23	12/15	0.288
Lebeau et al[27] (multicenter)	Alternating (74)	Concurrent (82)	CAE-CVE	55/50; 1/d	6, 7, 10, 11, 14–16	5–9	Yes	Good	17/13	11/6	0.15
Blackstock et al[28] (multicenter)	Alternating (57)	Concurrent (57)	CAV-PE	50; 1/d	2, 3, 5, 6, 8	1–5	Yes	Fair	31/36	27/22 (approx)	UK
Work et al[29,30] (single center)	Early alternating (99)	Late alternating (100)	CAV-PE	40–45; 1/d	1, 2, 6, 7	18, 19, 23, 24	Yes	Fair	20.2/18.8	13/12 (approx)	0.41

*CAE = cyclophosphamide, doxorubicin, etoposide; CAP = cyclophosphamide, doxorubicin, cisplatin; CAV = cyclophosphamide, doxorubicin, vincristine; CbPE = carboplatin, cisplatin, etoposide; CE = carboplatin, etoposide; COME = cyclophosphamide, vincristine, methotrexate, etoposide; CTx = chemotherapy regimen; CVE = cyclophosphamide, vincristine, etoposide; PE = cisplatin; etoposide; UK = unknown; approx = approximate.

concurrent therapy given in an early cycle,[31–33] as did two smaller trials. Of the two large multicenter trials that found no significant difference in survival, one did not use platinum chemotherapy[34–36] and the other is published only in abstract.[40] Leukopenia/neutropenia appeared to be more common with early TRTx.

A metaanalysis was performed in an attempt to obtain clearer results. All but one study selected for key questions 1 and 2 were viewed as comparing early and late TRTx, and were pooled to give a more robust analysis. We did not find statistically significant reductions in 2-year and 3-year mortality rates for early TRTx over late TRTx. At 2 years, the pooled random effects RR for death is 0.936 and the 95% confidence interval is 0.860 to 1.019 (Fig 1). At 3 years, the fixed effects RR is 0.995 (95% confidence interval, 0.958 to 1.032; Fig 2).

Key Question 3: For limited-stage SCLC, do outcomes (survival, toxicity, quality of life) of primary therapy differ if one varies dose rate, treatment interval, or fractionation scheme for delivering TRTx?

Evidence to compare dose rates, treatment intervals, or fractionation schemes is limited (Table 3). Two RCTs compared one vs two fractions per day for previously untreated SCLC. One compared an accelerated regimen vs the standard duration, whereas the other compared a split-course regimen vs the standard duration.

Compared to a single daily fraction, two daily fractions delivered concurrently with platinum chemotherapy improved overall survival (23 months vs 19 months; log rank $p = 0.04$) in a large multicenter trial[41,42] of good quality. The second trial[43–45] is difficult to interpret because multiple variables were studied simultaneously ($n = 161$), but there was no difference in survival with one vs two fractions per day. Esophagitis was more frequent with two fractions daily.

Key Question 4: What are the relative benefits and harms (survival, toxicity, and quality of life) of adding thoracic radiation therapy to chemotherapy for primary treatment of extensive-stage SCLC?

Among five RCTs,[46–50] one RCT ($n = 99$)[46] shown in Table 4 suggests that adding concurrent TRTx improves survival of patients with extensive-stage disease that responds to an initial three cycles of platinum/etoposide chemotherapy with a CR outside the thorax and at least a partial response in the thorax. Uncontrolled data from the same trial suggest little to no benefit for other patients. Grades 3/4 esophagitis were more common with TRTx.

Key Question 5: What are the benefits and harms (survival, toxicity and quality of life) of PCI?

Table 2—*Summary of Trials Comparing Times to Give Concurrent TRTx

Source	Early, No.	Late, No.	Chemotherapy Regimen	TRTx Dose, Gy	Fractions, No.	Timing of TRTx, wk: Early, No.	Timing of TRTx, wk: Late, No.	PCI	Quality Rating	Early/Late Survival, %: 2 yr	Early/Late Survival, %: 3 yr	p Value
Murray et al[31]/Coy et al[32]/Feld et al[33] (multicenter)	155	153	CAV/PE	40	1/d	4–6	16–18	Yes	Good	40/33.7	29.7/21.5	0.008
Perry et al[34]/Ahles et al[35]/Perry et al[36] (multicenter)	125	145	CAVE	50	1/d	1–5	10–14	Yes	Fair	24/30 (approx)	10/20 (approx)	0.144
Jeremic et al[37] (single center)	52	51	PE/CbE	54	2/d	1–4	6–9	Yes	Fair	71/53	48/39	0.052
Qiao et al[38] (single center)	45	45	CbE	50 or 60	1/d	1–5/6	12–16/17	UK	Fair	46.7/33.3	33/22	<0.05
Skarlos et al[39] (multicenter)	42	39	CbE	45	2/d	1–3	10–12	Yes	Fair	36/29	22/13	0.65
James et al[40] (multicenter)	159	166	CAV/PE	40	1/d	4–6	16–18	Yes	Not rated	22/31	16/22	0.23

*CAVE = cyclophosphamide, doxorubicin, vincristine, etoposide; CbE = carboplatin, etoposide. See Table 1 for expansion of abbreviations.

An individual patient data metaanalysis on seven RCTs (n = 987) conducted by the Cochrane PCI Overview Collaborative Group[51] shows that PCI improves survival of SCLC patients in CR after primary therapy. Table 5 shows that PCI increases the 3-year survival rate from 15.3 to 20.7% (p = 0.01), an absolute increase of 5.4%. PCI also significantly decreases the risk for brain metastasis and increases the likelihood of disease-free survival. The sole trial[52] reported after the metaanalysis generally agrees with these findings.

Subgroup analyses showed that PCI significantly decreases brain metastases for SCLC patients in CR regardless of age, disease stage, or performance status at diagnosis, and whether TRTx is part of the induction regimen. Survival benefit does not appear to differ among subgroups.

Additional subgroup analyses suggested that increasing the PCI dose from 8 to 40 Gy and starting PCI within the first 6 months after achieving complete response may reduce the likelihood of brain metastases. However, these hypotheses, derived from subgroup analyses, require formal testing in RCTs.

Although data are scant, acute toxicities of PCI seem tolerable at the doses used in these trials (8 to 40 Gy in 1.8 to 3-Gy fractions) and neurocognitive deficits no greater than existed before PCI.

Key Question 6: Does the addition of PET scanning improve the accuracy of staging for patients with SCLC over the use of other techniques, including CT and MRI, without PET?

The evidence is limited and of poor quality, and thus no conclusions can be drawn. Six studies[53–58] (n = 277) suggest that, except for brain metastases, PET added to conventional staging is more sensitive in detecting disease. However, there is so much

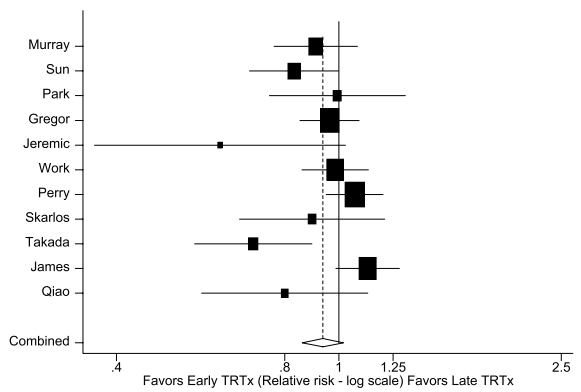

FIGURE 1. Two-year mortality random effects forest plot.

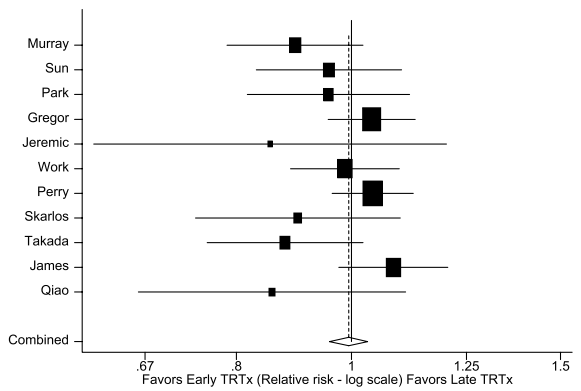

FIGURE 2. Three-year mortality fixed effects forest plot.

Table 3—Summary of Trials Comparing One vs Two Fractions of TRTx per Day*

Source	Two Fractions/d, No.	One Fraction/d, No.	Chemotherapy Regimen	TRTx Dose, Gy		Fractions × Size, Gy; TRTx Duration		TRTx Started	PCI	Two Fractions/d and One Fraction/d Survival, %		p Value
				Two Fractions/d	One Fraction/d	2/d	1/d			2 yr	3 yr	
Turrisi et al[41]/ Yuen et al[42]	211	206	PE	45	45	30 × 1.5; 3 wk	25 × 1.8; 5 wk	Wk 1	Yes	47/41	28/32 (approx)	0.04
Schild et al[43]/ Sloan et al[44]/ Bonner et al[45]	130	131	PE	48	50.4	32 × 1.5; 6 wk	28 × 1.8; 6 wk	Wk 13	Yes	44/44	31/33 (approx)	0.68

*See Table 1 for expansion of abbreviations.

uncertainty about the execution and interpretation of the reference standard in all of these studies that confidence is quite low in estimates of diagnostic and staging accuracy. The frequency of incorrect changes in stage attributable to PET is unknown because of incomplete reporting.

Key Question 7: What are the outcomes (survival, toxicity, and quality of life) of treatments used to manage patients with mixed SCLC/non-SCLCs?

There are few studies of any design that included patients with mixed histology. No conclusions can be drawn from the available evidence.

Key Question 8: What is the role of surgery and what is its impact on survival in patients with early stage SCLC? How do available studies define early stage SCLC?

We sought studies that compared surgery to no surgery in patients with very early limited SCLC, defined as no preoperative evidence of involved nodes (clinically N0). Two randomized controlled trials[59,60] and eight nonrandomized comparative studies[61–70] were reviewed. None studied a homogeneous group of patients with respect to nodal status, nor were separate outcomes reported for a subgroup of patients without evidence of nodal involvement. Thus, no conclusion can be drawn.

Key Question 9: What are the outcomes of second-line or subsequent-line therapy in patients with relapsed or progressive SCLC?

Nine RCTs address second-line or subsequent-line treatment of SCLC, each of which compared different sets of chemotherapy regimens.[71–79] Two randomized trials[76,78] directly compared chemotherapy with best supportive care for recurrent SCLC. Spiro et al[76] studied second-line methotrexate plus doxorubicin and found an overall response rate of 23% for the chemotherapy arm. O'Brien et al[78] reported that oral topotecan resulted in a statistically significant increase in survival (26 weeks vs 14 weeks) and slower decline in quality of life. High-grade neutropenia occurred in one third of patients. Another trial[71] compared oral vs IV topotecan; leukopenia and neutropenia were more frequent with the IV route, but survival and response were no greater. Other RCTs found higher rates of adverse events for one treatment over another but no associated survival advantage that would offset increased high-grade toxicity.

Five multicenter phase II trials[80–84] of note published since 2000 have reported overall response rates ≥20%. Only one study,[80] using topotecan plus cisplatin, enrolled >50 patients. Approximately one fourth of both sensitive and refractory patients responded. Three fourths or more of both patient groups had high-grade leukopenia and neutropenia.

Table 4—*Selected Characteristics of Trials Comparing Chemotherapy With vs Without TRTx

Source	With TRTx, No.	Without TRTx, No.	Chemotherapy Regimen	TRTx Timing	TRTx Dose, Gy	TRTx Schedule; Fractionation, Gy	PCI	Quality Rating	1 yr	2 yr	p Value
Jeremic et al[46] (single center)	55	54	PE/CbE	Concurrent	54	Weeks 10–13; 36 × 1.5, 2/d	Yes	Fair	65/46	38/28	0.041
Nou et al[47] (single center)	28	26	CAVML	Alternating	40	Weeks 10–13; 20 × 2, 1/d	No	Good	32/26	0/0	0.045
Lebeau et al[48] (multicenter)	10	8	LCAE/PEVe	Sequential	32–65	Weeks 36–39; 2, 1/d	Some	Poor	10/25 (approx)	10/12 (approx)	0.43
Rosenthal et al[49] (multicenter)	27 total; No./arm NRM-CAV		M-CAV	Alternating	40	Weeks 10–?; 20 × 2, ?/d	UK	Poor	NR	NR	0.796
Brincker et al[50] (single center)	16	14	CAV/LME	Alternating	12	Days 60 and 100; 6-Gy each	UK	Poor	25/30 (approx)	0/0	0.44

*NR = not reported; CAVML = cyclophosphamide, doxorubicin, vincristine, methotrexate, lomustine; LCAE = lomustine, cyclophosphamide, doxorubicin, etoposide; LME = lomustine, methotrexate, etoposide; M-CAV = methotrexate, cyclophosphamide, doxorubicin, vincristine; NR = not reported; PVe = cisplatin, vindesine. See Table 1 for expansion of abbreviations.

A small study[81] of irinotecan plus cisplatin found very high rates of partial response and low hematologic toxicity. The combination of paclitaxel, ifosfamide, and cisplatin[82] achieved a high overall response rate and high-grade leukopenia in nearly all patients. One fourth of those receiving paclitaxel plus carboplatin had a response, and approximately one half had high-grade neutropenia.[83,84] In a study[84] of doxorubicin plus carboplatin, nearly half of patients responded; however, four of five patients had grade 3 or 4 granulocytopenia.

Discussion and Future Research

The purpose of this systematic review is to characterize the scientific literature available to address nine key questions concerning SCLC. Recommendations regarding management of SCLC are contained in a separate article.[85] The strongest evidence available for this report is a patient-level metaanalysis showing that PCI improves survival of SCLC patients who achieved CR after primary therapy. No other question yielded evidence so robust. Our conclusions typically relied on a single trial showing treatment effects that were modest at best, and sometimes equivocal. This was apparent in our review of evidence for the sequence, timing, dosing, and fractionation of TRTx. For example, the case for concurrent over sequential delivery rests largely on a single multicenter trial.[23] Support for early concurrent therapy comes from the multicenter trial by Murray et al,[31] Coy et al,[32] and Feld et al[31–33]; however, two other multicenter trials by Perry-Ahles et al[34–36] and James et al[40] found no advantage. However, the metaanalysis of 11 studies did not find significant reductions in 2- and 3-year mortality for early TRTx. For some questions (*ie*, management of mixed histology disease; surgery for early limited SCLC), comparative trials were nonexistent. Results reported by Jeremic et

Table 5—*The Presence or Absence of PCI

Outcomes	Patients Evaluated, No.		Hazard Ratio	95% Confidence Interval		p Value	Event Free at 3 yr (Kaplan-Meier Analysis), %		
	With PCI	Without PCI		Lower	Upper		With PCI	Without PCI	Difference
Mortality	526	461	0.84	0.73	0.97	0.01	20.7	15.3	5.4
Disease-free survival	526	461	0.75	0.65	0.86	<0.00003			
Brain metastasis	524	457	0.46	0.38	0.57	<0.00001	33.3	58.6	25.3
Non-brain metastasis	325	332	0.89	0.69	1.15	0.4			
Locoregional recurrence	323	334	0.97	0.75	1.26	0.8			

*Metaanalytic results for efficacy outcomes as reported in the Cochrane Review.[51] K-M = Kaplan-Meier.

al[46] on TRTx for extensive-stage disease need replication in a multicenter setting.

PET may be more sensitive in detecting disease outside the brain than conventional staging modalities. Future studies should fully report the frequency of correct and incorrect staging changes when PET is added to conventional tests and should link diagnostic performance to outcomes such as improvement in survival or reduced morbidity. Studies should be conducted according to standards described by the Quality Assessment of Diagnostic Accuracy Studies[21] and reported according to the Standards for Reporting of Diagnostic Accuracy statement.[86,87]

Complicating the evaluation of SCLC treatment are overall poor outcomes and small effect sizes, necessitating large numbers of patients in trials. Furthermore, interventions are multimodal with a multiplicity of variables that might contribute to the effectiveness.

Trials that are poorly designed, conducted, or reported waste limited resources. To advance clinical knowledge and practice, the field should adhere to standards of research quality and set an agenda for research priorities. Given modest gains in survival, quality of life assessment should be integral to clinical trials and should adhere to recommended research methods, including handling of missing data.

Conclusions

PCI improves survival among those with a complete response to primary therapy. A research agenda is needed to optimize the effectiveness of TRTx and its components. PET for staging may be useful, but its role awaits clarification by rigorous studies. No relevant evidence was available to address management of mixed histology disease or surgery for early limited SCLC.

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Management of Small Cell Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

George R. Simon, MD, FCCP; and Andrew Turrisi, MD

Purpose: **This guideline is for the management of patients with small cell lung cancer (SCLC) and is based on currently available information. As part of the guideline, an evidence-based review of the literature was commissioned that enables the reader to assess the evidence as we have attempted to put the clinical implications into perspective.**

Methods: **We conducted a comprehensive review of the available literature and the previous American College of Chest Physicians guidelines of SCLC. Controversial and less understood areas of the management of SCLC were then subject to an exhaustive review of the literature and detail analyses. Experts in evidence-based analyses compiled the accompanying systematic review titled "Evidence for Management of SCLC." The evidence was then assessed by a panel of experts to incorporate "clinical relevance." The resultant guidelines were then scored according to the grading system outlined by the American College of Chest Physicians grading system task force.**

Results: **SCLC accounts for 13 to 20% of all lung cancers. Highly smoking related and initially responsive to treatment, it leads to death rapidly in 2 to 4 months without treatment. SCLC is staged as limited-stage and extensive-stage disease. Limited-stage disease is treated with curative intent with chemotherapy and radiation therapy, with approximately 20% of patients achieving a cure. For all patients with limited-stage disease, median survival is 16 to 22 months. Extensive-stage disease is primarily treated with chemotherapy with a high initial response rate of 60 to 70% but with a median survival of 10 months. All patients achieving a complete remission should be offered prophylactic cranial irradiation. Relapsed or refractory SCLC has a uniformly poor prognosis.**

Conclusion: **In this section, evidence-based guidelines for the staging and treatment of SCLC are outlined. Limited-stage SCLC is treated with curative intent. Extensive-stage SCLC has high initial responses to chemotherapy but with an ultimately dismal prognosis with few survivors beyond 2 years.** ***(CHEST 2007; 132:324S–339S)***

Key words: chemotherapy; guideline; radiation therapy; review; small cell lung cancer; staging

Abbreviations: BSC = best supportive care; CAV = cyclophosphamide, adriamycin, vincristine; CEV = cyclophosphamide, etoposide and vincristine; CI = confidence interval; CPT-11 = camptothecin-11; CR = complete response; ECOG = Eastern Cooperative Oncology Group; EP = cisplatin and etoposide; NSCLC = non-small cell lung cancer; PCI = prophylactic cranial radiation; PE = etoposide/cisplatin; PET = positron emission tomography; PS = performance status; SCLC = small cell lung cancer; TC = oral topotecan/IV cisplatin; TRTx = thoracic radiation therapy

This document presents an evidence-based guideline based on the current literature on the staging and optimal treatment of patients with small cell lung cancer (SCLC). The quality of the recommendation and the evidence on which it is based is graded as outlined by the American College of Chest Physicians grading system task force.[1] Accompanying this guide-

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line is an evidence report titled "Evidence for Management of SCLC." Nine key questions were addressed by the technical report and are the following (see chapter "SCLC Evidence").

Key Questions

1. What are the relative benefits or harms of combining thoracic radiotherapy (TRTx) with chemotherapy in alternating, concurrent, or sequential fashion?

2. Does early vs late administration of TRTx influence outcome?

3. Does the duration of administration of TRTx affect survival or toxicity?

4. In responding patients with extensive disease, does the administration of consolidative TRTx affect outcome?

5. What is the role of prophylactic cranial irradiation (PCI) in the treatment of SCLC?

6. Is there a role for positron emission tomography (PET) scanning in SCLC staging?

7. Do the pathologic subtypes of SCLC influence treatment outcome?

8. What is the role of surgery in the management of patients with SCLC, and how are patients selected for surgery?

9. What is the role and what are the relative benefits of second-line/salvage therapy?

Clinical research has slowed in this disease, and there are few contemporary studies that directly address many of these questions. Evidence-based guidelines rely on timely, contemporary, pertinent evidence that is largely lacking in many of these areas. Decreased disease frequency and difficulty in conducting large trials are oft-cited reasons for this lack of activity. With the exception of question 7 regarding pathology subtypes, all of these questions posed to the systematic review are discussed in the context of these guidelines.

Materials and Methods

We organized a systematic review of the published SCLC literature to update the previous American College of Chest Physicians guideline. Supplemental material appropriate to this topic was obtained by literature search of a computerized database (MEDLINE) and review of the Thoracic Oncology NetWork reference lists of relevant articles. Recommendations were developed by the writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter) and reviewed by all members of the lung cancer panel before approval by the Thoracic Oncology Network, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.

Accompanying this guideline is an "Evidence for Management of SCLC' chapter, comprehensive research of some of the most controversial but not infrequently encountered questions in SCLC. In relevant sections of this guideline, the reader will be referred to this evidence report (see "SCLC Evidence" chapter).

Guideline

SCLC constitutes approximately 13 to 20% of all lung cancers[2]; therefore, the estimated annual incidence of SCLC ranges from 22,000 to 34,000. If there are 170,000 annual lung cancer cases, this suggests approximately 22,000 cases at a minimum. With non-small cell lung cancer (NSCLC), SCLC shares a strong association with tobacco use, and without treatment it tends to lead an aggressive course.

Staging of SCLC

SCLC is staged according to a two-stage system developed by the Veteran's Administration Lung Cancer study group as limited disease or extensive disease. Patients with limited disease have involvement restricted to the ipsilateral hemithorax that can be encompassed within a safe radiation treatment plan. Extensive disease is defined as the presence of overt metastatic disease by imaging or physical examination. Patients with otherwise limited-stage disease with the presence of contralateral hilar or supraclavicular nodes or malignant pleural or pericardial effusions are excluded from clinical trials for limited-stage SCLC.

Complete evaluation of a patient with newly diagnosed SCLC consists of a history and physical examination, pathology confirmation or review, CT of the chest and abdomen to include the whole liver and adrenal glands, bone scan, and a CT with contrast or MRI examination of the brain. While the prevalence of brain metastases at diagnosis varies, the brain is a common site of treatment failure; therefore, evaluation of the brain prior to treatment remains mandatory. Scanning the asymptomatic brain is likely to lead to the diagnosis of more previously unsuspected brain metastases, but there is no evidence yet that it improves survival.[3] However, because it has a direct impact on the correct staging of the disease and consequently on developing a treatment plan, it is the opinion of the authors of this guideline that brain imaging should be performed for all patients currently undergoing staging for SCLC. Additionally, CBCs, electrolytes, BUN, creatinine, and liver function tests should be performed in all patients at baseline. The utility of PET in SCLC has been reported in several small prospective studies.[2,4–10] These studies are small, with varying reference stan-

dards and with uncertainty about the execution and interpretation of the results. Even though the cumulative evidence suggests that PET added to conventional staging improves the sensitivity in detecting extracranial disease, the frequency of changes in stage attributable to PET are still unknown and is plagued by wide confidence intervals (CIs) in the estimates of diagnostic and staging accuracy. Randomized prospective studies need to be conducted before the routine use of PET scan for staging SCLC can be recommended. Therefore, outside of a clinical trial, the routine use of PET in SCLC cannot be recommended. (Please refer to question 6 of the evidence report. (See "Evidence for Management of Small Cell Lung Cancer" chapter)

The routine use of bone marrow aspiration has been abandoned because it was rare to have disease detected in the bone marrow in the absence of obvious bony disease in the bone scan. In one study,[11] of 403 patients with SCLC, only 7 patients (1.7%) had extensive disease based on marrow involvement alone. Because bone marrow examination rarely changes the stage of cancer in noninvasively assessed patients, and because all patients with SCLC receive chemotherapy as part of their overall treatment strategy, routine use of this procedure is not recommend in the staging of SCLC. Other investigators[12,13] have also reached similar conclusions. Therefore, bone marrow examination, formerly standard, is rarely indicated and has been abandoned as a routine procedure for the staging of SCLC.

Recommendations

1. Routine staging of SCLC includes history and physical examination, CBCs and comprehensive chemistry panel, CT of the chest and abdomen or CT of the chest with cuts going through the entire liver and adrenal glands, CT or MRI of the brain, and bone scan. Grade of recommendation, 1B

2. PET is not recommended in the routine staging of SCLC. Grade of recommendation, 2B

Treatment for Extensive-Stage SCLC

First-Line Treatment

Platinum-based chemotherapy remains the mainstay of treatment for extensive SCLC. In a metaanalysis[14] of randomized trials (19 trials with 4054 evaluable patients) comparing cisplatin-based regimen with a noncisplatin-based regimen, patients randomized to regimens containing cisplatin had significantly increased response and survival rates without an increase in toxicity. Detailed analyses of the role of etoposide and cisplatin in SCLC have been performed by Berghmans et al[15] and reported in abstract form in September 1999. Thirty-six eligible trials[15] conducted between 1980 and 1998 were classified into four groups: (1) cisplatin vs noncisplatin (n = 1); (2) etoposide (without cisplatin) vs no etoposide (n = 17); (3) cisplatin/etoposide vs no cisplatin/etoposide (n = 9); and (4) cisplatin/etoposide vs etoposide (n = 1). The authors concluded that the use of cisplatin and/or etoposide offered a significant survival advantage in patients with SCLC.

A metaanalysis performed by Chute et al[16] evaluated 21 cooperative group trials performed in North America from 1972 to 1993. Patients with extensive-stage SCLC treated during a similar time interval listed in the Surveillance, Epidemiology, and End Results database were also examined. Trends were tested in the number of trials and the survival time of patients over time. In this analysis, a 2-month prolongation in median survival was demonstrated in extensive-stage SCLC. This improvement in survival was independently associated with both cisplatin-based therapy and in the improvement of best supportive care (BSC) and general medical management. This metaanalysis further strengthens the evidence in favor of cisplatin-based chemotherapy for the first-line treatment of extensive stage SCLC.

The issue of carboplatin vs cisplatin was reviewed by Brahmer et al,[17] who concluded that carboplatin plus etoposide seems to be as effective but less toxic (except for increased myelosuppression) than cisplatin plus etoposide. The Hellenic Oncology Group conducted a randomized phase II trial[18] comparing cisplatin and etoposide with carboplatin and etoposide. In this study, consisting of patients with limited-stage and extensive-stage disease, median survival times were 11.8 months for the cisplatin group and 12.5 months for the carboplatin group. The difference was not statistically significant, although the study did not have enough power to show a survival difference.

A Japanese trial[19] compared cisplatin and irinotecan (camptothecin-11 [CPT-11]) with cisplatin and etoposide. Patients randomized to the cisplatin/CPT-11 arm fared statistically significantly better than the patient cohort randomized to the cisplatin/etoposide arm (median survival, 420 days vs 300 days). Confirmatory trials were then launched in the United States. One of these trials using a different dosing schedule for cisplatin/irinotecan failed to show a survival advantage over cisplatin/etoposide. Fewer patients receiving cisplatin/irinotecan had hematologic toxicities (*ie*, grade 3/4 anemia, thrombocytopenia, neutropenia, and febrile neutropenia) compared with patients receiving cisplatin/etoposide. However, more patients receiving cisplatin/CPT-11 had nonhematologic toxicities in the form of

Table 1—*SCLC Combination Chemotherapy for Untreated Patients, Phase II Trials*

Treatment	Patients, No.	Responders, No.			Response Rate		Median Survival			Comments	Reference
		CR	Partial	Total	%	95% CI	Mo	1 yr, %	2 yr, %		
Cisplatin + etoposide + carboplatin	46	10	32	42	91	79–98	18, stage IIIB; 14, stage IV	22	15	Age ≤ 72 yr	21
Cisplatin + etoposide + paclitaxel	38	6	28	34	90	75–97	12		10		22
Cisplatin + etoposide + paclitaxel	23	5	14	19	83	61–95	11	46	14		23
Cisplatin + irinotecan	35	10	20	30	86	70–95	13	21.7			24
Cisplatin + vinblastine + mitomycin-C	30	1	21	22	73	66–96	6				25
Cisplatin + etoposide + all-trans-retinoic acid	22	1	9	10	45	24–68	11	41		13 patients discontinued retinoic acid prematurely because of toxicity	26
Cisplatin + paclitaxel + granulocyte colony-stimulating factor	34	3	20	23	61	53–8	8			Abstract	27
Topotecan + paclitaxel	28	6	11	17	60	41–79	14			Abstract	28
Etoposide + irinotecan	50			33	66	51–79	12			Abstract	29
Paclitaxel + carboplatin	69	5	37	42	61	48–72	12			Abstract	30
Paclitaxel + irinotecan	11	4	1	5	45	17–77				Abstract	31
Paclitaxel + doxorubicin	16	1	3	4	25	7–52				Abstract	32
Cisplatin + docetaxel	20	0	11	11	55	32–77				Abstract	33
Topotecan + paclitaxel	13			8	69	39–91	14			Abstract	34
Topotecan + paclitaxel	15	10	5	15	100	78–100				Abstract	35
Cisplatin + paclitaxel + topotecan	18	3	10	13	72	47–90					36
Etoposide + paclitaxel + epirubicin	12	6	6	12	100	74–100					37

grade 3/4 diarrhea and vomiting.[20] Several phase II trials with irinotecan, topotecan, paclitaxel, in combination with either cisplatin or etoposide, have been reported. These have been summarized in Table 1.[21–37]

An open-label, randomized, multicenter phase III study[38] compared oral topotecan/IV cisplatin (TC) with IV etoposide/cisplatin (PE) in patients with untreated extensive-disease SCLC. A total of 784 patients were randomly assigned to either oral topotecan at 1.7 mg/m^2/d for 5 days with IV cisplatin at 60 mg/m^2 on day 5 (n = 389), or IV etoposide at 100 mg/ m^2/d for 3 days with IV cisplatin at 80 mg/ m^2 on day 1 (n = 395) every 21 days. Overall survival rate (primary end point) was similar between groups. One-year survival rate was 31% (95% CI, 27 to 36%) in both groups. Response rates were similar between groups (TC vs PE, 63% vs 69%). Time to progression was slightly but statistically longer with PE (log rank p = 0.02; median TC vs median PE, 24 weeks vs 25 weeks). The regimens were similarly tolerable. Grade 3/4 neutropenia occurred more frequently with PE (84% vs 59%), whereas grade 3/4 anemia and thrombocytopenia occurred more frequently with TC (38% vs 21% and 38 vs 23%, respectively). Lung Cancer Symptom Scale scores were statistically better with PE, but the differences were small and of debatable clinical significance. Even though the TC arm may have a more convenient schedule, there was no demonstrable improvement in several of the key survival, toxicity, or quality of life parameters when compared to PE.[38]

Pemetrexed/platinum combinations have been investigated in extensive-stage SCLC. A randomized phase II trial[39] evaluated the use of cisplatin or carboplatin plus pemetrexed in previously untreated patients. Patients were randomly assigned to receive pemetrexed at 500 mg/m^2 plus cisplatin at 75 mg/m^2 or carboplatin (area under the concentration curve of 5). Treatment was administered once every 21 days for a maximum of six cycles. Seventy-eight patients were enrolled into this multicenter trial. Median survival time for cisplatin/pemetrexed was 7.6 months, with a 1-year survivorship of 33.4% and a response rate of 35% (95% CI, 20.6 to 51.7%). Median survival time for carboplatin/pemetrexed was 10.4 months, with a 1-year survivorship of 39.0% and a response rate of 39.5% (95% CI, 24.0 to 56.6%). Median time to progression for cisplatin/pemetrexed was 4.9 months and for carboplatin/pemetrexed was 4.5 months. Grade 3/4 hematologic toxicities included neutropenia (15.8% vs 20.0%) and

thrombocytopenia (13.2% vs 22.9%) in the cisplatin/pemetrexed and carboplatin/pemetrexed treatment groups, respectively. Pemetrexed/platinum doublets had activity and appeared to be well tolerated in first-line extensive-stage SCLC. This randomized phase II trial suggests that pemetrexed/platinum combinations may be comparable in efficacy in extensive-stage SCLC to the more traditional cisplatin-etoposide or cisplatin-irinotecan regimens.[39]

The issue of adding a third drug to cisplatin and etoposide has been investigated. The Hoosier Oncology Group[40] evaluated the addition of ifosfamide to cisplatin and etoposide in a phase III trial of 171 extensive-disease patients. At the expense of increased toxicity, 2-year survival increased from 5 to 13% with addition of ifosfamide. Mavroudis et al[41] compared paclitaxel, etoposide, and platinum with etoposide and platinum. The study was terminated early secondary to higher number of toxic deaths in the paclitaxel, etoposide, and platinum arm. Despite a statistically significant improvement in the time to progression for paclitaxel, etoposide, and platinum, there was no difference in overall survival.

The issue of adding TRTx to chemotherapy in the treatment of extensive-stage SCLC has also been evaluated. This has been discussed in the accompanying evidence report and technological assessment and to which the reader is referred to for a more detailed analysis. One randomized controlled trial[42] ($n = 99$) suggests that adding concurrent TRTx improves survival of patients with extensive-stage disease that responds to an initial three cycles of platinum/etoposide chemotherapy with a complete response (CR) outside the thorax and at least a partial response in the thorax. Uncontrolled data from the same trial[42] suggest little to no benefit for other patients. Grades 3/4 esophagitis was more common with TRTx.

In summary, for extensive-stage SCLC, a combination of cisplatin combined with either etoposide or CPT-11 or carboplatin combined with etoposide are currently considered standard regimens. The standard treatment arm for a comparative prospective study remains cisplatin (60 to 80 mg/m^2), and etoposide delivered in three to five divided doses between 250 and 360 mg/m^2. There is no evidence to support continuing treatment beyond six cycles. It is reasonable to administer consolidative TRTx in patients achieving a CR outside the chest and at least a CR or partial response in the chest, although the evidence for this is weak. This issue needs to be further addressed in phase III randomized trials.

Recommendations

3. Patients with extensive-stage disease should receive four to not more than six cycles of cisplatin or carboplatin-based combination chemotherapy. Cisplatin could be combined with either etoposide or CPT-11. Grade of recommendation, 1B

4. After chemotherapy, patients achieving a CR outside the chest and complete or partial response in the chest can be offered consolidative TRTx in the chest. Grade of recommendation, 2C

Maintenance Treatment

The topic of maintenance therapy in SCLC has been extensively reviewed in the European Journal of Cancer in 1998.[43] Several randomized trials have demonstrated that 4 to 6 months of treatment is equal to prolonged treatment when survival is considered as the end point. In the metaanalyses reported by Sculier et al,[43] 13 published randomized trials were included. One showed a statistically significant difference in survival in favor of maintenance, five studies showed survival advantage in subgroups of patients, one study showed significantly shorter survival with maintenance therapy, and six studies showed no difference. The Eastern Cooperative Oncology Group (ECOG) conducted a phase III trial in which patients showing response or stable disease after four cycles of cisplatin and etoposide were randomized to observation alone or four cycles of topotecan.[44] Despite an improvement in progression-free survival, the addition of topotecan did not improve overall survival results.

Treatments other than chemotherapy for maintenance were also tested in randomized clinical trials. A phase III randomized trial[45] evaluated the efficacy of anti-GD3 immunization as maintenance treatment. There was no benefit in overall survival. Metalloproteinase inhibitors and inhibitors of angiogenesis including thalidomide are currently being investigated in the maintenance setting.

Recommendation

5. Outside of a clinical trial, maintenance treatment for patients with extensive-stage or limited-stage disease achieving a partial or complete remission is not recommended. Grade of recommendation, 1B

Treatment of Relapsed or Refractory SCLC (Systematic Review Question 9)

Despite high initial response rates to chemotherapy (45 to 75% CRs) reported in limited disease and

20 to 30% CRs in extensive disease, response duration is usually short, with a median progression-free survival of approximately 4 months for extensive-stage disease. Most patients are destined to relapse, and the prognosis for this group of patients who relapse is poor. Patients who relapse < 3 months after first-line therapy are commonly called *refractory*, and patients who relapse 3 months after therapy are labeled as *sensitive*.

In a randomized multicenter study, von Pawel et al[46] compared cyclophosphamide, adriamycin, and vincristine (CAV) with topotecan as a single agent in patients who had relapse at least 60 days after completion of initial therapy. Patients received either topotecan as a 30-min/d infusion for 5 days every 21 days, or CAV infused on day 1 every 21 days. A total of 211 patients were enrolled. The response rates were 24.3% in patients treated with topotecan and 18.3% in patients treated with CAV ($p = 0.285$). Median times to progression were 13.3 weeks for the topotecan arm and 12.3 weeks for the CAV arm. Median survival times were 25 weeks for topotecan and 24.7 weeks for CAV. The proportion of patients with symptom improvement was greater in the topotecan arm than in the CAV group for four of the eight symptoms evaluated. The authors[46] concluded that topotecan was at least as effective as CAV in the treatment of patients with recurrent SCLC and resulted in improved symptom control. However, toxicity rates were high in both arms and alternative dose schedules of topotecan are currently favored.

Another study[47] randomly assigned patients with relapsed SCLC not considered as candidates for standard IV therapy to BSC alone (n = 70) or oral topotecan (2.3 mg/m/d, days 1 through 5, every 21 days) plus BSC (topotecan; n = 71). In an intent-to-treat analysis, survival (primary end point) was prolonged in the topotecan group (log rank $p = 0.0104$). Median survival time with BSC was 13.9 weeks (95% CI, 11.1 to 18.6), and with topotecan it was 25.9 weeks (95% CI, 18.3 to 31.6). Partial responses were seen in 7% of patients receiving topotecan, with an additional 44% of patients achieving stable disease. Patients receiving topotecan had slower quality of life deterioration and greater symptom control. Principal toxicities with topotecan were hematologic: grade 4 neutropenia, 33%; grade 4 thrombocytopenia, 7%; and grade 3/4 anemia, 25%. Toxic deaths occurred in four patients (6%) in the topotecan arm. All-cause mortality rates within 30 days of random assignment were 13% with BSC and 7% with topotecan. Hence, in patients unable to tolerate IV chemotherapy, treatment with oral topotecan is an option.[47] Several reported phase II trials in relapsed/refractory SCLC are summarized in Table 2.[31,48–51]

In the chapter "Evidence for Management of SCLC," nine randomized trials comparing various second-line chemotherapy regimens are discussed. Two randomized trials compared chemotherapy to BSC. It is wise to be cautioned about the potential for toxicity outweighing survival in many trials. Patients who achieve CRs to front-line therapy and then experience relapse appear to benefit most from second-line therapy.

Recommendation

6. Patients who experience relapse or have refractory disease with SCLC should be offered further chemotherapy. Grade of recommendation, 1B

Treatment of Elderly (or Poor Performance Status) Patients With SCLC

Performance status (PS) and the physiologic status of the patient should guide treatment decision rather than the patient's chronologic age. It is clear that elderly patients with good PS (ECOG 0 or 1) and normal organ function should be treated with optimal chemotherapy (and radiotherapy if indicated) as in their younger counterparts. Simi-

Table 2—*SCLC Combination Chemotherapy for Refractory or Relapsed Disease in Patients, Phase II Trials*

Treatment	Patients, No.	Responders, No.			Relative Risk		Median Survival		Comments	Reference
		CR	Partial	Total	%	95% CI	Mo	1 yr (%)		
Etoposide + irinotecan	24	3	14	17	71	53–89	9			48
Cisplatin + topotecan	28	1	7	8	29	13–49			Abstract; all patients had responded to previous chemotherapy	49
Etoposide + hexmethylmelamine	30	1	5	6	22	8–39	5	21	Abstract	50
Irinotecan + paclitaxel	11	1	4	5	45	17–77			Abstract	31
Carboplatin + paclitaxel	18	0	3	3	17	4–41			Abstract	51

lar outcomes for elderly patients (in comparison to their younger counterparts) with limited-stage SCLC have been shown in the Intergroup trial 0096 in which cisplatin, etoposide, and thoracic radiotherapy was administered once per day or twice daily.[52] The National Cancer Institute of Canada performed a retrospective review of their BR3 and BR6 trials and also concluded that age did not appear to impact the delivery, tolerance, or efficacy of thoracic irradiation in the combined modality management of limited-stage SCLC.[53] Greater myelosuppression is to be expected because equivalent exposure to drug will lead to more myelosuppression in the elderly. This has been shown to be the case with etoposide.[54] Greater ancillary support therefore will be required in the elderly. However, despite treatment delays, elderly patients with good PS derive the same level of benefit relative to younger patients.

Elderly patients with poor PS or with compromised organ function may be offered single-agent chemotherapy or polychemotherapy in attenuated doses. However, several randomized studies[55,56] have indicated that such "gentler" chemotherapy is inferior to optimal combination chemotherapy. Options available to these patients include oral etoposide for 14 days combined with carboplatin on day 1 every 28 days[57]; abbreviated chemotherapy with CAV in full doses followed up 3 weeks later by cisplatin and etoposide in optimal doses[58]; or chemotherapy with platinum, adriamycin, vincristine, and etoposide, with all four drugs in reduced doses.[59] A phase III trial[60] compared carboplatin/gemcitabine with cisplatin/etoposide in patients with poor-prognosis SCLC, with carboplatin and gemcitabine exhibiting a more favorable overall toxicity profile at the expense of increased myelotoxicity but with equivalent efficacy. Another phase III trial[61] compared single-agent carboplatin with CAV, with carboplatin producing response rates, relief of tumor-related symptoms, and survival similar to that seen with CAV. There was a lower risk of life-threatening sepsis and less need for hospitalization in the group that received carboplatin.

Recommendations

7. Elderly patients with good PS (ECOG PS 0 or 1) with intact organ function should be treated with platinum-based chemotherapy. Grade of recommendation, 1A

8. Elderly patients with poor prognostic factors such as poor PS or medically significant concomitant comorbid disease may still be considered for chemotherapy. Grade of recommendation, 2C

Studies with SCLC cell lines have shown that they have greater radiosensitivity than human adenocarcinomas or squamous cell lung cancer cell lines. Because of these observations, many early trials of combining radiation with chemotherapy in SCLC used lower total radiation doses. It has become increasingly clear that higher doses than those of the old regimens of 30 Gy in 10 fractions or 45 Gy in 25 fractions are needed to provide durable local control because lower doses are associated with local relapse rates in excess of 50%.

A number of trials conducted in the 1970s and 1980s compared chemotherapy alone to chemotherapy plus TRTx in patients with limited SCLC. There were differences in radiation dose, timing, and choice of chemotherapeutic agents, but most were performed with alkylating agent and doxorubicin-based therapy rather than cisplatin and etoposide. The analysis by Warde and Payne[62] showed improved local control and survival with the addition of TRTx, particularly in patients $\leq$ 60 years old. Pignon et al[63] obtained individual patient data from these trials and was able to update analyses from the time of original publication. They found that the addition of TRTx resulted in an increase in 3-year survival from 8.9 to 14.3%, an absolute improvement of 5%, and a relative improvement of nearly 50%. With the publication of these two metaanalyses, the debate shifted from whether to use TRTx to how best to integrate it with chemotherapy.

In limited disease, the ability to use concurrent therapy is predicated on avoiding drugs with intrathoracic organ toxicity that compound with radiotherapy. The optimal chemotherapy to utilize with radiation therapy has been a subject of investigation as well. A prospective randomized trial[64] comparing cisplatin and etoposide (PE) to cyclophosphamide, etoposide and vincristine (CEV) was reported by Sundstrom et al. A total of 436 eligible patients were randomized to chemotherapy with PE (n = 218) or CEV (n = 218). Patients were stratified according to extent of disease (limited disease, n = 214; extensive disease, n = 222). The PE group received five courses of etoposide at 100 mg/m^2 IV and cisplatin at 75 mg/m^2 IV on day 1, followed up by oral etoposide 200 mg/m^2/d on days 2 to 4. The CEV group received five courses of epirubicin at 50 mg/m^2, cyclophosphamide at 1,000 mg/m^2, and vincristine at 2 mg, all IV, on day 1. In addition, patients with limited disease received TRTx concurrent with chemotherapy cycle 3, and those achieving CR during the treatment period received PCI. The 2-year and

5-year survival rates in the PE arm (14% and 5%; p = 0.0004) were significantly higher compared with those in the CEV arm (6% and 2%). Among patients with limited disease, median survival time was 14.5 months vs 9.7 months in the PE and CEV arms, respectively (p = 0.001). The 2-year and 5-year survival rates of 25% and 10% in the PE arm compared with 8% and 3% in the CEV arm (p = 0.0001). Quality-of-life assessments revealed no major differences between the randomized groups. The authors concluded that PE is superior to CEV in patients with limited-disease SCLC. Therefore, PE is the recommended chemotherapy regimen to combine with TRTx in the treatment of limited-stage SCLC.

Sequencing and Timing of Radiation and Chemotherapy

Whether to administer radiation and chemotherapy concurrently, sequentially, or in an alternating fashion, and whether radiation should be administered early or late in the overall course of treatment continue to be a matter of debate. In many trials, these issues have been confounded by a lack of clarity in the clinical trial design and the resulting ambiguous interpretation of results. "Alternating therapy," interdigitating weeks of radiotherapy with weeks of chemotherapy in lower doses of each, is a tacit acknowledgment of the fact that certain chemotherapy-radiotherapy combinations were quite toxic. This term is a quaint reference to trials in the late 1980s and has no currency or application in the cisplatin/etoposide era.

Murray et al[65] performed a metaanalysis of trials that combined chemotherapy and TRTx, using progression-free survival at 3 years as a surrogate end point for long-term survival, and favored the earlier initiation of concurrent TRTx with chemotherapy. If initiation of radiation was delayed beyond 5 weeks of initiation of chemotherapy, the benefit decreased and survival approached that seen with chemotherapy alone. However, this analysis did not separate issues of timing from those of concurrency.

There have been at least nine randomized trials that have addressed the issue of the timing of radiation in limited SCLC (Table 2 in the evidence report and technical assessment; see chapter "SCLC Evidence"). There are major differences in trial design, choice of chemotherapeutic agents, and radiation dose and fractionation schedules.

De Ruysscher et al[66] undertook a systematic review and literature-based metaanalysis to determine whether the timing of chest radiotherapy may influence the survival of patients with limited-stage SCLC. Eligible randomized controlled clinical trials were identified according to the Cochrane Collaboration Guidelines, comparing different timing of chest radiotherapy. Early chest irradiation was defined as beginning within 30 days after the start of chemotherapy. Considering all seven eligible trials, the overall survival at 2 years or 5 years was not significantly different between early or late chest radiotherapy. When only trials were considered that used platinum chemotherapy concurrent with chest radiotherapy, a significantly higher 5-year survival was observed when chest radiotherapy was started within 30 days after the start of chemotherapy (2-year survival: odds ratio, 0.73; 95% CI, 0.51 to 1.03; p = 0.07; 5-year survival: OR, 0.64; 95% CI, 0.44 to 0.92; p = 0.02). This was even more pronounced when the overall treatment time of chest radiotherapy was < 30 days. These data seem to indicate that 5-year survival rates of patients with limited-stage SCLC are in favor of early chest radiotherapy, with a significant difference if the overall treatment time of chest radiation is < 30 days and if a platinum-based chemotherapy is used concurrently.

In another report, Spiro et al[67] examined the effect on survival of the timing of TRTx in patients with limited-disease SCLC. Patients received three cycles of cyclophosphamide, doxorubicin, and vincristine, alternating with three cycles of EP. Three hundred twenty-five chemotherapy- and radiotherapy-naive patients were randomly assigned to either early TRTx administered concurrently in the second cycle or late TRTx administered concurrently with the sixth cycle. The dose was 40 Gy in 15 fractions over 3 weeks. TRTx was received by 92% and 82% of patients in the early and late arms, respectively (p = 0.01). Sixty-nine percent of patients in the early arm received all six courses of chemotherapy, compared with 80% in the late arm (p = 0.003). There was no evidence of a survival difference; median overall survival times were 13.7 months and 15.1 months in the early and late arms, respectively (p = 0.23). This study suggests that it may be essential to ensure optimal delivery of platinum-based chemotherapy with early TRTx to see a survival advantage.

The reader is again referred to the accompanying evidence report and technical assessment for an exhaustive review and analyses of the literature. Several reasonable conclusions emerge from these data.

1. Trials that used alkylating agents and doxorubicin-based chemotherapy showed little effect of radiation timing and sequencing. They also reported significant difficulty delivering planned treatment (both chemotherapy and radiation) when radiation was administered given concur-

rently with or alternating between cycles of chemotherapy. Long-term survival in most of these trials was in the range of 10%, which is minimally different from that seen with chemotherapy alone.

2. When platinum/etoposide regimens are used, concurrent TRTx is superior to sequential TRTx.
3. When EP and concurrent TRTx are used, the data are inconclusive concerning early vs late treatment. Table 2 in the evidence chapter deals with the issue (see chapter "SCLC Evidence"). Inadequate underpowered trials make a categoric recommendation inappropriate; however, the existing data suggest that there may be a survival advantage for early initiation of TRTx with cisplatin-based chemotherapy.

Radiation Dose

Please see question 3 of the evidence report and technical assessment for a detailed analysis of the literature on this issue. No trial has asked a direct question to establish optimal dose in any schedule, and relatively few trials have addressed the issue of optimizing TRTx dose at all. Retrospective analysis[68] of patients treated at the Massachusetts General Hospital report improved local control as radiation dose has increased from 30 to 70 Gy delivered with one daily fraction. The Cancer and Leukemia Group-B[69] has tried to define the maximal tolerated dose for concurrent TRTx and cisplatin/etoposide chemotherapy when these were administered after three courses of induction chemotherapy with cyclophosphamide/cisplatin/etoposide. They examined both daily radiation therapy schedules with 2-Gy fractions and twice-daily schedules with 1.5-Gy fractions. They defined dose-limiting toxicity as acute esophagitis, and the maximum tolerated dose was reported to be 45 Gy in 3 weeks for twice-daily fractionation and 70 Gy in 7 weeks for daily fractionation. Because all grades of esophagitis recover and stricture formation is rare, using esophagitis as a dose-limiting toxicity seems inappropriate. Because the best local control rates certainly may not be optimal, exploration of dose escalation seems warranted. Studies in NSCLC have clearly shown the feasibility of administering higher radiation doses to conformal planned fields with concurrent chemotherapy, and this approach may also be necessary in limited-stage SCLC. Though success of using doses in the range of 60 to 70 Gy has never been established as safer or better by any measure, there has been a tendency to use higher doses in the single-fractionation schedule.

Radiation Fractionation

Fractionation refers to the dose per treatment, number of treatments per day, and overall time of treatment. Ordinarily one expects to deliver 10 Gy/wk. Using more than one treatment per day is commonly called *hyperfractionation*. Delivering more than the anticipated 10 Gy/wk in standard daily fractions is called *accelerated fractionation*. Cancer cell kill and tumor control, as well as acute and late radiation effects, change with method of treatment delivery. Protracting total time of treatment may provide an ability to tolerate larger doses, but the excess time may be detrimental to tumor control. Shortening time may add to acute toxicity but may be more efficient at killing rapidly proliferating tumor cells before resistance develops or they metastasize.

The rapid growth rate of SCLC both *in vitro* and *in vivo* and the radiobiologically small shoulder on the *in vitro* survival curve seen on many SCLC cell lines encouraged the exploration of treatment acceleration by administering two fractions per day with a modest reduction in fraction size from the usual 1.8 to 2.0 Gy to 1.5 Gy. Two prospective trials have compared this approach to conventional daily fractionation. The North American Intergroup Trial 0096[70] compared 45 Gy in 25 fractions over 5 weeks to the investigational arm of 45 Gy in 30 fractions over 3 weeks. Chemotherapy consisted of four cycles of PE. The accelerated regimen resulted in improved local control (intrathoracic failure reported in 36% on the accelerated arm and 52% on the standard arm) and long-term survival, which was 26% for the twice-daily regimen and 16% for the standard regimen. There was an increased rate of grade 3 esophagitis (26% vs 11%) but no other significant differences in toxicity.[70] Unfortunately, intrathoracic failure included "not achieving a CR." The partial response patients survived identically to the completely responding ones in the accelerated fractionated group, but as expected poorly in the 45-Gy single-fraction group. We lack local controlled data for the mostly phase II trials using doses > 50 Gy. For the commonly used 60 to 70 Gy doses, we have only reliable safety data. Reliable local control or patterns of failure data are lacking with the higher dose studies.

The North Central Cancer Treatment Group also compared a twice-daily fractionation to daily fractionation, but with a significantly different twice-daily scheme and overall study design[71] than that used in the Intergroup trial reported by Turrisi et al.[72] In both arms, radiation was administered concurrent with the fourth and fifth cycles of chemotherapy. The once-daily radiation regimen was 50.4 Gy in 28 fractions over 5 weeks. The twice-daily arm used 48 Gy, with a 2.5-

week split after the initial 24 Gy, and the total treatment time was > 5 weeks. Thus, unlike the Intergroup trial,[70] there was no overall acceleration of the radiation delivery. In this trial, there were no differences in local control or survival between the two arms. The trial did not replicate the accelerated treatment outcome, and it mildly ameliorated toxicity.

Radiation Target Volume

SCLC often presents with bulky mediastinal adenopathy, and often with a confusing mixture of tumor and atelectasis in lung parenchyma. Radiation target volumes are often large, limiting achievable doses. In attempting to define the minimal appropriate dose, two issues can be considered:

1. Radiation to normal-appearing lymph nodes has become an important issue for toxicity and local control. This issue has not been studied prospectively. However, the North American Intergroup trial,[72] which produced the best 5-year survival reported by a cooperative group, limited elective radiation, with no intentional radiation to the contralateral hilum or to supraclavicular nodes unless there was bulky superior mediastinal adenopathy.
2. Regarding radiation therapy after induction chemotherapy, retrospective review of data from the Mayo Clinic[71] and North Central Cancer Treatment Group[73] suggests that this can be performed without compromise in local control or survival because recurrences tended to be at the center of the tumor rather than at the periphery.[74] An earlier trial by the Southwest Oncology Group[75] that randomized patients having partial responses to chemotherapy to radiation to before or after chemotherapy volumes also reported no difference in recurrence rates.

In summary, the standard therapy "control treatment" for future randomized studies of limited SCLC remains four cycles of PE concurrently combined with day-1, cycle-1 45 Gy delivered in 3 weeks (in twice-daily fraction, as administered in the Intergroup trial[70]). Induction chemotherapy commonly used is not evidence based in the PE treatment era and protracts "start to end of radiotherapy." When induction therapy is used to reduce radiotherapy target size, the postchemotherapy residual may be used as a reasonable target without evidence that this compromises local control or survival. The use of protracted once-daily radiation scheduled to 60 to 70 Gy has established safety from phase I and II trials, but there is no evidence outside of these clinical trials that these schedules are superior to 45 Gy delivered in 3 weeks in an accelerated hyperfractionated manner.[70]

Recommendations

10. Patients with limited-stage SCLC should be treated with combined concurrent chemoradiotherapy. Patients require referral to a radiation oncologist and a medical oncologist for the consideration of combined modality treatment. Grade of recommendation, 1A

11. If the PS and comorbid illnesses allow, patients with limited-stage disease should be treated with chemotherapy and radiation therapy concurrently. Grade of recommendation, 1C

12. In patients eligible to receive early concurrent chemoradiotherapy, patients should be treated with accelerated hyperfractionated radiation therapy concurrently with platinum-based chemotherapy. Grade of recommendation, 1B

PCI

Brain metastases are common in SCLC. In patients who achieve a CR to induction therapy, CNS metastases will emerge over the next 2 years in approximately 50 to 60% of patients; and in 20 to 30% of patients, the brain will be the only apparent site of disease.[76] Overt metastatic disease in the brain, while often responding temporarily to radiation or chemotherapy, is rarely if ever cured. The hypothesis that lower doses of radiation administered to patients without detectable CNS involvement might eradicate occult metastatic disease has been entertained for > 20 years,[77] but data have emerged to allow a reasonable consensus that the PCI can reduce the risk of CNS failure, improve survival, and do so without excessive toxicity.[78–80] A metaanalysis of randomized trials of PCI in patients with CR (predominately with limited disease) concluded that it significantly reduced CNS failure by approximately 50% and produced a modest (approximately 5%) but significant improvement in median survival. There was a trend to better results with higher doses (30 to 36 Gy using 2-Gy fractions) than with 20 Gy, but this was not protected by randomization. An Intergroup trial is currently comparing 25 Gy in 10 fractions to 36 Gy in 18 fractions.

Earlier trials of PCI had variably reported late neurotoxicity, with deterioration in memory, ability to calculate, and quality of life. The relation of these toxicities to treatment was unclear. In several trials in which cognitive function has been assessed prospectively, significant differences between SCLC patients and age- and gender-matched control subjects have been observed before any treatment, with up to 40% of patients showing significant impairment.[81] Significant further deterioration after PCI was not seen in a large trial[82] in the United Kingdom. Van

Oosterhout et al[83] performed careful neurologic and neurophysiologic examinations of 59 survivors who are alive > 2 years after diagnosis and who underwent cranial CT or MRI. Groups were neurophysiologically compared with matched control subjects. The authors[83] concluded that although more intensively treated patients showed more neurologic impairment, there was no statistical evidence for additional neurotoxicity caused by the administration of PCI.

In summary, the evidence report and technological assessment was most solid for the robust evidence in favor of PCI for patients achieving a CR to therapy. There was no group singled out (*ie*, elderly, continued smokers) that did not benefit. PCI for documented patients with CR is standard therapy. The dose and schedule remain less clear. In practice, 25 Gy in 10 fractions has been a cooperative group standard that currently is being compared to higher or accelerated doses of 36 Gy. Late neurocognitive effects are reported in the population and are not different in those who have survived 2 years, regardless of whether they have been treated with PCI. The frequency of neurocognitive defects at 2 years is < 10%, and it is approximately 7% for those receiving PCI and 5% for those observed. Neurocognitive defects are much more likely in patients relapsing with brain metastasis, and salvage therapeutic radiation is less effective at restoring symptoms, PS, and quality of life.

Recommendations

13. Patients with limited-stage SCLC achieving a CR or resected patients with stage I disease should be offered PCI. Grade of recommendation, 1B

14. Patients with extensive-stage SCLC achieving a CR should be offered PCI. Grade of recommendation, 1C

Role of Surgery in Early Stage SCLC

The role of surgery in early stage SCLC has been reviewed.[84] Surgery as a primary modality of treatment was abandoned after the British Medical Council published the results of their study[85] comparing primary radiation therapy with surgery in patients with resectable SCLC with a 10-year follow-up. The overall survival was better for the radiation therapy-alone arm, and there were no long-term survivors in the surgery arm. However, subsequent reports published in the 1970s and early 1980s showed long-term survival in patients treated with surgery alone in very early disease. The most favorable subset of patients had T1N0 tumors identified either at the time of surgery or at the time of postoperative pathology examination.[86–89] Even though the role of adjuvant therapy has not been evaluated in prospective randomized trials, there are several reports[88,90–96] suggesting benefit for adjuvant chemotherapy even in the earliest stages of the disease.

The role of surgery in patients with node-positive disease was evaluated prospectively by the Lung Cancer Study Group.[97] Patients with stage I were excluded from this trial. Patients were initially treated with five cycles of CAV. Responding patients were randomized to undergo surgery or no surgery. All patients received radiation therapy to the chest and brain. There was no difference in survival between the arms. For all patients, median survival time was 15 months, and 2-year survival rate was 20%.

All patients who are to undergo surgery require mediastinoscopy before resection. Its usefulness in SCLC has been validated in a small prospective Japanese trial.[98] The evidence review and technological evidence researching this issue in question 8 found two randomized controlled studies and eight nonrandomized comparative observational studies. There was inadequate objective evidence to support any categorical recommendation regarding surgery in these patients. However, the authors favor surgery in patients with node-negative disease with small tumor size (< 3 cm) because of the lower likelihood of metastasis with small tumor sizes.

Recommendations

15. In patients with SCLC and stage I disease who are being considered for curative-intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI, abdominal CT plus bone scan) performed in all patients should be offered. Grade of recommendation, 1A

16. In patients with stage I SCLC who have undergone curative intent surgical resection, platinum-based adjuvant chemotherapy is recommended. Grade of recommendation, 2C

Management of Tumors With Mixed SCLC/NSCLC Histology

The evidence report and technological assessment researched this issue and found few studies of any design that included patients with mixed histology. No conclusions can be drawn from the evidence available in the literature. Before a biopsy result is labeled as a mixed histology, it is imperative to obtain

a detailed pathologic consultation. Large-cell tumors with neuroendocrine features are now classified as NSCLC and should be treated as such.

If, however, after a detailed pathologic review it is clear that the patient has mixed SCLC/NSCLC, then it is the bias of the authors of this article that the natural history of such a mixed-histology disease would be defined by the natural history of the more rapidly growing small cell component. Hence, we treat these patients like patients with SCLC. Again, as noted, evidence for this is scant. Implicit in this statement is the fact that most chemotherapeutic regimens and combined chemotherapy and radiation therapy strategies used for the treatment of SCLC should work effectively for NSCLC as well. PE and TRTx is commonly used for NSCLC,[99] albeit in a different schedule. The most commonly used treatment regimen for patients with stage IV NSCLC had been cisplatin or carboplatin and etoposide, and is a reasonable, though some would argue, not optimal chemotherapy for NSCLC.[100]

Recommendation

17. Patients with mixed SCLC/NSCLC histology should be treated like patients with SCLC. All the treatment recommendations made for SCLC should apply to this category of patients. Grade of recommendation, 2C

Summary of Recommendations

1. Routine staging of SCLC includes history and physical examination, CBCs and comprehensive chemistry panel, CT of the chest and abdomen or CT of the chest with cuts going through the entire liver and adrenal glands, CT or MRI of the brain, and bone scan. Grade of recommendation, 1B

2. PET is not recommended in the routine staging of SCLC. Grade of recommendation, 2B

3. Patients with extensive-stage disease should receive four to not more than six cycles of cisplatin or carboplatin-based combination chemotherapy. Cisplatin could be combined with either etoposide or CPT-11. Grade of recommendation, 1B

4. After chemotherapy, patients achieving a CR outside the chest and complete or partial response in the chest could be offered consolidative TRTx in the chest. Grade of recommendation, 2C

5. Outside of a clinical trial, maintenance treatment for patients with extensive-stage or limited-stage disease achieving a partial remission or CR is not recommended. Grade of recommendation, 1B

6. Patients with SCLC with relapsed or refractory disease should be offered further chemotherapy. Grade of recommendation, 1B

7. Elderly patients with good PS (ECOG PS 0 or 1) with intact organ function should be treated with platinum-based chemotherapy. Grade of recommendation, 1A

8. Elderly patients with poor prognostic factors such as poor PS or medically significant concomitant comorbid disease may still be considered for chemotherapy. Grade of recommendation, 2C

9. Outside of a clinical trial, there is no role of either dose dense/intense initial/induction or maintenance treatment for extensive-stage or limited-stage SCLC. Grade of recommendation, 1A

10. Patients with limited-stage SCLC should be treated with combined concurrent chemoradiotherapy. Patients require referral to a radiation oncologist and a medical oncologist for the consideration of combined modality treatment. Grade of recommendation, 1A

11. If the PS and comorbid illnesses allow, patients with limited-stage disease should be treated with chemotherapy and radiation therapy administered concurrently. Grade of recommendation, 1C

12. In patients eligible to receive early concurrent chemoradiotherapy, patients should be treated with accelerated hyperfractionated radiation therapy concurrently with platinum-based chemotherapy. Grade of recommendation, 1B

13. Patients with limited-stage SCLC achieving a complete remission or patients with stage I disease who have had resection should be offered PCI. Grade of recommendation, 1B

14. Patients with extensive-stage SCLC achieving a complete remission should be offered PCI. Grade of recommendation, 1C

15. In patients with SCLC and stage I disease who are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI, abdominal CT plus bone scan) performed in all patients should be offered. Grade of recommendation, 1A

16. In patients with stage I SCLC who have undergone curative intent surgical resection, platinum-based adjuvant chemotherapy is recommended. Grade of recommendation, 2C

17. Patients with mixed SCLC/NSCLC histology should be treated like patients with SCLC. All the treatment recommendations made for SCLC should apply to this category of patients. Grade of recommendation, 2C

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Complementary Therapies and Integrative Oncology in Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **This chapter aims to differentiate between "alternative" therapies, often promoted falsely as viable options to mainstream lung cancer treatment, and complementary therapies, adjunctive, effective techniques that treat symptoms associated with cancer and its mainstream treatment, and to describe the evidence base for use of complementary therapies.**
Methods and design: **A multidisciplinary panel of experts in oncology and integrative medicine evaluated the evidence for complementary (not alternative) therapies in the care of patients with lung cancer. Because few complementary modalities are geared to patients with only a single cancer diagnosis, symptom-control research conducted with other groups of patients with cancer was also included. Data on complementary therapies such as acupuncture, massage therapy, mind-body therapies, herbs and other botanicals, and exercise were evaluated. Recommendations were based on the strength of evidence and the risk-to-benefit ratio.**
Results: **Patients with lung and other poor-outlook cancers are particularly vulnerable to heavily promoted claims for unproved or disproved "alternatives." Inquiring about patients' use of these therapies should be routine because these practices may be harmful and can delay or impair treatment. Mind-body modalities and massage therapy can reduce anxiety, mood disturbance, and chronic pain. Acupuncture assists the control of pain and other side effects and helps reduce levels of pain medication required. Trials of acupuncture for chemotherapy-induced neuropathy and posttho-racotomy pain show promising results. Herbal products and other dietary supplements should be evaluated for side effects and potential interactions with chemotherapy and other medications.**
Conclusions: **Complementary therapies have an increasingly important role in the control of symptoms associated with cancer and cancer treatment.** ***(CHEST 2007; 132:340S–354S)***

Key words: acupuncture; botanicals; cancer; complementary and alternative medicine; complementary therapies; fitness; herbs; integrative medicine; massage therapy; mind-body therapies; music therapy; oncology

Abbreviations: CAM = complementary and alternative medicine; MSKCC = Memorial Sloan-Kettering Cancer Center; NIH = National Institutes of Health

A distinction between "complementary" and "alternative" therapies is required. Complementary therapies, used as adjuncts to mainstream care, are supportive measures that help control symptoms, enhance well-being, and contribute to overall patient care.[1] Alternative therapies, conversely, are often

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Table 1—*Categories and Examples of Complementary and Alternative Therapies*

Biologically Based Practices	Herbal remedies, vitamins, other dietary supplements
Mind-body techniques	Meditation, guided imagery
Manipulative and body-based practices	Massage, reflexology
Energy therapies	Magnetic field therapy
Ancient medical systems	Traditional Chinese medicine, ayurvedic medicine, acupuncture

unproved or disproved, promoted for use instead of mainstream treatment, or are offered as viable therapeutic options. This is especially problematic in oncology, when delayed treatment can diminish the possibility of remission and cure.[2] Over time, some complementary therapies are proven safe and effective. These become integrated into mainstream care, producing integrative oncology, a combination of the best of mainstream cancer care and rational, data-based, adjunctive complementary therapies.[3]

Most complementary and alternative medicine (CAM) practices can be loosely grouped into five categories according to the National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (Table 1). The therapies in these categories are quite mixed; some are helpful, others are bogus. There is also considerable overlap among the categories. For example, traditional Chinese medicine uses biologically active botanicals and acupuncture. Yoga has mind-body and manipulative components and Ayurvedic principles in theory. Some interventions, such as music therapy, do not fit easily into a category (Table 1).

Most complementary therapies are not specific to a particular cancer diagnosis. Instead, they are used typically to treat symptoms shared by patients across most cancer diagnoses. This is generally appropriate because symptoms tend to stem less from the primary diagnosis than from involvement of a particular organ or toxicities associated with treatment, which evoke similar symptoms in patients across cancer diagnoses. For example, bone metastases cause pain regardless of whether the primary lesion was from breast or prostate; chemotherapy-induced nausea and vomiting are associated more closely with the emetogenic potency of the drug used than with the underlying cancer diagnosis. In these guidelines, we summarize data relevant to clinical problems encountered by patients with lung cancer and make practical recommendations based on the strength of the evidence.

The use of complementary therapies is common among cancer patients. "Alternative therapies" draw a far smaller percentage of patients but remain a serious problem. The difference between "complementary" and "alternative" therapies is important and essential to recognize. "Alternative" therapies are typically promoted as literal, viable options for use *in lieu* of mainstream care. They are not. There are no viable "alternatives" to mainstream care. Instead, these are bogus products and regimens that draw patients with unsubstantiated, often fanciful, claims of easy cure. Typically they are unproven or disproved, invasive, and biologically active. Such "alternatives" are heavily promoted to all patients with all cancer diagnoses, and patients with lung and other poor-outlook cancers are particularly vulnerable.

The Society for Integrative Oncology and its MEDLINE-listed journal, formed by leading oncologists and major cancer centers and organizations, deliberately uses terminology meant to distinguish itself from purveyors of foolish therapies and bogus "alternatives," as well as to display quality research and appropriate application of useful, adjunctive complementary modalities (www.IntegrativeOnc.org). This chapter includes minimal discussion of useless approaches and recommends that readers obtain additional information about them at www.mskcc.org/aboutherbs or www.quackwatch.org.

Although the external validity of most clinical trials in adult oncology may be questioned because only a small fraction of eligible patients participate, this is a lesser problem in trials involving complementary therapies because they address symptom control and quality of life with noninvasive therapies that produce few if any side effects. Patients generally are more amenable to such studies.

This chapter addresses complementary therapies, which are noninvasive adjuncts to mainstream care. Complementary therapies are applied not to treat lung cancer or any other malignancy but rather to treat the symptoms associated with cancer and its mainstream treatments. This category also includes the study of herbs and other botanicals. Clinical trials of some herbs and other botanicals aside, few complementary modalities are geared to patients with only a single cancer diagnosis. Thus, symptom-control research conducted with other groups of cancer patients is noted as well because these data are likely to have broad applicability in lung cancer practice.

Health-care professionals should be able to provide evidence-based, patient-centered advice to guide patients to receive benefit while avoiding harm. A panel of experts in oncology and integrative medicine was assembled to evaluate the current level of evidence regarding complementary (not alternative) therapies relevant to the care of patients with lung cancer. Specific recommendations are made based on the strength of evidence and the risks/benefit ratio.

Because the use of CAMs by cancer patients is common, a strong recommendation is made to inquire about the use of these therapies as a routine part of the initial evaluation of lung cancer patients. Complementary therapies can be helpful in symptom control, whereas the use of alternative therapies can delay or impair treatment. It is strongly recommended that guidance should be provided in an open, evidence-based, and patient-centered manner by a qualified professional to those patients who use or who are interested in CAM so that they can approach these therapies appropriately.

Mind-body modalities are strongly recommended to be incorporated into a multidisciplinary approach in reducing anxiety, mood disturbance, or chronic pain in cancer patients. A strong recommendation is made to consider massage therapy as part of a multimodality treatment approach in lung cancer patients who experience anxiety or pain. Application of deep or intense pressure during massage therapy should be avoided near cancer lesions or anatomic distortions such as postoperative changes as well as in patients with a bleeding tendency (weak recommendation). Therapies based purely on the putative manipulation of bioenergy fields or other nonrational ideas are considered bogus and are not recommended.

Acupuncture is strongly recommended as a complementary therapy for pain control when pain is poorly controlled, when side effects from other modalities are clinically significant, or when reducing the amount of pain medicine becomes a clinical goal. Acupuncture is also strongly recommended as a complementary therapy when nausea and vomiting associated with chemotherapy are poorly controlled or when side effects from other modalities are clinically significant. Electrostimulation wristbands should not be used to reduce chemotherapy-induced nausea and vomiting because it appears to become a conditioned stimulus. The value of acupuncture in treating nicotine addition, dyspnea, or fatigue is not supported by conclusive evidence. A trial[4] of acupuncture for chemotherapy induced neuropathy showed positive results. Acupuncture for postthoracotomy pain is undergoing study. Given some reports of potential benefit, a trial of acupuncture is acceptable when symptoms are severe and not responding adequately to other treatments. Acupuncture is generally safe when performed by qualified practitioners. Caution should be exercised in patients with bleeding tendency.

Taking dietary supplements can be beneficial in some circumstances and harmful in others. Supplementation of vitamin B12 and folic acid is required in patients receiving pemetrexed treatment. A strong recommendation is made for dietary supplements used by patients, particularly herbal products, to be evaluated for side effects and potential interaction with other drugs. Those that are likely to interact with chemotherapeutic agents should not be used during chemotherapy.

It is strongly recommended that patients be advised to avoid the use of "alternative" therapies *in lieu* of mainstream care. Such practice can lead to significant harm to lung cancer patients because it delays effective treatment and causes unpredictable adverse effects.

Despite the long history of many complementary therapies, only a few have been evaluated with modern scientific research tools in a handful of indications. A large gap exists between our current level of scientific evidence and what we need to provide evidence-based advice. More rigorous scientific research is being conducted to enrich our knowledge base. Meanwhile, the risk-to-benefit ratio associated with the strong recommendations noted is consistent with good clinical care. In the context of a devastating diagnosis that most patients do not survive, nontoxic complementary therapies can successfully provide symptom relief to lung cancer patients.

Detailed Methodology

A multidisciplinary panel of experts in oncology was gathered to prepare this chapter. The team included the following: thoracic medical oncologist Jorge E. Gomez, MD, at Memorial Sloan-Kettering Cancer Center (MSKCC); radiation oncologist and acupuncturist Peter A. S. Johnstone, MD, at Emory University School of Medicine; Gary E. Deng, MD, PhD, an internist specializing in integrative oncology at MSKCC; Nagi Kumar, PhD, a nutritionist/researcher at the Moffitt Cancer Center; Andrew Vickers, PhD, a biostatistician/research methodologist specializing in integrative oncology; and corresponding author Barrie Cassileth, Chief of Integrative Medicine Service, MSKCC.

Sources searched included English-language clinical trials or reviews in MEDLINE and relevant chapters in recent major oncology text books and government Web sites. MEDLINE was searched for articles published from 1980 to 2006. These searches were conducted from December 2005 through April 2006.

Limitations: Gaps in Research

Despite the long history of most complementary modalities, rigorous scientific research on these therapies is a recent phenomenon. The research is

further limited by lack of sufficient funding, lack of qualified investigators, and methodologic and ethical issues unique to studying complementary therapies. Therefore, gaps in research are the norm rather than the exception in this field, and these gaps represent the major limitation. Many complementary therapies derived from complete traditional medical system were used historically to treat almost every ailment. Only a few modalities have been evaluated with modern scientific research tools in a few indications. Those data related to lung cancer are discussed in this article. Our current knowledge base is simply insufficient. A tremendous amount of work needs to be performed before we can offer more comprehensive evidence-based recommendations.

Integrative medicine evaluated the evidence for complementary (not alternative) therapies in the care of lung cancer patients. Because few complementary modalities are geared to patients with only a single cancer diagnosis, symptom-control research conducted with other groups of cancer patients was also included. Data on complementary therapies such as acupuncture, massage therapy, mind-body therapies, herbs and other botanicals, and exercise were evaluated. Recommendations were based on the strength of evidence and the risk-to-benefit ratio.

Recommendations and Discussion

The recommendations are organized according to modalities. Within each modality, recommendations supported by a strong level of evidence are made and discussed first (grade A and B). Recommendations are presented in text boxes for easy recognition. Selected topics where only grade C recommendations can be made are then discussed. These topics are selected based on their clinical significance. Such selectiveness is necessary because of the nascent nature of research in this area. For many issues relevant to lung cancer patients, there is currently insufficient evidence to make any meaningful recommendation. For other issues, relevant but not exclusive to lung cancer, existing data from other cancer diagnoses can be safely extrapolated.

Use of CAM

Recommendation

1. It is recommended that all patients with lung cancer be asked specifically about the use of CAM. Grade of recommendation, 1C

Rationale and Evidence: The most comprehensive and reliable findings on Americans' use of CAM in general come from the National Center for Health Statistics 2002 National Health Interview Survey. The National Center for Health Statistics is an agency of the Centers for Disease Control and Prevention.[5] Of 31,044 adults surveyed, 75% used some form of CAM. When prayer specifically for health reasons is excluded, the percentage is 50%.

By various accounts, 10% to > 60% of cancer patients have used CAM, depending primarily on the definitions applied.[6–10] The Datamonitor 2002 Survey indicated that 80% of cancer patients used an alternative or complementary modality.[11] There is some indication of a growth in CAM use by cancer patients in recent years.[12] When compared to other cancer diagnoses, prevalence of CAM use was the highest in lung cancer patients (53%) according to a nationwide survey in Japan.[13] This is not the case in a Europe-wide survey, in which 24% of lung cancer patients reported CAM use.[14] Consistent across all surveys, CAM users typically are younger, more educated, and more affluent, representing a more health-conscious segment of the population who are willing and able to play an active role in their own care.

Recommendation

2. It is recommended that all patients with lung cancer be given guidance about the advantages and disadvantages of complementary therapies in an open, evidence-based, and patient-centered manner by a qualified professional. Grade of recommendation, 1C

Rationale and Evidence: Surveys show that most cancer patients rely on friends and family members, the media, and the Internet, rather than health-care professionals as top sources of CAM information.[13,14] Information obtained from these nonprofessional sources is often inaccurate. A majority of patients used botanicals or other supplements, expecting them to suppress the growth of cancer or even cure cancer,[13,14] not realizing that most such effects come from *in vitro* or animal studies. There has been little evidence to date showing any CAM therapies can achieve those effects in clinical settings. Many supplements are often produced with minimal if any quality control.[15] They may interact with many prescription medications, including chemotherapy, possibly decreasing efficacy or increasing toxicity.[16,17] Some patients use dietary supplements nondiscriminatorily for possible benefits in cancer prevention and cancer treatment. However, some supplements may do more harm than good (*eg*, supplementation of beta-carotene may actually increase the risk of

lung cancer in those who currently smoke and in those who recently quit smoking).[18,19] However, therapies backed by supportive evidence for symptom control and favorable risk/benefit ratios, such as acupuncture and mind-body techniques, were used less frequently than were botanicals.[13,14]

Two further barriers that hinder open communication on CAM use are the perceived lack of familiarity with CAM modalities and the widespread dismissive attitude among mainstream health-care professionals. Medical degree courses rarely include review of common CAM therapies, and many physicians who provide care to cancer patients are unable to discuss these approaches in an open, patient-centered fashion. Increasing numbers of educational resources, including review articles, books, continuing medical education courses, and reliable Web sites, are available to interested physicians, nurses, and other practitioners.

Major cancer centers in North America and elsewhere have established integrative medicine programs to study and combine helpful complementary therapies with mainstream oncology care, while educating cancer patients to avoid potentially harmful "alternative" therapies and herb-drug interactions. They are valuable and yet underutilized resources for busy oncologists who may not have the time for an in-depth discussion with patients on CAM. An international organization has been established to encourage appropriate clinical integration and scientific evaluation and dissemination of evidence-based information (Society for Integrative Oncology, http://www.integrativeonc.org).

Mind-Body Techniques

RECOMMENDATION

3. In lung cancer patients, mind-body modalities are recommended as part of a multidisciplinary approach to reduce anxiety, mood disturbance, or chronic pain. Grade of recommendation, 1B

Rationale and Evidence: Mind-body modalities, including meditation, hypnosis, relaxation techniques, cognitive-behavioral therapy, biofeedback, and guided imagery are increasingly becoming part of mainstream care over the years. A survey found that 19% of American adults used at least one mind-body therapy in a 1-year period.[20] The 2002 US nationwide survey[5] showed 12% of the respondents used deep breathing relaxation techniques and 8% used meditation. A metaanalysis[21] of 116 studies found that mind-body therapies could reduce anxiety, depression, and mood disturbance in cancer patients, and assist their coping skills. Mind-body techniques also may help reduce chronic low back pain, joint pain, headache, and procedural pain.[22]

Meditation: Meditation focuses attention on increasing mental awareness and clarity of mind (concentrative meditation) or opens attention to whatever goes through the mind and to the flow of sensations experienced from moment to moment (mindfulness meditation). In a randomized wait-list control study[23] of 109 cancer patients, participation in a 7-week mindfulness-based stress reduction program was associated with significant improvement in mood disturbance and symptoms of stress. A single-arm study[24] of patients with breast and prostate cancer showed significant improvement in overall quality of life, stress, and sleep quality, but symptom improvement was not significantly correlated with program attendance or minutes of home practice.

Yoga: Yoga, which combines physical movement, breath control, and meditation, improved sleep quality in a trial of 39 patients with lymphoma. Practicing a form of yoga that incorporates controlled breathing and visualization significantly decreased sleep disturbance when compared to wait-list control subjects.[25] Mindfulness-based stress reduction techniques must be practiced to produce beneficial effects.[26]

Hypnosis: Hypnosis is an artificially induced state of consciousness in which a person is highly receptive to suggestions. A trancelike state (similar to deep daydreaming) can be achieved by first inducing relaxation and then directing attention to specific thoughts or objects. For best results, the patient and the therapist must have a good rapport with a level of trust; the environment must be comfortable and free from distractions; and the patient must be willing to undergo the process and must desire to be hypnotized. Research shows that hypnosis is beneficial in reducing pain, anxiety, phobias, and nausea and vomiting.

In one study, 20 patients who underwent excisional breast biopsy were randomly assigned to a hypnosis or control group (standard care). Postsurgery pain and distress were reduced in the hypnosis group.[27] In another study, children undergoing multiple painful procedures such as bone marrow aspiration or lumbar puncture were randomized to receive hypnosis, a package of cognitive behavioral coping skills, or no intervention. Those who received either hypnosis or cognitive behavioral therapy experienced more pain relief than did control patients. The effects were similar between hypnosis and cognitive behavioral therapy. Both therapies also reduced anxiety and distress, with hypnosis showing

greater effectiveness.[28] Hypnosis was studied in a randomized controlled trial[29] of 60 patients undergoing elective plastic surgery. Perioperative and postoperative anxiety and pain were significantly reduced in the hypnosis group when compared to the control group who just received stress reduction training. Reduction in anxiety and pain was achieved along with significant reduction in intraoperative requirements for sedatives and analgesics.[29]

In a study[30] of 67 patients who underwent bone marrow transplantation, subjects were randomized to one of the four intervention groups: hypnosis training, cognitive behavioral coping skills training, therapist contact control, or usual care. Oral pain from mucositis was reduced in the hypnosis group. An NIH Technology Assessment Panel found strong evidence for hypnosis in alleviating cancer-related pain.[31] Hypnosis effectively treats anticipatory nausea in pediatric[32] and adult cancer patients[33] and reduces postoperative nausea and vomiting.[29]

Selection of proper patients and qualifications of the hypnotherapist contribute to safe hypnotherapy. A small percentage of patients may experience dizziness, nausea, or headache. These symptoms usually result from patients being brought out of trances by inexperienced hypnotherapists.

Relaxation Techniques: Relaxation techniques were shown in randomized controlled trials to ameliorate anxiety and distress significantly. A randomized study of relaxation therapy vs alprazolam showed that both approaches significantly decreased anxiety and depression, although the effect of alprazolam was slightly quicker for anxiety and stronger for depressive symptoms.[34] Relaxation achieves the effect without side effects and at a lower cost. A randomized trial[35] of 82 radiation therapy patients found significant reductions in tension, depression, anger, and fatigue for those who received relaxation training or imagery.

A metaanalysis[36] of 59 studies showed improved sleep induction and maintenance with psychological interventions. Although pharmaceuticals may produce a rapid response, some studies suggest that behavioral therapies help to maintain longer-term improvement in sleep quality. The NIH consensus panel[31] concluded that behavioral techniques, particularly relaxation and biofeedback, produce improvements in some aspects of sleep, but the magnitude of improvement in sleep onset and time may not achieve clinical significance.

Manipulative and Body-Based Practices

Recommendations

4. In lung cancer patients experiencing anxiety or pain, massage therapy delivered by a massage therapist trained in oncology is recommended as part of a multimodality treatment approach. Grade of recommendation, 1C

5. The application of deep or intense pressure is not recommended near cancer lesions or anatomic distortions such as postoperative changes, as well as in patients with a bleeding tendency. Grade of recommendation, 2C

Rationale and Evidence: The many types of body-based practices have in common the manipulation or movement of parts of the body to achieve health benefits. Massage therapists apply pressure to muscle and connective tissue to reduce tension and pain, improve circulation, and encourage relaxation. Massage therapy has variations in techniques, such as Swedish massage, Thai massage, and Shiatsu. Other body-work techniques, such as Alexander Technique and Pilates, address posture and movement, whereas yoga, Tai Chi, Reiki, and polarity therapy incorporate strong mind-body components.[37]

Massage therapy helps relieve symptoms commonly experienced by cancer patients. It reduces anxiety and pain[38–41] as well as fatigue and distress.[38] Anxiety and pain were evaluated in a crossover study[39] of 23 inpatients with breast or lung cancer receiving reflexology (foot massage) or usual care. Patients experienced significant decreases in anxiety; in one of three pain measures, breast cancer patients experienced significant decreases in pain as well.[39] In the largest study[40] to date, 87 hospitalized cancer patients were randomized to receive foot massage or control. Pain and anxiety scores decreased with massage, with differences between groups achieving statistical and clinical significance. The use of aromatic oil seemed to enhance the effect of massage in early studies,[41,42] but significant enhancement was not seen in more recent randomized controlled trials.[43–45] For noncancer subacute and chronic back pain, massage therapy was found effective in a systematic review of randomized controlled trials, and preliminary data suggest it may help reduce the costs of care.[46]

Massage therapy is generally safe when practiced by credentialed practitioners. Serious adverse events are rare and associated with exotic types of massage or untrained practitioners.[47] In work with cancer patients, the application of deep or intense pressure should be avoided, especially near lesions or anatomic distortions such as postoperative changes. Patients with bleeding tendencies should receive only gentle, light-touch massage.

Energy Therapies

RECOMMENDATION

6. For lung cancer patients, therapies based on manipulation of putative bioenergy fields are not recommended. Grade of recommendation, 1C

Rationale and Evidence: Energy therapies are based on the theory that manipulation of "energy fields" around a patient has therapeutic value. Two types of energy fields are involved: biofield and electromagnetic field.

Biofield therapies are intended to affect energy fields that purportedly surround and penetrate the human body. Because no convincing scientific evidence has emerged despite decades of attempt to prove the existence of such fields, some of the therapies, although originally developed from the theory of bioenergy fields, likely exert their effects on patients through light touch or mind-body interaction. Such therapies include Qi-gong, Reiki, and therapeutic touch. This type of therapy is reviewed in the "Mind-Body Techniques" section.

Bioelectromagnetic-based therapies involve the unconventional use of electromagnetic fields, such as pulsed fields, magnetic fields, or alternating-current fields or direct-current fields. Most research in bioelectromagnetics focuses on genotoxicity of environmental electromagnetic fields, such as whether exposure to power lines or cell phones increases the risk of cancer.[48–50] There has been no report showing the bioelectromagnetic therapies to be effective in cancer treatment or symptom control.

Acupuncture

Acupuncture is a modality that originated from traditional Chinese medicine. The theory was that one can regulate the flow of "Qi" (vital energy) by the stimulation of certain points on the body with needles, heat, or pressure. Scientific research[51,52] suggests that the effects of acupuncture are likely mediated by the nervous system. Release of neurotransmitters and change of brain-functional MRI signals are observed during acupuncture. Acupuncture was used traditionally for almost every ailment; few such applications are supported by rigorous clinical studies. However, evidence supports the use of acupuncture in treating some common symptoms experienced by cancer patients and others.

RECOMMENDATION

7. Acupuncture is recommended as a complementary therapy when pain is poorly controlled or when side effects such as neuropathy or xerostomia from other modalities are clinically significant. Grade of recommendation, 1A

Rationale and Evidence: Pain is the most common and the best-studied indication for acupuncture. Acupuncture relieves both acute (*eg*, postoperative dental pain) and chronic (*eg*, headache) pain.[53,54] An NIH consensus statement[53] in 1997 supported acupuncture for adult postoperative pain, chemotherapy-related nausea and vomiting, and postoperative dental pain. Insufficient evidence was available to support other claims of efficacy at that time; but in the ensuing years, many publications have documented the utility of acupuncture as an adjunct treatment for pain, emesis, and other symptoms.

A randomized controlled trial[55] of 570 patients with osteoarthritis of the knee found that a 26-week course of acupuncture significantly improved pain and dysfunction when compared to sham acupuncture control. In this study, all patients received other usual care for osteoarthritis. At 8 weeks, both pain and function improved, but the difference between groups was significant only for function.[55] A companion article[56] reported the results of a randomized controlled trial of acupuncture for chronic mechanical neck pain. Acupuncture was found to reduce neck pain and produce a statistically, but not clinically, significant effect compared with placebo. Data on acute low back pain are inconclusive.[57]

Acupuncture appears effective against cancer-related pain. A randomized placebo-controlled trial[58] tested auricular acupuncture for patients with pain despite stable medication. A total of 90 patients were randomized to have needles placed at correct acupuncture points (treatment group) vs acupuncture or pressure at nonacupuncture points. Pain intensity decreased by 36% at 2 months from baseline in the treatment group, a statistically significant difference compared with the two control groups, for whom little pain reduction was seen.[58] Skin penetration *per se* showed no significant analgesic effect. The authors selected acupuncture points by measuring electrodermal signals. These results are especially important because most of the patients had neuropathic pain, which is often refractory to conventional treatment.

Brain imaging technology is now being used to examine the specific nervous pathways involved in acupuncture. In functional MRI studies, true acupuncture induces brain activation in the hypothalamus and nucleus accumbens, and deactivates areas of the anterior cingulate cortex, amygdala, and hippocampus. Such changes are not observed in control stimulations, which affect only sensory

cortex change. Deactivation of the amygdala and hippocampus has been observed also with electroacupuncture. These data suggest that acupuncture modulates the affective-cognitive aspect of pain perception.[52] Correlations between signal intensities and analgesic effects also have been reported.[59]

Recommendations

8. Acupuncture is recommended as a complementary therapy when nausea and vomiting associated with chemotherapy are poorly controlled. Grade of recommendation, 1B

9. Electrostimulation wristbands are not recommended for managing chemotherapy-induced nausea and vomiting. Grade of recommendation, 1B

Rationale and Evidence: Acupuncture helps lessen chemotherapy-induced nausea and vomiting.[60] In one study,[61] 104 breast cancer patients receiving highly emetogenic chemotherapy were randomized to receive electroacupuncture at the PC6 and ST36 acupuncture points, minimal needling at nonacupuncture points, or pharmacotherapy alone. Electroacupuncture significantly reduced the number of episodes of total emesis from a median of 15 to 5 when compared with pharmacotherapy only. Most patients did not know the group to which they had been assigned.[61] The effects of acupuncture do not appear entirely because of attention, clinician-patient interaction, or placebo.

The combination of acupuncture and serotonin receptor antagonists, the newest generation of antiemetics, showed mixed results. In a trial[62] of patients with rheumatic disease, the combination decreased the severity of nausea and the number of vomiting episodes more than ondansetron alone in patients receiving methotrexate (an agent also used in chemotherapy). However, a study[63] of cancer patients receiving high-dose chemotherapy and autologous stem-cell transplantation reported no significant benefit for ondansetron plus acupuncture vs ondansetron plus placebo acupuncture. Acupuncture also suppresses nausea and vomiting caused by pregnancy,[64] surgery,[65] and motion sickness.[66,67]

Acupressure wristbands that render continuous stimulation of the PC6 point also have been tested for chemotherapy-related nausea and vomiting. In a randomized controlled trial[68] of 739 patients, nausea on the day of chemotherapy was reduced significantly in patients wearing wristbands compared with no-band control subjects. No significant differences were found for delayed nausea or vomiting. Unlike acupressure wristbands, expected efficacy of electrostimulation wristbands was not significantly related to any component of nausea or to antiemetic use. It was believed that the electrical stimulus generated by the electrostimulation band could act as a conditioned stimulus (akin to a reminder) of the nausea that patients are trying to control, and thereby actually accentuate the development of nausea in some individuals.[68]

Recommendation

10. When the patient with lung cancer does not stop smoking despite use of other options, a trial of acupuncture is recommended to assist in smoking cessation. Grade of recommendation, 2C

Rationale and Evidence: Smoking cessation has the largest impact in preventing lung cancer. Educational, behavioral, and medical interventions are the mainstay for smoking cessation. The effect of acupuncture has been studied with mixed results. A metaanalysis[69] of 22 studies concluded that acupuncture is no more effective than placebo in smoking cessation; however, the same metaanalysis found that acupuncture did no worse than any other intervention. A more recent randomized trial[70] of 141 subjects tested auricular acupuncture, education, or the combination in achieving smoking cessation. The authors found that both modalities, alone or in combination, significantly reduced smoking. The combination showed a significantly greater effect in subjects with a greater pack-year history.[70]

Brain imaging studies show that smoking suppresses blood flow to anterior cingulate cortex, hippocampus, and amygdala.[71] Curiously, these are the same areas suppressed by acupuncture.[52] Given the huge public health impact of smoking and the imperfect results of existing smoking cessation techniques, it is acceptable, although not encouraged, for someone who has been unable to quit smoking to try acupuncture. Further studies using refined acupuncture techniques guided by recent advances in acupuncture research appear warranted.

Recommendation

11. In patients with lung cancer with symptoms such as dyspnea, fatigue, chemotherapy-induced neuropathy, or postthoracotomy pain, a trial of acupuncture is recommended. Grade of recommendation, 2C

Rationale and Evidence: Lung cancer patients with advanced disease almost always experience

dyspnea attributable to parenchymal tumor burden or pleural effusion. Oxygen and opioids remain the mainstay of symptomatic treatment, although confusion and constipation are common side effects. An uncontrolled study[72] in cancer patients receiving palliative care showed marked reduction of dyspnea scores after a session of acupuncture. However, subsequent randomized, sham, controlled trials[73] did not show significant improvement in subjective sensation of dyspnea in patients with advanced lung or breast cancer.

Fatigue after chemotherapy or irradiation, another major and common problem, has few reliable treatments in patients without a correctable cause such as anemia.[74] In an uncontrolled trial[75] of fatigue after chemotherapy, acupuncture reduced fatigue 31% after 6 weeks of treatment. Among those with severe fatigue at baseline, 79% had nonsevere fatigue scores at follow-up,[75] whereas fatigue was reduced only in 24% of patients receiving usual care in another center.[76]

Although acupuncture is commonly used to treat neuropathy, most previous research was performed in HIV-related neuropathy or diabetic neuropathy. Patients with HIV-related peripheral neuropathy were treated with standardized acupuncture regimen or control point regimen in a randomized controlled trial[77] of 239 patients. Reduction of pain scores was observed in both groups, and no significant difference between the groups was seen. Forty-six diabetic patients with chronic painful peripheral neuropathy were treated with acupuncture in a single-arm study. Significant improvement of symptoms was reported by 77% of patients, a percentage higher than the usual response to placebo observed in pain trials. There was no significant change in the peripheral neurologic examination scores.[78] No clinical trial of acupuncture for chemotherapy-induced neuropathy has been reported, although a recent small case series[4] showed positive results. A randomized clinical trial to evaluate acupuncture in the treatment of postthoracotomy neuropathic pain is underway.

If these symptoms become a significant clinical problem in a particular patient despite conventional treatment, it is not unreasonable to accept a patient's choice to try acupuncture for symptom reduction. The lack of conclusive evidence supporting its effectiveness is balanced to the favorable safety record of acupuncture and the lack of other viable treatment options.

Recommendation

12. In patients with a bleeding tendency, it is recommended that acupuncture be performed by qualified practitioners and used cautiously. Grade of recommendation, 1C

Rationale and Evidence: Acupuncture needles are regulated as medical device in the United States. They are filiform, sterile, single use, and very thin (28 to 40 gauge). Insertion of acupuncture needles causes minimal or no pain and less tissue injury than phlebotomy or parenteral injection. Acupuncture performed by experienced, well-trained practitioners is safe. Only six cases of potentially serious adverse events were reported in a recent study of 97,733 patients receiving acupuncture in Germany. They included exacerbation of depression, hypertensive crisis, vasovagal reaction, asthma attack, and pneumothorax. The most common minor adverse events included local bleeding and needling pain, both in $< 0.05\%$ of patients.[79] It is prudent to avoid acupuncture at the site of tumor or metastasis, limbs with lymphedema, areas with considerable anatomic distortion attributable to surgery, and in patients with thrombocytopenia, coagulopathy, or neutropenia. Cancer patients require certified practitioners who are experienced in treating patients with malignant diseases.

Diet and Dietary Supplements Including Herbal Products

Many epidemiology studies demonstrate an association of diet and cancer incidence. Other than smoking cessation, a healthy diet is perhaps the most important lifestyle change a person can make to help prevent cancer, as well as cardiovascular disease and diabetes. However, aside from interventions to counter specific protein, calorie, vitamin, or mineral nutritional deficits, special dietary regimens do not have any significant role in cancer treatment. Some dietary regimens have been promoted for cancer treatment, such as macrobiotic diet or alkaline diet. None has been supported by clinical studies.

The use of biological-based CAM such as herbs and other dietary supplements is very popular among cancer patients.[13,14,80] Most users expect the supplements to help cancer treatment or reduce side effects. Such expectations are often unmet.[14] The purported benefits of the supplements are usually only supported by preclinical studies. Only a few were evaluated in clinical trials. The concurrent use of supplements, especially high-dose antioxidants or complex botanical agents, during chemotherapy or radiation therapy can be problematic because of drug-supplement interaction.[81,82] Some botanicals, based on their chemical structure, may have adverse effects in perioperative use. Their antiplatelet ac-

tivity may adversely interact with corticosteroids and CNS depressant drugs; they may produce GI effects, hepatotoxicity, and nephrotoxicity; and can produce additive effects when used concomitantly with opioid analgesics.[83] Quality control and adulteration of dietary supplements are additional major issues.[84]

Recommendations

13. It is recommended that dietary supplements, in particular herbal products, be evaluated for side effects and potential interaction with other drugs. Those that are likely to interact with other drugs, such as chemotherapeutic agents, should not be used concurrently during chemotherapy or radiation, or before surgery. Grade of recommendation, 1B

14. In lung cancer patients who either do not respond to or decline antitumor therapies, it is recommended use of botanical agents occur only in the context of clinical trials. Grade of recommendation, 1C

Rationale and Evidence: Dietary supplements include vitamins, minerals, herbs or other botanicals, amino acids, and other substances intended to supplement the diet. They are usually natural products with a record of historical use. By law, the manufacturers are not allowed to claim that their product will diagnose, cure, mitigate, treat, or prevent a disease. However, patients often take them with such expectations.

Botanicals and other natural products are a valuable source for the development of therapeutic agents, where they are carefully studied for safety and efficacy. Approximately one fourth of prescription drugs contain active ingredients derived from plants, including several chemotherapeutic agents (paclitaxel, docetaxel), camptothecins (irinotecan, topotecan), and vinca alkaloids (vincristine, vinorelbine). Sold as dietary supplements, however, they are rarely produced to the same high standards. Some herbs cause significant side effects. Detrimental herb-drug interactions may occur. Finally, product inconsistency and contamination have been reported.[84,85]

Most claims made by producers of herbal supplements are based on historical experience, unconfirmed by clinical trials. Many herbs show direct antitumor activity in *in vitro* or animal experiments,[86,87] but translating preclinical to clinical use often fails because the active constituents, often unknown, are insufficiently potent or metabolized before reaching their target. The composition of herbs is complex and typically containing hundreds of constituents. Moreover, some herbal remedies function through the synergistic effects of their multiple constituents, hindering identification of active components.

Herbs and other botanical products that enhance immune function are especially popular among cancer patients and may prove useful in cancer treatment or prevention. Some show immunomodulatory effects in preclinical studies, assisting tumor rejection or resistance to pathogens.[88–90] However, the most popular immune boosting herb in the United States used commonly to treat colds, echinacea, showed disappointing results in randomized controlled trials.[91–93]

Because botanicals contain biologically active constituents, they carry health risks if not used properly. The botanical kava kava, for example, proved more effective than placebo in treating anxiety, stress, and insomnia,[94,95] and it was considered a viable alternative to benzodiazepines because of its benefits and absence of dependency and addiction. However, later reports associate this herbal remedy with severe hepatotoxicity resulting in death.[96]

Herbal medicine was practiced historically by those with at least some knowledge of side effects of the herbs. Today, however, many herbal and other botanical products are readily available to US consumers under the Dietary Supplement Health and Education Act of 1994, which regulates them only as food supplements and requires no previous studies of safety and efficacy. A few herbal products have been removed from the market by the Food and Drug Administration because of adverse events. A recent example is agents that contain ephedra because its sympathomimetic activity has been associated with cardiovascular complications, including death.

Herbs may attenuate or lessen the effect of a drug either by direct action on its target or by altering its pharmacokinetics.[17,97] Herbs such as feverfew, garlic, ginger, and ginkgo have anticoagulant effects and should be avoided by patients using warfarin, heparin, aspirin, and related agents. Red clover, Dong quai, and licorice, because of their phytoestrogen components, should not be used by patients using tamoxifen or aromatase inhibitors. St. John wort was a popular product for depression, at least equivalent in efficacy to tricyclics and selective serotonin reuptake inhibitors in mild to moderate depression and with a side effect profile superior to both.[98,99] It was found, however, that St. John wort induces cytochrome P450 CYP3A4. Reduced plasma levels of SN38, an active metabolite of irinotecan, have been reported after simultaneous use.[100] Such metabolic interactions preclude St. John wort for patients on medications metabolized by CYP3A4.[101]

Although not an herb, grapefruit juice was found

to significantly change the plasma level of many prescription drugs. Further study found that furanocoumarin derivatives inhibit intestinal CYP3A4, which consequently increases the bioavailability of drugs that are substrate to first-pass metabolism by this enzyme.[102,103] Interestingly, such interaction initially was discovered by accident in an ethanol-calcium channel blocker interaction study in which grapefruit juice was used as the vehicle for the alcohol.[104] Details of herbs-drug interactions can be found at several sources.[85,105]

Recommendation

15. It is recommended that patients be advised to avoid therapies promoted as "alternatives" to mainstream care. Grade of recommendation, 1A

Rationale and Evidence: Alternative therapies that claim to improve survival have largely been demonstrated to be ineffective in clinical trials.[106] Randomized trials have shown no benefit or, in some cases, shorter survival for high-dose vitamin C,[107,108] shark cartilage,[109] hydrazine sulfate,[110–113] and mistletoe extracts.[114–117] Cohort or phase II studies have shown no benefit to DiBella therapy,[118,119] antineoplastons,[120] Livingston-Wheeler therapy,[121] amygdalin,[122] and Pau D'arco.[123] In a population-based study,[124] patients using alternative therapy have been shown to have shorter survival, after adjustment for known prognostic factors, than those avoiding such therapies.

Research Priorities

We view the following as high-priority areas of research: effectiveness of complementary therapies in the management of symptoms or disease processes for which our current treatment options are not satisfactory; mechanisms of action as explained by contemporary biomedical science; definitive database of drug-supplement interactions; and new cancer therapies derived from botanicals or other supplements or their synergistic effect with conventional medicine.

Conclusion

The use of CAM is common among cancer patients. These therapies are very diverse in their origin, theory, practice, safety, and efficacy. Some of the therapies have been shown in studies to be helpful in reducing symptoms experienced by cancer patients. These complementary therapies (used as adjuncts to mainstream cancer treatment) are increasingly integrated into regular oncologic care, leading to integrative oncology. Dietary supplements, herbs, and other botanicals can be problematic because of their adverse effects or interactions with chemotherapy, radiotherapy, or surgery. There are those therapies promoted as "alternative" to mainstream cancer treatment. Patients who use these "alternative" therapies are at risk for missing the window of opportunity for effective treatment. It is important for all involved in the care of cancer patients to help patients distinguish between the two, and to approach complementary and alternative therapies appropriately to receive benefit while avoiding harm. Specific advice should be provided after considering the level of evidence and the risk-to-benefit ratio. Health-care professionals should know where to find reliable sources of information.

Summary of Recommendations

1. It is recommended that all patients with lung cancer be specifically asked about the use of CAM. Grade of recommendation, 1C

2. It is recommended that all patients with lung cancer be given guidance about the advantages and disadvantages of complementary therapies in an open, evidence-based, and patient-centered manner by a qualified professional. Grade of recommendation, 1C

3. In lung cancer patients, mind-body modalities are recommended as part of a multimodality approach to reduce anxiety, mood disturbances, or chronic pain. Grade of recommendation, 1B

4. In lung cancer patients experiencing anxiety or pain, massage therapy delivered by an oncology-trained massage therapist is recommended as part of a multimodality treatment approach. Grade of recommendation, 1C

5. The application of deep or intense pressure is not recommended near cancer lesions or anatomic distortions, such as postoperative changes, as well as in patients with a bleeding tendency. Grade of recommendation, 2C

6. For lung cancer patients, therapies based on putative manipulation of bioenergy fields are not recommended. Grade of recommendation, 1C

7. Acupuncture is recommended as a complementary therapy when pain is poorly controlled or when side effects, such as neuropathy or xerostomia from other modalities, are clinically significant. Grade of recommendation, 1A

8. Acupuncture is recommended as a complementary therapy when nausea and vomiting associated with chemotherapy are poorly controlled. Grade of recommendation, 1B

9. Electrostimulation wristbands are not recommended for managing chemotherapy-induced nausea and vomiting. Grade of recommendation, 1B

10. When the patient with lung cancer does not stop smoking despite use of other options, a trial of acupuncture is recommended to assist in smoking cessation. Grade of recommendation, 2C

11. In patients with lung cancer with symptoms such as dyspnea, fatigue, chemotherapy-induced neuropathy, or postthoracotomy pain, a trial of acupuncture is recommended. Grade of recommendation, 2C

12. In patients with a bleeding tendency, it is recommended that acupuncture be performed by qualified practitioners and used cautiously. Grade of recommendation, 1C

13. It is recommended that dietary supplements, particularly herbal products, be evaluated for side effects and potential interactions with other drugs. Those that are likely to interact with other drugs, such as chemotherapeutic agents, should not be used concurrently during chemotherapy or radiation, or before surgery. Grade of recommendation, 1B

14. In patients with lung cancer who either do not respond to or decline antitumor therapies, it is recommended that use of botanical agents occur only in the context of clinical trials. Grade of recommendation, 1C

15. It is recommended that patients be advised to avoid therapies promoted as "alternatives" to mainstream care. Grade of recommendation, 1A

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Follow-up and Surveillance of the Lung Cancer Patient Following Curative Intent Therapy*

ACCP Evidence-Based Clinical Practice Guideline (2nd Edition)

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Background: **To develop an evidence-based approach to follow-up of patients after curative intent therapy for lung cancer.**
Methods: **Guidelines on lung cancer diagnosis and management published between 2002 and December 2005 were identified by a systematic review of the literature, and supplemental material appropriate to this topic was obtained by literature search of a computerized database (Medline) and review of the reference lists of relevant articles.**
Results: **Adequate follow-up by the specialist responsible for the curative intent therapy should be ensured to manage complications related to the curative intent therapy and should last at least 3 to 6 months. In addition, a surveillance program should be considered to detect recurrences of the primary lung cancer and/or development of a new primary lung cancer early enough to allow potentially curative retreatment. A standard surveillance program for these patients, coordinated by a multidisciplinary tumor board and overseen by the physician who diagnosed and initiated therapy for the original lung cancer, is recommended based on periodic visits with chest imaging studies and counseling patients on symptom recognition. Smoking cessation and, if indicated, facilitation in participation in special programs is recommended for all patients following curative intent therapy for lung cancer.**
Conclusions: **The current evidence favors follow-up of complications related to curative intent therapy, and a surveillance program at regular intervals with imaging and review of symptoms. Smoking cessation after curative intent therapy to prevent recurrence of lung cancer is strongly supported by the available evidence.** ***(CHEST 2007; 132:355S–367S)***

Key words: lung cancer; metachronous tumors; recurrence; surveillance

Abbreviations: ACCC = Association of Community Cancer Centers; ACCP = American College of Chest Physicians; CXR = chest radiograph; NCCN = National Comprehensive Cancer Network; NSCLC = non-small cell lung cancer; PET = positron emission tomography

Approximately 172,000 new cases of lung cancer are diagnosed annually in the United States.[1] Unfortunately, only approximately 20% of patients with newly diagnosed lung cancer will have localized disease and will be candidates for potentially curative treatment.[2] Furthermore, some patients with localized non-small cell lung cancer (NSCLC) may either refuse potentially curative surgical therapy or may be

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unable to tolerate surgery because of limiting comorbid cardiopulmonary or other disease. Consequently, it has been estimated that only 35,000 patients underwent curative intent surgical resection for NSCLC in 1998.[3] Small numbers of patients will receive curative intent radiation therapy for localized NSCLC and some combination of curative intent chemotherapy and radiation therapy for localized small cell carcinoma.

Two distinctly different issues should be taken into account when planning patient care following curative intent therapy for lung cancer. First, adequate follow-up should be ensured to manage complications related to the curative intent therapy itself. This should be a specialist-directed process. The thoracic surgeon should be responsible for managing complications related to any surgical procedures performed, as should the radiation oncologist and the medical oncologist for managing complications related to radiation therapy and chemotherapy, respectively. In most cases, this specialist-directed follow-up should be transient.

Second, a surveillance program should be considered to detect recurrences of the primary lung cancer and/or development of a new primary lung cancer early enough to allow potentially curative retreatment. Numerous guidelines have been published regarding the management of lung cancer. Several of these guidelines include recommendations for a posttreatment surveillance program. These recommendations will be summarized and compared. Available data on rates, patterns, and diagnostic tools for identifying recurrence of the primary lung cancer and/or development of a second primary lung cancer will be reviewed as the basis for recommendations on an ongoing surveillance program following curative intent therapy for lung cancer. Issues related to follow-up for palliative therapy of lung cancer will not be discussed (see section on Palliative Treatment).

To update the previous recommendations on the follow-up and surveillance of lung cancer patients following curative intent therapy,[4] guidelines on lung cancer diagnosis and management published between 2002 and December 2005 were identified by a systematic review of the literature using search terms including "follow-up," "surveillance," "lung cancer," and "lung neoplasms" (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter). Those guidelines including recommendations specific to the follow-up and surveillance of lung cancer after curative intent therapy were identified for inclusion in this section. Supplemental material appropriate to this topic was obtained by literature search of a computerized database (Medline) and review of the reference lists of relevant articles. Recommendations were developed by the section editor and writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), and then reviewed by all section editors, the Executive Committee of the panel, and then further reviewed by the Thoracic Oncology Network, Health and Science Policy Committee, and Board of Reagents of the American College of Chest Physicians (ACCP).

Follow-up of Complications Related to the Original Mode of Curative Intent Therapy

Follow-up for complications should be performed by the specialist responsible for the curative intent therapy and should last at least 3 to 6 months.[5] Complications related to pulmonary resection include hospital readmission, loss of lung function, and chronic pain. Handsy et al[6] reported that 19% of patients discharged after pulmonary resection were readmitted within 90 days, most for pulmonary problems, postsurgical infections, and cardiac issues. Loss of lung function after surgery is directly related to the extent of the resection performed. Six months after lobectomy, FEV_1 is approximately 10 to 15% lower than preoperative values, and after pneumonectomy approximately 25 to 35% lower.[7] Similarly, maximal exercise capacity stabilizes at 6 months after lobectomy at a 10% reduction and a 20% decrease after pneumonectomy compared with preoperative value.[7] Postthoracotomy pain has been reported in 55% of patients at 18 to 24 months after resection, with 10% of patients requiring narcotic analgesia or more aggressive therapy, such as intercostal nerve blocks.[8–10] Patients undergoing resection for localized lung cancer have significantly lower baseline quality of life when compared with the normal population, and resection causes further deterioration in quality of life, especially during the first 3 to 6 months after surgery. Some studies[11,12] suggest that quality of life returns to baseline levels at 6 to 9 months after surgery, whereas others show significant impairments up to 12 months after surgery. Of note, persistent cigarette smoking after lung cancer resection significantly worsens quality of life measures.[13]

Unusual complications related to pulmonary resection may occur after hospital discharge. Case series[14,15] from the 1960s reported that persistent air in the pleural space was noted for weeks to months following lobectomy and pneumonectomy but usually resolved without complications. An autopsy series[16] from the same time period confirmed residual air in the pleural space after pneumonectomy in 27 of 37 cases, even

though surgery had been performed years before. In very rare situations, empyema may develop in these spaces.[14] Torsion of the mediastinum developing after pneumonectomy may lead to mainstem bronchus obstruction.[17]

Complications of radiation therapy with curative intent for lung cancer include acute radiation pneumonitis and radiation-induced pulmonary fibrosis, as well as injury to the skin, heart, pericardium, esophagus, and spinal cord. Pulmonary radiation toxicity is related to the volume of lung irradiated, the cumulative dose effects of radiation sensitizing agents, and undefined factors determining the biological predisposition of the patient. In a large study[18] using high-dose radiation therapy, acute toxicity was seen in 11% of the patients, with most injury relating to esophageal problems and only a third to lung toxicity. Acute radiation pneumonitis usually occurs within 3 months of treatment and is associated with nonproductive cough, dyspnea, and fever.[19] It may resolve without treatment, but severe cases may be responsive to corticosteroid therapy. Inoue et al[20] reported that 94 of 191 evaluable patients (49%) had acute radiation pneumonitis after thoracic radiotherapy for lung cancer, and 25 patients (13%) had severe cases. $PaO_2 < 80$ mm Hg prior to radiotherapy may have indicated an increased risk for acute radiation pneumonitis in this study. Severe radiation pneumonitis was associated with poorer overall survival. Other work[21] suggests that increased serum levels of KL-6 may be a useful marker of radiation pneumonitis. Radiation-induced fibrosis represents irreversible tissue damage, occurs in approximately 8% of patients treated with curative intent, and may present as early as 3 months and as late as 24 months after treatment.[18] Even without producing overt pneumonitis, effective radiation therapy may result in a loss of pulmonary function. Miller et al[22] described an average decrease in median FEV_1, FVC, and diffusing capacity of the lung for carbon monoxide of 10% at 6 months after irradiation therapy, similar to that reported after lobectomy. All values were closer to baseline at 1 year after treatment but continued to decline by 7 to 10%/yr.[22] However, Choi and Kanarek[23] found that patients with poor lung function before treatment had little decrease in FEV_1 after irradiation therapy.

Complications related to chemotherapeutic agents used for NSCLC and small cell lung cancer are usually detected during the course of therapy. A long-term morbidity of concern in patients who have completed chemotherapy is a mild-to-moderate peripheral neuropathy, which results from multiple treatments with the commonly used platin, vinca alkaloid, and taxane compounds. In addition, induction chemotherapy with cisplatinum and gemcitibine has been associated with a fall in diffusing capacity of the lung for carbon monoxide.[24]

Recommendation

1. In lung cancer patients treated with curative intent therapy, follow-up for complications related to the curative intent therapy should be managed by the appropriate specialist and should probably last at least 3 to 6 months. At that point, the patient should be reevaluated by the multidisciplinary tumor board for entry into an appropriate surveillance program for detecting recurrences and/or metachronous tumors. Grade of recommendation, 2C

Issues in Surveillance for Recurrence of the Original Lung Cancer and Development of New Primary Lung Cancers

Definitions

As previously reviewed,[4] a difficult but fundamental issue in surveillance of the lung cancer patient following curative intent therapy is distinguishing between recurrence of the original lung cancer and identification of a new primary, or metachronous, lung cancer. Martini and Melamed[25] proposed criteria for making this distinction in 1975. However, more recent considerations suggest that these criteria should be revised (Table 1). More definitive distinction will be possible in the future based on routine performance of analysis of panels of molecular, genetic markers, and/or proteomics. Whichever criteria are used, Martini and Melamed[25] remind us

Table 1—*Distinguishing Between Recurrence of the Original Lung Cancer and Development of a New Lung Cancer During Surveillance*

Metachronous Tumors, Martini and Melamed Criteria*	Metachronous Tumors, Proposed Revision
Histology different	Histology different
Histology the same, if:	Histology the same, if:
Free interval between cancers at least 2 years, or	Free interval between cancers at least 4 yr, or
Origin from carcinoma *in situ*, or	Origin from carcinoma *in situ*, and
Second cancer in different lobe or lung, but	No extrapulmonary metastases at time of diagnosis
No carcinoma in lymphatics common to both, and	
No extrapulmonary metastases at time of diagnosis	

*Adapted from Martini and Melamed.[25]

Table 2—*Recommendations for Surveillance Methods in Patients With NSCLC Following Curative Intent Therapy*

Guideline/Source	Baseline	First 2 yr	Years 3 to 5	After Year 5
ACCC[29]		Hx, PE, CXR, CBC, chemistries every 3 mo	Hx, PE, CXR, CBC, chemistries every 6 mo	Hx, PE, CXR, CBC, chemistries every 12 mo
ACCP[4]		Hx, PE, CXR or chest CT every 6 mo	Hx, PE, CXR or chest CT every 12 mo	Hx, PE, CXR or chest CT every 12 mo
ACR[27]	Chest CT at 3 mo after therapy	CXR every 2 to 4 mo; chest CT every 12 mo	CXR every 6 mo; chest CT every 12 mo	CXR every 12 mo; chest CT every 12 mo
ASCO[26]		Hx, PE every 3 mo	Hx, PE every 6 mo	Hx, PE every 12 mo
ESMO[30]		Hx, PE every 3 mo	Hx, PE every 6 mo	Hx, PE every 6 mo
NCCN[28]		Hx, PE, contrast CT every 6 mo	Hx, PE, non-contrast CT every 12 mo	Hx, PE, non-contrast CT every 12 mo

*ACR = American College of Radiology; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; Hx = history; PE = physical examination.

that the distinction between a new primary lung cancer and recurrence of the original lung cancer is not as important as determining whether the tumor can be treated with curative intent.

Review of Current Guidelines

Five guidelines[26–30] provide specific recommendations for surveillance methods in patients with NSCLC (Table 2), and two guidelines[29,31] provide specific recommendations for patients with small cell lung cancer following curative intent therapy (Table 3). These guidelines were developed by consensus of expert panels and not necessarily by more rigorous metaanalysis. Two other guidelines[30,32] provided only general recommendations. One guideline[30] noted the lack of evidence that surveillance of the asymptomatic patient with small cell lung cancer following curative intent therapy is needed. Specific examinations in these patients should be performed as clinically indicated. The other guideline[32] supported the need for randomized clinical trials to define the most appropriate follow-up regimen, and to evaluate patient quality of life and the cost-effectiveness of the strategy.

The guidelines uniformly recommend more frequent visits during the first 2 years following curative intent therapy. Visits are less frequent for years 3 through 5 and decrease to a minimal level of annually after year 5. This pattern of visits is based on the expectation that recurrences of the original lung cancer will be more likely during the first 2 years after curative intent therapy but that there will be an increased lifelong risk of a new primary lung cancer developing. The guidelines uniformly emphasize symptoms as an extremely important indication of recurrence, with physical examination included as an adjunctive, but less valuable, tool for identifying recurrences or new primaries.

There is wide divergence among the guidelines regarding recommendations for chest imaging after curative intent therapy for lung cancer. The issues of radiographic detection of asymptomatic recurrent or metachronous cancer after treatment with curative intent are similar to those of early detection of primary cancer currently being investigated in high-risk patients (see section on "Screening for Lung Cancer"). Accordingly, the American Society of Clinical Oncology guidelines for NSCLC specifically state that there is no proven value for either chest radiograph (CXR) or CT in surveillance.[26] However, the Association of Community Cancer Centers (ACCC) guidelines recommend routine CXR for surveillance.[29] Guidelines from the American College of Radiology[27] recommend a postresection chest

Table 3—*Recommendations for Surveillance Methods in Patients With Small Cell Lung Cancer Following Curative Intent Therapy*

Guideline/Source	Baseline	First 2 yr	Years 3 to 5	After Year 5
ACCC[29]		Hx, PE, CXR, CBC, chemistries every 3 mo	Hx, PE, CXR, CBC, chemistries every 6 mo	Hx, PE, CXR, CBC, chemistries every 12 mo
ACCP[4]		Hx, PE, CXR, or chest CT every 6 mo	Hx, PE, CXR, or chest CT every 12 mo	Hx, PE, CXR or chest CT every 12 mo
NCCN[28]		Hx and PE (chest imaging and blood work as clinically indicated) every 2 to 3 mo	Hx and PE (chest imaging and blood work as clinically indicated) every 4 to 6 mo	Hx and PE (chest imaging as clinically indicated) every 12 mo

*See Table 2 for expansion of abbreviations.

CT scan to establish a new baseline and then annually in addition to interval CXR every 2 to 4 months. The most recent guidelines from the National Comprehensive Cancer Network (NCCN)[28] rely entirely on chest CT scanning for surveillance imaging (Table 2).

With regards to other tests, the ACCC guidelines incorporate regular complete blood counts and serum chemistries into surveillance monitoring for NSCLC. Other groups found little value in performing these tests routinely for NSCLC, but these tests are recommended routinely in small cell lung cancer surveillance. Sputum cytology and various bronchoscopic techniques were specifically not incorporated into guidelines for surveillance practices.

Patterns of Recurrence

Numerous studies[33–41] have reported on recurrence rates and patterns in patients with NSCLC treated with curative intent surgical resection. In patients with stage I disease confirmed at surgery, 5-year recurrence rates 20 to 39% have been reported.[34,37,38] Most of these recurrences were distant metastases.[34,37,39] Although most recurrences were detected within the first 4 years following curative intent surgery,[37,38] recurrences may be discovered $\geq$ 5 years following curative intent therapy.[34,37,39,40] In patients with nodal involvement, recurrence rates increase[35,36,41] and recurrences probably occur earlier.[33,35,41]

It has been estimated from published studies[42,43] on treatment outcomes that the approximate rate of a new primary lung cancer developing after curative intent therapy for a NSCLC is 1 to 2% per patient per year. Prospective lung cancer chemoprevention trials with vitamin A[44] and isotretinoin[45] also suggest similar rates for the development of metachronous tumors. In contrast, large population-based studies, such as the review of the regional cancer registry in Switzerland, suggest that in this population the rate may actually be slightly less than this estimate at approximately 0.5% per patient per year.[46] However, this type of study may underestimate the incidence rate of metachronous tumors because of incomplete surveillance and misclassification of tumors as recurrences.[45] Experience with long-term survivors of lung cancer indicate that new primary lung cancers may develop up to 20 years after the original cancer had been treated,[47] but the available data are unclear on whether the rate of development of metachronous tumors increases or decreases over time.[34,39,43] An important point is that following curative intent therapy for NSCLC, patients are also at increased risk for other aerodigestive cancers (*eg*, carcinoma of the oropharynx and esophagus).[46,48]

Roentgenographically occult lung cancers detected by sputum cytology have been reported to have an especially high rate of metachronous tumors. Saito et al[49] described 13 metachronous tumors occurring in a group of 127 patients who underwent surgical resection for roentgenographically occult NSCLC. The cumulative rate at 5 years of metachronous tumors was 11%, and the incidence per patient year of surveillance was 2.2%. Bechtel and colleagues[50] reported that seven metachronous tumors were identified in a group of 27 patients following surgical resection of a roentgenographically occult NSCLC. Consistent with these findings has been the observation that central lung cancers, treated with sleeve resection, may have a high rate of metachronous tumors approaching 7 to 8%.[51]

Patients treated for small cell lung cancer and surviving for 2 years have also been reported to have an especially high rate of metachronous NSCLCs developing. In two separate observational studies,[52] NSCLC was diagnosed in 12 to 15% of patients surviving at least 2 years after therapy for small cell lung cancer (six cases in one group of 40 patients, and six cases in another group of 47 patients). It has been estimated that the rate of NSCLC developing 2 years after effective therapy for small lung cancer is 2 to 13% per patient per year.[43] Another study[53] confirmed that the rate of NSCLC developing following therapy for small cell lung cancer was significantly greater than expected from population data. A more recent study[54] estimated that 10% of 2-year survivors of small cell lung cancer will eventually have NSCLC.

Curative Intent Therapy for Recurrence and/or New Primary

Most recurrences of lung cancer are found outside the thorax.[33–37,52,53] Effective treatment of isolated metastases may be possible (see section on "Special Treatment Issues"). However, locoregional intrathoracic recurrences are only infrequently treated with curative intent surgical therapy,[37,40,55] and more often are treated with radiation therapy.[56,57] Regardless of therapy, the available data indicate that survival with locoregional recurrence of lung cancer appears to be poor.[58]

Although curative intent surgical therapy may be possibly more feasible with metachronous lung tumors than with locoregional recurrences of the primary lung cancer,[47] patients with metachronous tumors often present with advanced stage disease or are unable to tolerate surgical resection due to pulmonary insufficiency.[43] Limited data suggest that, even controlling for stage of disease, survival following curative intent surgical resection of metachro-

nous lung tumors may not be as favorable as for the original lung cancer (Table 4). Despite limitations in the approach to curative intent therapy of metachronous lung cancers, 5-year survival rates of 25 to 53% (Table 4) have been reported when surgical resection is possible.

Intensity of the Surveillance Program

There may be differences in how recurrences and metachronous tumors are identified. Recurrences seem to be more often detected through assessment of symptoms. Pairolero et al[34] scheduled visits for their stage I NSCLC patients every 4 months for the first 2 years and then every 4 to 6 months thereafter following curative intent surgery. A history, physical examination, CXR, blood tests, urine analysis, and pooled sputum cytology were performed at each visit. Most recurrences were detected at scheduled visits (59%), but a substantial number of recurrences were detected at unscheduled visits. Most patients with recurrences were symptomatic (53%), and symptom assessment was the most sensitive method for detecting recurrences. The blood tests, urine analysis, physical examination, and sputum cytology added little to detecting recurrences. Others have reported similar findings. Chiu and colleagues[59] followed up 38 patients following curative intent surgical resection for NSCLC with a history, physical examination, sputum cytology, CXR, and CT at 3-month intervals for 2 years and then at 6-month intervals for the next 3 years. Of the 14 patients who had recurrences, 7 patients (50%) presented with symptoms. Ichinose[60] described a similarly intensive surveillance program and also reported that most recurrences were recognized by symptoms; neither CT nor standard blood tests provided appreciable additional benefit in identifying recurrences.

In contrast, some case series[61–63] have reported that 68 to 100% of patients with metachronous lung cancers were asymptomatic and had the new primary lung cancer detected by radiographic methods. Lamont et al[58] described a retrospective chart review of 124 patients following curative intent surgical resection of NSCLC. They had all been entered into a regular surveillance program, including a history, physical examination, and CXR at 4- to 6-month intervals and an annual CT. Of the 124 patients, metachronous lung cancers developed in 19 patients (15.3%; 2.1%/yr), and all 19 patients were asymptomatic at the time. Eleven of the 19 metachronous tumors were first detected by CT; 16 of the 19 patients had stage IA disease, and 14 patients underwent curative intent reoperation. Nine of 14 patients were alive without evidence of recurrent disease at a median of 20 months. These authors[58] recommended annual CT for detecting metachronous tumors because disease can be identified early and resected, although the study was not designed to show a survival advantage for this group.

Other studies have provided an expanded view of the methods used for detecting recurrences and/or metachronous tumors by considering the costs involved in a surveillance program. Walsh et al[64] retrospectively evaluated the course of 358 patients following curative intent surgical resection for NSCLC. There were 135 recurrences, and most (76%) were recognized through symptoms. Although the asymptomatic patients had a longer survival time following detection of the recurrence, the authors[64] believed that this reflected lead-time bias and not a

Table 4—*Survival After Surgical Resection for Metachronous Lung Cancers*

Source	Patients With Metachronous Tumors, No.	Patients Undergoing Surgical Resection, No. (%)	Patients With Stage I Disease, No. (%)	Five-Year Survival After Surgical Resection of Metachronous Cancer, % (Five-Year Survival After Surgical Resection of Primary Lung Cancer, %)
Rosengart et al[47]	78	54 (69)	60 (77)	23 (70)
Watanabe et al[55]	8	8 (100)	6 (75)	53*
Wu et al[103]	20	20 (100)	Notstated	42*
Van Bodegom et al[104]	89	45 (51)	35 (39)	Notstated
Deschamps et al[105]	44	44 (100)	34 (77)	34 (55)
Westermann et al[106]	8	8 (100)	7 (88)	Notstated
Antakli et al[61]	39	21 (54)	Notstated	23*
Adebonojo et al[62]	37	36 (97)	29 (78)	37*
Asaph et al[63]	37	37 (100)	25 (68)	33*
Van Rens et al[107]	127	127 (100)	90 (71)	26 (70)
Battafarano et al[108]	69	69 (100)	50 (73)	33 (61)

*Five-year survival comparative data following surgical resection of primary lung cancer not provided.

true survival benefit. Similar percentages of symptomatic (29%) and asymptomatic (30%) patients could be treated with curative intent. Seven metachronous lung cancers were recognized in this study, but information on therapy and survival for these patients was not provided. The authors[64] concluded that intensive surveillance was not cost-effective and suggested a reduced surveillance approach consisting of a history, physical examination, and CXR every 6 months for the first year following curative intent surgery and then annually. Egermann and colleagues[65] reached similar conclusions from their study of 563 patients who were cancer-free at 3 months following curative intent lobectomy for NSCLC. A history, physical examination, and CXR were performed at 3-month intervals for 2 years, and then at 6-month intervals for up to 5 years and then annually. Only 4.1% of the 361 patients had a potentially resectable lung cancer identified during follow-up. In 21 patients, metachronous tumors were detected and resected with curative intent. Survival analysis indicated a maximum survival benefit of 9 months; based on these data and estimated healthcare costs in Switzerland, a calculated cost for the surveillance plan was $56,000 (US dollars) per life-year gained. The authors believed that this cost was too high to justify this intensive follow-up and recommended follow-up at 6-month intervals. A decision-analysis model approach to estimating the cost-effectiveness of chest CT in following patients after resection of stage 1A NSCLC arrived at a similar theoretical cost ($47,676 per quality-adjusted life-year gained).[66] However, this analysis suggested that use of chest CT in surveillance might be cost-effective in patients < 65 years old; in clinical practices where the cost of chest CT was < $700, the annual incidence of second primary lung cancers was at least 1.6% per patient, and the false-positive rate of surveillance was < 14%.[66]

Virgo and colleagues[67] compared two groups retrospectively following surgery for NSCLC. One group of 120 patients had intensive surveillance, consisting of at least four visits with serum chemistries and CXR per year, and annual bronchoscopy and/or sputum cytology with CT. The other group of 62 patients had less intensive surveillance, with on average only two visits with serum chemistries and CXR per year. No differences were found between the groups in either time to detection of recurrences or metachronous tumors or survival time. They agreed that intensive surveillance was not cost-effective and supported the surveillance schedule suggested by Walsh et al.[64] Two other retrospective analyses of intensive surveillance methods provided similar results. Younes and colleagues[68] found that intensive surveillance yielded no survival advantage and was more expensive than a symptom-based approach, although more patients in the symptom-based group had disease identified through emergency room visits. Gilbert and coworkers[69] showed that more recurrences were found by family physicians based on symptomatic presentation than were identified through regularly scheduled surveillance visits to the surgical clinic. These investigators[69] also found that the costs of identifying recurrences would be much lower using family physicians than intensive surveillance through the surgical clinic. Reviews[70,71] of this topic have endorsed the concept of less intense surveillance because "more intensive diagnostic testing has yet to demonstrate survival and quality of life benefits."[70]

The concept of less intensive surveillance has been challenged by work by Westeel et al,[72] who instituted a very intensive surveillance program in 192 patients surviving 30 days after complete surgical resection for NSCLC. Visits were scheduled every 3 months for 3 years, with history, physical examination, and CXRs. Bronchoscopy and CT were performed at 6-month intervals. From the fourth year after surgery, visits with CXRs were at 6-month intervals, and CT and bronchoscopy were performed annually. At year 8, surveillance was reduced to a visit and CXR annually. They claimed good compliance with this surveillance regimen in a subset of the entire group. Of 136 patients with recurrent cancers, 35 cases (25.7%) were asymptomatic and detected by diagnostic procedures. Of these, 15 patients (11% of recurrences) had intrathoracic recurrences that could be treated with curative intent; these were diagnosed by CXR (n = 5), bronchoscopy (n = 5), or CT (n = 5). Survival after recurrence for the 36 patients with asymptomatic recurrences was significantly better than for the 100 patients with symptomatic recurrences. In their economic analysis, Westeel et al[72] suggested that this very intensive surveillance regimen provided an acceptable cost per additional year of life gained. However, the improved survival, as measured after time of recurrence rather than after time of resection, in the asymptomatic patients may have reflected lead-time bias, and the proposed costs for procedures used in the surveillance strategy were relatively low.

Reconciling the conflicting findings from these various studies in order to provide clinical guidance is difficult. To begin, a clinically intuitive but often not stated principle is that patients who have a poor performance status or inadequate pulmonary function are not candidates for curative resection of either recurrent or metachronous lung cancer. Consequently, such patients are not candidates for intensive and aggressive surveillance programs designed to detect asymptomatic tumors. Instead, they should

be educated to seek early attention and should have ready access to their providers for follow-up of new symptoms that might herald recurrent cancer. For patients with adequate performance status and lung function, the panel recognizes that periodic patient encounters following curative intent therapy for lung cancer are essential and strongly feels that imaging studies of the chest should be included in these visits. CT is accepted as more sensitive for detecting pulmonary nodules than CXR and has been shown to be more accurate for evaluating lung cancer response during chemotherapy.[73] Small series[59,74,75] have shown that CT can detect changes consistent with recurrence earlier than CXR. CT is also being widely studied as a method for early detection of lung cancer (see "Screening for Lung Cancer" section). Unfortunately, the performance characteristics of CT (*ie*, sensitivity and specificity) for distinguishing nonspecific posttreatment changes related to surgery, radiation therapy, and/or chemotherapy from a recurrence and/or metachronous lung cancer have not been defined. Many studies[58] report a high incidence of nodules in groups followed up with chest CT, and the appropriate protocols for differentiating benign from malignant nodules without excess morbidity and cost from diagnostic procedures have yet to be defined. Consequently, the panel was evenly divided between recommending CXR and CT as the imaging procedure of choice.

Recommendation

2. In lung cancer patients treated with curative intent therapy, and those having adequate performance and pulmonary function, surveillance with a history, physical examination, and imaging study (either CXR or CT) is recommended every 6 months for 2 years and then annually. All patients should be counseled on symptom recognition and be advised to contact their physician if worrisome symptoms are recognized. Grade of recommendation, 1C

Physician Factors Influencing Current Surveillance Methods

Numerous reports have evaluated individual factors that might influence the surveillance methods used by thoracic surgeons. These studies[76] showed that many thoracic surgeons do perform regular surveillance for detecting recurrences and/or metachronous lung cancers following curative intent surgical therapy. The most commonly used methods were the history, physical examination, CXR, CBC count, and serum chemistries. Infrequently used surveillance methods were CT, bronchoscopy, sputum cytology, bone scan, and head CT. There was wide variation in the frequency at which these methods were used. This wide variation was probably due to the common belief that the clinical benefits of a surveillance program, particularly in terms of improving survival, had not been demonstrated. Interestingly, the age of the surgeon, the geographic region of practice, and the stage of the original lung cancer did not seem to influence the surveillance methods used by individual thoracic surgeons.[77–79] Motivating factors for continued surveillance seemed to be pleasing the patient, avoiding malpractice litigation, and potentially improving the patient's quality of life.[80] A more important issue, not specifically addressed in the surveys, was articulated by Shields[81]: "The least desirable course of action (in regard to care of the lung cancer patient following curative intent surgical therapy) is to pass the patient from one team member to another without continued surveillance by the primary responsible physician."

Recommendation

3. Ideally, surveillance for recognition of a recurrence of the original lung cancer and/or development of a metachronous tumor should be coordinated through a multidisciplinary team approach. If possible, the physician who diagnosed the primary lung cancer and initiated the curative intent therapy should remain as the health-care provider overseeing the surveillance process. Grade of recommendation, 2C

Alternative Surveillance Techniques

There is considerable interest in developing noninvasive, easily performed, safe and accurate techniques for detecting recurrences and/or metachronous tumors at the earliest possible time. Positron emission tomography (PET) scanning is an established modality for identifying malignant pulmonary nodules, mediastinal nodal involvement in confirmed cases of lung cancer, and extrathoracic metastases (see sections on "Solitary Pulmonary Nodule" and "Noninvasive Staging"). As a metabolic imaging technique, PET may be able to distinguish recurrent cancer from the parenchymal scarring, distortion of bronchovascular anatomy, pleural thickening, and mediastinal fibrosis commonly seen on conventional imaging after initial treatment.[82] Pooled data from studies to date indicate that PET has 96% sensitivity and 84% specificity for detecting recurrent lung cancer after treatment with surgery, chemotherapy, or radiotherapy.[82–87] The accuracy of PET has been dependent on the standardized uptake value used to define a positive test result, the delay between initial treatment and the PET scan, and the size of recur-

rent lesions and prevalence of bronchoalveolar cell carcinoma.[84,85,87,88] Of note, the specificity of PET scan after definitive treatment is lower than at initial staging due to increased uptake on PET scan from inflammatory changes related to tumor necrosis and radiation pneumonitis.[82] In addition, uptake on PET scans has been reported in the pleura of the shielded, nonirradiated lung even in the absence of overt radiation pneumonitis.[89] It has been recommended that PET scans for evaluating recurrent disease not be performed after curative intent therapy for at least 3 to 6 months to minimize the possibility of false-positive findings, and that suspicious lesions on a surveillance PET scan be confirmed by CT imaging and biopsy.[82,90] Importantly, there are no data showing that incorporating PET scanning into a surveillance program improves either survival or quality of life following curative intent therapy for NSCLC.

Another approach to early identification of recurrences of lung cancer is based on measuring serum levels of tumor markers. Ichinose[60] has recommended using serum carcinoembryonic antigen levels as a marker of tumor recurrence. Others[91,92] have also shown that elevated carcinoembryonic antigen levels following curative intent surgery for NSCLC may suggest recurrence. Other serum markers potentially useful for detecting tumor recurrence are levels of cytokeratin-19 fragments,[93] serum amyloid A and macrophage migration inhibitory factor,[94] and levels of pro–gastrin-releasing peptide in small cell lung cancer.[95] Further studies will be needed to confirm the performance characteristics of tumor markers for identifying tumor recurrence.

Pilot studies[96,97] have been performed using fluorescence bronchoscopy to detect metachronous tumors after curative intent surgical resection of NSCLC. In a group of 73 patients who underwent fluorescence bronchoscopy at a median of 13 months following surgical resection, one invasive carcinoma and three cases of intraepithelial neoplasia were identified. The carcinoma was identified on routine white-light bronchoscopy, but fluorescence bronchoscopy was useful in identifying two of the three cases of intraepithelial neoplasia.[96] In a smaller study[97] of 25 patients studied on average about 20 months after curative intent surgery, fluorescence bronchoscopy was again found to be more sensitive that routine white-light bronchoscopy in detecting intraepithelial neoplasia. The impact of early detection of intraepithelial neoplasia on survival should be confirmed in larger studies before fluorescence bronchoscopy should be incorporated into surveillance programs.

Recommendation

4. In lung cancer patients following curative intent therapy, use of blood tests, PET scanning, sputum cytology, tumor markers, and fluorescence bronchoscopy is not currently recommended for surveillance. Grade of recommendation, 2C

Smoking Cessation

Smoking is common in patients with lung cancer. Gritz and colleagues[98] studied smoking behavior in 840 adults with stage I NSCLC who had participated in clinical trials. At the time of diagnosis, 60% of the patients were smokers. By 2 years after diagnosis, 40% of these smokers had quit smoking. Smoking cessation at the time of diagnosis of lung cancer may reduce the rate of development of metachronous tumors. Richardson et al[99] found that the relative risk of a second lung cancer developing following curative intent therapy of small cell lung cancer was lower for those who stopped smoking. Tucker and coworkers[100] found that continuing smoking increased the risk of metachronous lung cancers in small cell lung cancer survivors. Because smoking cessation remains a challenge for such patients, they should be offered intensive tobacco cessation programs, including counseling, behavioral therapy, the use of sustained-release bupropion and nicotine replacement, and telephone follow-up, which significantly increase successful abstinence.[101,102]

Recommendation

5. Lung cancer patients who smoke should be strongly encouraged to stop smoking, and offered pharmacotherapeutic and behavioral therapy, including follow-up. Grade of recommendation, 1A

Summary

Following curative intent therapy of lung cancer, patients should be followed up for at least 3 to 6 months by the appropriate specialist for potential complications. In addition to this follow-up, recurrence of the original lung cancer and/or development of a second primary lung cancer should be expected possibilities. Most recurrences of the original lung cancer will occur within 4 years of curative intent therapy, but occurrences may occur $\geq$ 5 years after surgery. Following curative intent therapy of lung cancer, the risk of a second primary, or metachro-

nous, lung cancer developing may be 1 to 2% per patient per year lifelong. The risk for metachronous lung cancer may be even higher when the original primary is either roentgenographically occult, central, treated by sleeve resection only, or a small cell carcinoma.

Curative intent therapy is less likely to be possible with locoregional recurrences of the original lung cancer than with metachronous tumors. Although survival is not as good with treatment of metachronous tumors as for the original primary, reasonable 5-year survival rates should be expected with surgical resection of metachronous lung cancers.

Benefits in terms of survival advantages or improvements in quality of life have not been demonstrated with intensive surveillance programs compared with either a symptom-based approach or a less intensive regimen. In addition, the intensive surveillance programs seem more expensive. A clinically reasonable and cost-effective surveillance approach would include a history, physical examination, and imaging study (either CXR or CT) every 6 months for 2 years and then annually, assuming no suspicious findings were seen. In addition, patients would be counseled on symptom recognition and be advised to contact the appropriate physician on symptom recognition. Further studies are needed to determine whether very intensive surveillance programs might be warranted in selected subsets of lung cancer patients: patients with roentgenographically occult primary lung cancers, and patients surviving >2 years with small cell lung cancer and a complete response to original therapy, who have a very high expected rate of metachronous lung cancer.

Ideally, surveillance programs for recognition of a recurrence of the original lung cancer and/or development of a metachronous tumor following curative intent therapy should be coordinated through a multidisciplinary team approach. If possible, the physician who diagnosed the primary lung cancer and initiated the curative intent therapy should remain as the health-care provider overseeing the surveillance process. Patients with either a recurrence of their original cancer or a new primary lung cancer identified through the surveillance process should be reevaluated by the entire multidisciplinary team for potentially curative retreatment.

Although advanced imaging techniques, such as PET scanning, appear to be more sensitive than CXR for identifying recurrences and/or metachronous tumors, their value in improving either survival or quality of life following curative intent therapy for NSCLC is as of yet unproven. Incorporating PET scanning into a surveillance program should await the results of adequately designed and controlled, prospective trials. Similarly, serum levels of various tumor markers and fluorescence bronchoscopy should be demonstrated to be sensitive and specific predictors of tumor recurrence in adequately designed and controlled, prospective trials before being incorporated into surveillance programs.

Summary of Recommendations

1. In lung cancer patients treated with curative intent therapy, follow-up for complications related to the curative intent therapy should be managed by the appropriate specialist and should probably last at least 3 to 6 months. At that point, the patient should be reevaluated by the multidisciplinary tumor board for entry into an appropriate surveillance program for detecting recurrences and/or metachronous tumors. Grade of recommendation, 2C

2. In lung cancer patients treated with curative intent therapy, and those having adequate performance and pulmonary functions, surveillance with a history, physical examination and imaging study (either CXR or CT) is recommended every 6 months for 2 years and then annually. All patients should be counseled on symptom recognition and be advised to contact their physician if worrisome symptoms were recognized. Grade of recommendation, 1C

3. Ideally, surveillance for recognition of a recurrence of the original lung cancer and/or development of a metachronous tumor should be coordinated through a multidisciplinary team approach. If possible, the physician who diagnosed the primary lung cancer and initiated the curative intent therapy should remain as the health-care provider overseeing the surveillance process. Grade of recommendation, 2C

4. In lung cancer patients following curative intent therapy, use of blood tests, PET scanning, sputum cytology, tumor markers, and fluorescence bronchoscopy is not currently recommended for surveillance. Grade of recommendation, 2C

5. Lung cancer patients who smoke should be strongly encouraged to stop smoking, and offered pharmacotherapeutic and behavioral therapy, including follow-up. Grade of recommendation, 1A

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Palliative Care in Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Goals/objectives: **To review the scientific evidence on symptoms and specific complications that are associated with lung cancer, and the methods available to palliate those symptoms and complications.**
Methods: **MEDLINE literature review (through March 2006) for all studies published in the English language, including case series and case reports, since 1966 using the following medical subject heading terms: bone metastases; brain metastases; cough; dyspnea; electrocautery; hemoptysis; interventional bronchoscopy; laser; pain management; pleural effusions; spinal cord metastases; superior vena cava syndrome; and tracheoesophageal fistula.**
Results: **Pulmonary symptoms that may require palliation in patients who have lung cancer include those caused by the primary cancer itself (dyspnea, wheezing, cough, hemoptysis, chest pain), or locoregional metastases within the thorax (superior vena cava syndrome, tracheoesophageal fistula, pleural effusions, ribs, and pleura). Respiratory symptoms can also result from complications of lung cancer treatment or from comorbid conditions. Constitutional symptoms are common and require attention and care. Symptoms referable to distant extrathoracic metastases to bone, brain, spinal cord, and liver pose additional problems that require a specific response for optimal symptom control. There are excellent scientific data regarding the management of many of these issues, with lesser evidence from case series or expert opinion on other aspects of providing palliative care for lung cancer patients.**
Conclusions: **Palliation of symptoms and complications in lung cancer patients is possible, and physicians who provide such care must be knowledgeable about these issues.**
(CHEST 2007; 132:368S–403S)

Key words: bone metastases; brain metastases; cough; dyspnea; electrocautery; hemoptysis; interventional bronchoscopy; laser; pain management; pleural effusions; spinal cord metastases; superior vena cava syndrome; tracheoesophageal fistula

Abbreviations: APC = argon plasma coagulation; CI = confidence interval; NSAID = nonsteroidal antiinflammatory drug; NSCLC = non-small cell lung cancer; OR = odds ratio; PCI = prophylactic cranial irradiation; PDT = photodynamic therapy; RCT = randomized controlled trial; SCLC = small cell lung cancer; SVC = superior vena cava; TEF = tracheoesophageal fistula; WBRT = whole-brain radiation therapy

The histologic type, biological behavior, and the anatomic location of lung cancer within the thoracic cage determine the type and severity of respiratory symptoms manifested by patients with lung cancer. Pulmonary symptoms that may require palliation include those caused by the primary cancer itself (dyspnea, wheezing, cough, hemoptysis, chest pain),[1–7] or locoregional metastases within the thorax (superior vena cava [SVC] syndrome, tracheoesophageal fistula [TEF], pleural effusions, ribs, and pleura).[8–18] Respiratory symptoms can also result from complications

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of lung cancer treatment (such as radiation- and chemotherapy-induced lung toxicity, airway stenosis and necrosis, fistula formation, hemoptysis from neovascularization).[13,14,16,19–27] Comorbid conditions (such as COPD, heart failure, pulmonary embolism, prior lung resection, malnutrition) cause or contribute to respiratory symptoms. Constitutional symptoms (depression, fatigue, insomnia, anorexia-cachexia syndrome) are common and require attention and care. Symptoms referable to distant extrathoracic metastases to bone, brain, spinal cord and liver pose additional problems that require a specific response for optimal symptom control.

Pharmacologic (noninvasive) approaches to alleviating the above-mentioned respiratory symptoms from lung cancer are discussed in this chapter and elsewhere in the guidelines. However, a significant number of patients have respiratory symptoms as the result of mechanical (anatomic) effects of lung cancer, such as major airway obstruction, postobstructive pneumonia, fistulae between airways and other intrathoracic organs, pleural effusion, and paralysis of diaphragm and vocal cords. In such patients, pharmacologic (noninvasive) therapies may be inadequate to palliate respiratory symptoms. Several invasive techniques are available to benefit this selected group of patients and will be discussed in the appropriate section of this chapter.

Methods and Materials

The key words for various palliative care topics, as listed in above-mentioned "Key words" section, were searched using Ovid MEDLINE and PubMed from 1966 through March 1, 2006. Randomized controlled trials (RCTs) were especially sought for all such topics; where this type of study was available, it is clearly identified as such in the appropriate section of this chapter. For many of the topics, evidence is of substantially less quality, and it typically consists of case series of varying size. This has led to recommendations that are based on publications describing clinical experience with varying sizes of patient population. The sections that discuss approaches to treatment of airway obstruction and hemoptysis, as well as palliation of malignant pleural effusion are examples where the evidence-based literature pertaining to palliative therapy is limited.

Results

Pain Control

Studies reveal that adults with lung cancer have more symptoms than patients with other types of cancer.[28] Pain is a common symptom in lung cancer patients, yet inadequate pain management is prevalent, harmful to patients, and costly.[29] A comprehensive document for the management of cancer pain was developed and published in 1994 as part of a response to Public Law 101–239 (the Omnibus Reconciliation Act of 1989), under the aegis of the Agency for Health Care Policy and Research. The name subsequently was changed to the Agency for Healthcare Research and Quality.[30] The document on cancer pain management was updated in October 2001.[31]

In 2005, the American Pain Society revised and updated their recommendations for improving the quality of cancer pain management, and subsequently published guidelines on this topic.[32] The comments in this section are adapted from these resources. The scope of these efforts is beyond what can be discussed in detail in this document, and the reader is referred to these resources for additional information. In their 2005 recommendations, the American Pain Society calls caregivers' attention to five areas of pain management: (1) recognize and treat pain promptly; (2) involve the patients and families in the pain-management plan; (3) improve treatment patterns by eliminating inappropriate practices and providing multimodal therapy; (4) reassess and adjust the pain management plan as needed, focusing not only on pain intensity but on functional status and side effects as well; and (5) monitor the processes and outcomes of pain management, using national performance indicators.[32]

The potential causes of cancer pain are multiple and can include tumor progression and related pathology (*eg*, nerve damage), surgery and other procedures used for treatment and diagnosis, toxic side effects of chemotherapy, and radiation. Approximately 75% of patients with advanced cancer have pain. Failure to relieve pain leads to unnecessary suffering. Decreased activity, anorexia, and sleep deprivation caused by pain can further weaken already debilitated patients.

Effective management of pain from cancer can be achieved in most patients. Clinical trials[33–35] indicate that patients consider pain management effective if it decreases the pain intensity 33 to 50%, such that a clinician's goal and/or promise to the patient of "no pain" is ill founded and unnecessary. Proper management of a patient's pain involves more than analgesia, and the program of pain control for any one patient must be individualized. Approaches that may augment analgesia include cognitive/behavioral strategies, physical modalities, palliative radiation and antineoplastic therapies, nerve blocks, and palliative and ablative surgery. Studies[1,36–40] reveal that palliative chemotherapy in advanced lung cancer can have a modest increase in survival, and often has the additional benefit of improving pain and other symptoms. Any analgesic medication program should be kept as simple as possible, both with regard to the frequency and route of administration. Oral medications are preferred, because of convenience and

cost-efficacy. If the patient cannot take medications by mouth, rectal and transdermal routes should be considered because they are relatively noninvasive. IM routes of administration should be avoided because of the associated pain and inconvenience, and also because of unreliable absorption.

A nonsteroidal antiinflammatory drug (NSAID) or acetaminophen should be used unless there is a contraindication (*eg*, increased risk of cardiovascular events and GI bleeding with NSAID medications). If pain persists or becomes worse, an opioid should be added and not substituted. Using opioids and acetaminophen or NSAIDs often provides more analgesia than can be accomplished by either class of drug alone. Further, the use of acetaminophen or NSAIDs may have a dose-sparing effect for opioids, which can provide the benefit of fewer side effects from the opioids. When pain persists despite this approach, the dose of opioids should be increased or a more potent agent chosen. The World Health Organization ladder has been shown to be an effective method to ensure the rational titration of therapy for cancer pain (Fig 1).

Morphine is the most commonly used opioid for moderate or severe pain. It is available in a wide variety of dosage forms that include immediate and controlled-release preparations. Morphine is relatively inexpensive. Transdermal and rectal routes of administration can be used for most patients who cannot take medications by mouth. Morphine, hydrocodone, and oxymorphone suppositories are available. Fentanyl is the opioid most frequently used for transdermal administration. Meperidine should not be used because it has a short duration of action and its metabolite normeperidine is toxic and causes CNS stimulation with dysphoria, agitation, and seizures.

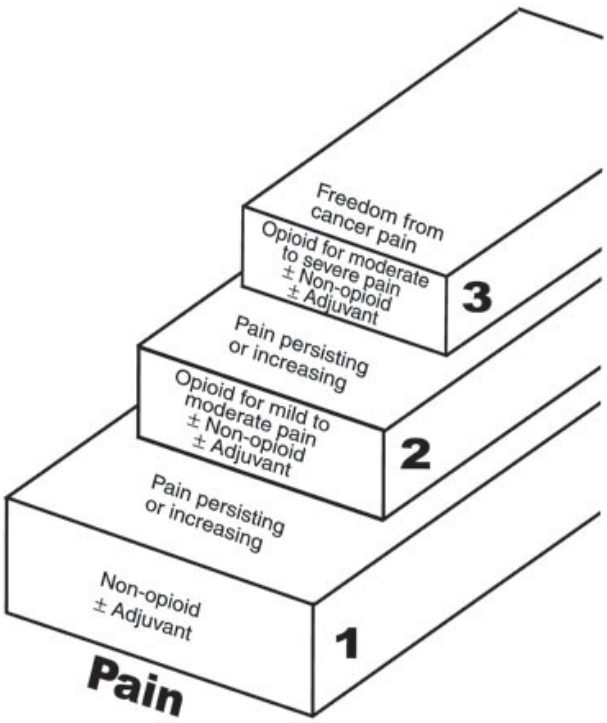

FIGURE 1. The World Health Organization three-step analgesic ladder.

Both the cancer patient and family members may shun the use of opioids because of a fear of addiction. Physicians must educate both the patient and the family about pain and how it is to be managed as part of the treatment plan. Effective pain control begins by asking the patient about pain. An easily administered pain rating scale should be used for assessment of pain, both at the time of initial presentation and periodically at regular intervals during the course of the disease. The most common pain scales are numeric (0 to 10 pain intensity), simple descriptive in nature (no pain, mild, moderate, severe), and a visual analog scale. Quality pain management requires a comprehensive assessment of the patient's pain, described as learning the "who", "how," and "when" of the pain.[29] Focusing only on pain intensity is insufficient and can lead to poor pain relief.

Analgesic medications should be administered around-the-clock with a long-acting opioid, with extra doses of an immediate-release opioid on an as-needed basis for breakthrough pain because this approach helps to prevent recurrence of pain. A written pain-management plan should be given to patients with cancer pain and their families. Constipation is a side effect of opioid medications, and should be anticipated, treated prophylactically, and monitored constantly. Mild constipation can be managed by an increase in fiber consumption and a mild laxative such as milk of magnesia. Bulk-forming laxatives such as fiber supplements should be avoided. Unless there are contraindications, cathartic agents should be administered on a regular schedule.

Ketamine is a parenteral general anesthetic that has been used in subanesthetic doses to relieve pain, particularly in opioid-tolerant patients. In the absence of large controlled trials providing recommended dosing schedules, clinicians with limited experience in using ketamine should seek expert consultation to develop an appropriate treatment and patient-monitoring plan.[41]

Adjuvant drugs may be used to enhance the efficacy of opioids. Corticosteroids produce effects that include mood elevation, relief of inflammation, and reduction of cerebral or spinal cord edema when there is intracranial metastasis or spinal cord compression. Anticonvulsants such as phenytoin, carbamazepine, and clonazepam are used to manage neuropathic pain. Tricyclic antidepressants are used

as an adjuvant to analgesics for the management of neuropathic pain. They augment the effects of opioids and have innate analgesic properties. Their mood-elevating properties may be helpful as an adjuvant to strict analgesics. Other adjunctive pharmacologic approaches include neuroleptics such as the major tranquilizers, hydroxyzine, bisphosphonates, and calcitonin for bone metastases.

There are many different nonpharmacologic methods to manage pain, many of which are very simple, effective, and inexpensive. Nonpharmacologic methods to manage pain include cutaneous stimulation techniques (heat and cold applications), accupuncture, psychosocial methods of care, and pastoral care. For patients with intractable and persistent pain despite use of all modalities that are known and familiar to the practitioner, referral to a clinic that specializes in the management of pain should be considered. Pain-control specialists can help to select additional methods that may improve the overall palliation of pain.

Recommendations

1. All lung cancer patients and their families must be reassured that pain can be relieved safely and effectively. All patients should be questioned regularly about their pain, using the patient's self-report of pain and a simple rating scale as the primary source of assessment. Grade of recommendation, 1A

2. For all patients, individualize medications that are used to control pain. Administer medications regularly and treat pain appropriately. Document the effectiveness of pain management at regular intervals during treatment. Grade of recommendation, 1A

3. For all patients with mild-to-moderate pain, manage the pain initially with acetaminophen or an NSAID, assuming there are no contraindications to their use. Use opioids when pain is more severe or when it increases. Grade of recommendation, 1B

4. For any patient, if it is anticipated that there will be a continuous need for opioid medication, meperidine is not recommended. It has a short duration of action, and its metabolite normeperidine is toxic and can cause CNS stimulation resulting in dysphoria, agitation, and seizures. Grade of recommendation, 1B

5. For patients whose pain is not controlled by pure analgesic medications, adjunctive medications such as tricyclic antidepressants, anticonvulsants, and neuroleptic agents will often augment the effects of pure analgesic medications. Grade of recommendation, 1C

6. For all patients, administer medications by mouth because of convenience and cost-effectiveness. In patients with lung cancer who cannot take pain medications by mouth, rectal and transdermal administration are recommended. Administration of analgesics by the IM route is not recommended because of pain, inconvenience, and unreliable absorption. Grade of recommendation, 1C

7. For all patients receiving opioids, because constipation is common, anticipate it, treat it prophylactically and constantly monitor it. Grade of recommendation, 1B

8. Encourage all patients to remain active and to care for themselves whenever possible. Avoid prolonged immobilization whenever possible. Grade of recommendation, 1B

9. In patients who have pain associated with muscle tension and spasm, it is recommended that complimentary methods for pain relief such as cutaneous stimulation techniques (heat and cold applications), acupuncture, psychosocial methods of care, and pastoral care be incorporated into the pain-management plan, but not as a substitute for analgesics. Grade of recommendation, 1C

10. For patients with advanced lung cancer, provide palliative radiation therapy to control pain. Palliative chemotherapy to decrease pain and other symptoms is recommended, even though the increase in survival may be only modest. Grade of recommendation, 1B

11. In patients with lung cancer who have pain unresponsive to standard methods of pain control, referral to a specialized pain clinic or palliative care consultant is recommended. Grade of recommendation, 1C

Palliation of Dyspnea

Dyspnea is the subjective experience of difficult, labored, and uncomfortable breathing. Dyspnea and cough are the most commonly reported symptoms in lung cancer, with 15% of patients having dyspnea at diagnosis and 65% at some point during their illness.[42,43] A prospective cohort study[44] of seriously ill, hospitalized adults in five teaching hospitals in the United States reported that among 939 patients with stage III or IV non-small cell lung cancer (NSCLC), severe dyspnea was recorded in 32%. Near death, 90% of patients with NSCLC have dyspnea. It is more common in men, older patients, and those with lower quality of life scores, and the incidence of dyspnea is higher when pain and anxiety are high.[45,46] Because of its frequency, clinicians should routinely assess the lung cancer patient for dyspnea. The intensity of the dys-

pnea can be discerned by the patient using a modified Borg scale of 0 to 10. Often patients will modify their activities to reduce the sensation of dyspnea, such that a report of intensity alone disguises the advancing dyspnea. It behooves the clinician also to ask what activities the patient has curtailed because of dyspnea.[47] The causes of dyspnea in patients with lung cancer can be classified into five broad groups: (1) the result of direct involvement of the respiratory system by lung cancer; (2) the result of indirect respiratory complications caused by lung cancer (such as postobstructive pneumonia and pleural effusion); (3) the result of specific therapies to treat lung cancer (such as radiation- and chemotherapy-induced lung toxicity, and anemia); (4) the result of respiratory complications that occur more frequently in these patients (such as pulmonary embolism and lung infections); and (5) comorbid conditions (such as COPD, heart failure, prior lung resection, and malnutrition).

Regardless of the stage of lung cancer, dyspnea usually impacts the patient's physical, social, and psychological well being. Anxiety, fear of impending death, and pain caused by lung cancer are among the factors that contribute to the subjective symptoms of dyspnea. A prospective study of 100 terminally ill cancer patients (49 patients with lung cancer) observed that dyspnea, measured on visual analog scale, was significantly associated with anxiety ($p = 0.001$).[48] From the perspectives of the patient and health-care providers, dyspnea can be perceived as panic, chest congestion and tightness, and suffocation. One study[46,49] of 52 patients with lung cancer noted that both physical and emotional sensations were associated with descriptions of breathlessness, such as the feeling of being unable to get enough breath, or of panic or impending death. Increased anxiety has been connected with worse dyspnea in patients with obstructive lung disease, chronic pulmonary disease, and/or cancer.[50–52] One study[46] of 120 patients with stage I-IV lung cancer observed no difference in dyspnea based on cancer stage, cell type, or performance status. However, pain and anxiety scores were higher in patients with high dyspnea scores.

The treatment of dyspnea should follow a stepwise approach, starting with treatment of the specific cause of the dyspnea if it can be identified (*eg*, pleural effusion, obstructed major airway, SVC syndrome, pericardial effusion and/or tamponade, carcinomatous lymphangitis, congestive heart failure, pulmonary embolism, and COPD and/or asthma).[47,53] If the specific cause cannot be identified, or if moderate-to-severe dyspnea persists despite attempted palliation of the cause, nonpharmacologic treatments should be considered. If these are not or only partly successful, pharmacologic therapies should be added to the treatment plan.

Nonpharmacologic Treatments

Nonpharmacologic treatments start with patient self-care strategies and coping strategies. Self-care strategies are particularly helpful in the patient who has coexisting COPD, and include simple measures such as body position (*eg*, leaning forward with arms and shoulders supported), pursed-lip breathing, paced breathing during activity (*eg*, inhale at the pause on the step while climbing stairs, exhale with the next step), and diaphragmatic breathing. Coping strategies can include practicing desensitization to the symptom, learning relaxation techniques (guided imagery, self-hypnosis, meditation/prayer, music therapy), and energy conservation techniques.[54]

Complementary methods for the control of dyspnea often include intervention by allied health personnel. A multicenter RCT of 119 patients with small cell lung cancer (SCLC) or NSCLC or with mesothelioma, who had completed first-line treatment and reported dyspnea, used various strategies. These included breathing control, activity pacing, relaxation techniques, and psychosocial support, in addition to standard management and treatment available for dyspnea. The group assigned to intervention by nurses improved significantly at 8 weeks in breathlessness, performance status, and physical and emotional status compared to the control group.[55,56] Similarly, using these techniques within specialist palliative care settings in a "breathlessness clinic" demonstrated a significant improvement in breathlessness, functional capacity, activity levels, and distress levels in lung cancer patients.[57]

Patient and family education about dyspnea and its treatments is the foundation of successful treatment. In patients with advanced disease, families should be educated about controlling the impact of things such as ambient weather and the indoor environment and its effect on the patient's perception of dyspnea. Patients with dyspnea at rest or with minimal activity often prefer an open and cool room with a clear line of sight to the outside. They also can receive benefit from a fan blowing on their face or a cool compress applied to the forehead, both mediated by the trigeminal nerve.[47]

The American College of Chest Physicians is in the process of developing evidence-based clinical practice guidelines for the management of dyspnea in advanced lung disease, including lung cancer. The reader is referred to the American College of Chest Physicians journal *CHEST* for this resource currently not yet published.

Oxygen: Supplemental oxygen is perhaps the most commonly prescribed therapy to relieve dyspnea in patients with lung cancer.[58] Significant involvement

of the respiratory system by lung cancer or underlying obstructive airways disease usually produces or aggravates dyspnea and hypoxemia. A limited number of studies have shown the beneficial effects of supplemental oxygen therapy. A prospective, double-blind, crossover trial[59] assessed the effects of supplemental oxygen on the intensity of dyspnea in 14 patients with advanced cancer. Patients were randomized to receive either oxygen or air delivered at 5 L/min by mask. Dyspnea was evaluated with a visual analog scale. The results showed that 12 patients consistently preferred oxygen to air; and patients reported little or no benefit from air compared with moderate to much benefit from oxygen.[59]

Regardless of the oxygenation status, supplemental oxygen therapy should be considered if patients with lung cancer experience dyspnea. Multiple blood gas analyses should be avoided to justify oxygen therapy. Percutaneous oximetry should suffice to assess adequate oxygenation. Providing supernormal oxygenation in patients with lung disease has shown an increase in exercise tolerance by relieving or decreasing the sensation of dyspnea, likely by suppressing the carotid body response.[60]

Pharmacologic Treatments

Pharmacologic treatments for dyspnea caused by lung cancer have included bronchodilators, corticosteroids, anxiolytics, antidepressants, and opioids. One retrospective study[58] at a medical center specializing in cancer assessed the resource utilization associated with the management of dyspnea caused by lung cancer in 45 patients. The most common therapies administered in the emergency department were oxygen (31%), β_2-agonists (14%), antibiotics (12%), and opioids (11%).[58]

Inhaled Bronchodilators and Corticosteroids: Standard bronchodilators such as β_2-agonists, anticholinergics, and aerosolized corticosteroids are commonly prescribed to lung cancer patients who also have underlying COPD or asthma. There is no evidence that the presence of lung cancer induces bronchospastic disease. However, the onset of lung cancer in patients with underlying obstructive lung diseases usually aggravates symptoms of preexisting obstructive lung disease. There are not many studies to prove a beneficial effect of bronchodilators in patients with lung cancer. However, a prospective study[48] of 100 terminally ill cancer patients (49 patients with lung cancer) observed that the potentially correctable causes of dyspnea included bronchospasm (in 52%) and hypoxia (in 40%). It is important to ensure that bronchodilator therapy is optimized if the patient has obstructive airways disease. Inhaled furosemide also has been studied in patients with obstructive airways disease and in those with terminal dyspnea, and has been shown to improve airflow and exercise tolerance.[61]

Systemic Corticosteroids: The role for systemic corticosteroids is limited for relieving dyspnea from lung cancer. As is the case with bronchodilator therapy, patients with obstructive airways disease may benefit from systemic corticosteroids to decrease mucus production and inflammatory changes in the airway mucosa. It is also important to recognize that patients with lung cancer who are actively receiving specific therapy, such as radiotherapy and/or chemotherapy, may experience varying degrees of dyspnea.[62] This may reflect pulmonary toxicity to such therapies. Pulmonary parenchymal toxicity leading to dyspnea may require discontinuation of tumor-specific therapies and administration of systemic corticosteroids.

Analgesics: Dyspnea has been shown to be more severe in patients with severe pain.[46,50] Dyspnea caused or aggravated by cancer-induced pain may respond to nonnarcotic analgesic therapy. However, dyspnea due to pain caused by bony metastases, malignant pleural effusions, or fatigue is unlikely to respond to conventional analgesic therapy. Such circumstances require more aggressive pain control, including palliative radiotherapy for skeletal metastasis. In patients with dyspnea caused by milder pain and discomfort, nonnarcotic analgesics should be tried for a brief period.

Anxiolytics and Antidepressants: Anxiety can aggravate the sensation of dyspnea, but studies of anxiolytics used to treat dyspnea, including benzodiazepines, phenothiazines and buspirone, have not shown benefit over placebo. Similarly, although antidepressants such as nortriptyline, desipramine, paroxetine, and selective serotonin reuptake inhibitors can be used to treat depression, their use to treat dyspnea is not supported.[48]

Opioid Treatment: Opioids are frequently used to alleviate dyspnea in patients with advanced lung cancer, advanced obstructive airway disease, and cardiac failure.[63] A wide variety of opioid analgesics have been used to control both dyspnea and pain in patients with cancer of the lung and other organs. They include hydrocodone, acetaminophen with codeine, morphine, oxycodone, hydromorphone, and others. Opioids have been used orally, parenterally, and by aerosol, although the latter technique has not produced reliable results.[64] It is unclear if all opioids

are equally efficacious in decreasing dyspnea perception in patients with lung cancer. In a study[46] of 104 patients with lung cancer, opioids administered to treat pain did not decrease dyspnea, although one study[65] showed an improvement in dyspnea when a subcutaneous dose of morphine 50% above the pain-relief dose was administered.

An open, uncontrolled study[63] evaluated the role of oral morphine to relieve dyspnea in 15 patients with advanced malignancy receiving standard care and noted that regular, titrated oral morphine may improve dyspnea but can cause significant short-term adverse effects. The relief of dyspnea is usually noted within 24 h, and the relief stays at a plateau with continued opioid therapy.[63]

A metaanalysis[66] of 18 RCTs revealed a statistically significant positive effect of opioids on breathlessness. Oxygenation and carbon dioxide did not change in the 11 studies that included those variables. Some patients withdrew because of nausea, vomiting, and/or constipation. The effect of nebulized opioids was not different from placebo. A subsequent RCT[67] also showed significant improvement in refractory dyspnea using a sustained-release, low-dose, oral morphine.

Continuous IV infusion of morphine has been used in patients with terminal lung cancer with severe dyspnea, unrelieved by oxygen, nonnarcotic drugs, or intermittent bolus narcotics.[68] Even when patients achieve good dyspnea relief, the major side effect is sedation. Health-care providers, the patient, and family should be cognizant of the possibility of severe hypoventilation and hypercarbic respiratory failure and death. This side effect has been described also with inhaled morphine.[69] Nonetheless, the ethical principle of "double effect" supports the palliative use of opioids to relieve symptoms such as dyspnea and pain.[47]

Invasive Approaches to Palliation of Dyspnea

Airway Obstruction: Primary lung cancer or metastatic malignancy in the thoracic cage can lead to airway obstruction as a result of tumor growth inside the airway lumen (intraluminal or intramural), airway wall (luminal or mural), or outside the airway lumen (extraluminal or extramural).[70–73] Central airway obstruction refers to significant obstruction of the trachea and main bronchi. Patients with this complication are more likely to have significant dyspnea and hemoptysis, at times life threatening, and require urgent therapy. Onset of stridor and its progression indicates the possibility of impending airway obstruction. The obstruction caused by the neoplasm can be aggravated by associated factors such as excessive mucous secretion and formation of mucous plugs, and blood and blood clots in the airway lumen. Palliative bronchoscopy plays a major role in such situations.

Clinical evaluations including imaging techniques and flow-volume curves may indicate the degree of airway obstruction. However, bronchoscopy is the singularly important technique for the diagnosis as well as therapy of airway obstruction. Bronchoscopic visualization usually determines the nature and severity of the obstruction and helps determine the appropriate diagnostic and therapeutic procedures.

Almost all bronchoscopic therapies are palliative in patients with lung cancer involving the major airways. A small number of patients with *in situ* lung cancer who cannot undergo resection because of comorbid conditions may get cured with endobronchial therapies. Bronchoscopic relief of disabling dyspnea is the most beneficial effect of the procedure. The next important symptom that can be treated by bronchoscopy is hemoptysis. Cough relief by bronchoscopy is less satisfactory because none of the palliative therapies will totally eradicate the tumor that is responsible for the cough.

The type of bronchoscopic therapy should be determined by the type and severity of respiratory symptoms, and the overall condition of the patient. The types of bronchoscopic therapy include endotracheal intubation, bronchoscopic debulking of intraluminal tumor, balloon dilatation, laser therapy, electrocautery, cryotherapy, argon plasma coagulation (APC), endobronchial irradiation (brachytherapy), or airway stent insertion (Table 1).[74] Some patients require a combination of techniques to obtain complete and lasting relief of symptoms.[75] All of these therapeutic techniques will provide significant relief of dyspnea and hemoptysis in the majority of patients.[76] While most of the techniques provide rapid relief of these symptoms, some procedures take a longer time and repeated applications. Expertise in these specialized techniques is imperative.

Endotracheal Intubation: Endotracheal intubation is recommended in a patient who faces impending death because of tracheal obstruction and no therapeutic bronchoscopy is available. As soon as dyspnea is relieved and optimal oxygenation is accomplished, bronchoscopic visualization should be performed to assess the proper placement of the endotracheal tube and the extent of airway obstruction. Endotracheal intubation is useful in both luminal and extraluminal obstructions.[77–80] The risk of bleeding during endotracheal intubation and the difficulty of intubation should be recognized. Therapeutic endotracheal intubation is temporary, and plans should be made for more permanent relief of symptoms.

Table 1—*Palliative Bronchoscopic Therapies

Therapy	Type of Lesion	Type of Bronchoscope	Rapidity of Positive Result	Repeatability of Therapy	Complications
Mechanical debridement	Intraluminal or submucosal	Rigid or flexible	++++	+++	Hemorrhage
Laser	Intraluminal	Rigid or flexible	++++	++++	Hemorrhage, fistula
APC	Intraluminal	Rigid or flexible	++++	++++	Hemorrhage, fistula
Brachytherapy	Intraluminal or submucosal	Flexible	+	+	Hemorrhage, fistula
Cryotherapy	Intraluminal	Rigid or flexible	++	+++	Necrotic tissue may obstruct airway lumen
Balloon dilatation	Intraluminal or submucosal	Rigid or flexible	++++	++++	Minimal
PDT	Intraluminal	Flexible	++	+++	Necrotic tissue; therapy may obstruct airway lumen
Electrocautery	Intraluminal	Rigid or flexible	+++	++++	Hemorrhage, fistula
Stent	Intraluminal or compression	Rigid or flexible	++++	+++	Stent migration, extrinsic granulation tissue, infection, stent malfunction

*Adapted from Prakash.[358] + = least effective therapeutic response; ++ = modest rate of therapeutic response; +++ = excellent therapeutic response; ++++ = most rapid or repeatable therapeutic response.

Bronchoscopic Debridement: Bronchoscopic debridement (resection) of intraluminal tumor can quickly relieve airway obstruction and resultant dyspnea. In many patients, this technique alone may suffice to relieve dyspnea. The rigid bronchoscope is much quicker than the flexible bronchoscope in accomplishing this task. The most important advantage of the rigid bronchoscope is that the instrument itself can be used as a tumor-debulking instrument, much like coring an apple. The other important advantages of the rigid bronchoscope include the ability to secure and maintain the airway, delivery of oxygen and anesthetic gases, and the ability to employ other therapeutic techniques. One retrospective study[77] evaluated the role of urgent rigid bronchoscopy, including Nd-YAG laser resection or stenting, in patients with acute respiratory failure from malignant central airways obstruction. Airway obstructions were caused by lung cancer in 14 patients. Urgent therapeutic bronchoscopy permitted immediate discontinuation of mechanical ventilation in $>$ 52% of these patients (including 19 patients with benign lesions).[77] A study[73] of 143 patients who underwent 309 stent procedures of which 67% were for malignant disease observed that 82% required urgent or emergency intervention, and 77% had compromise of more than three fourths of the airway lumen. Flexible bronchoscopic debridement requires longer time because of the limitation of the ancillary instruments to adequately resect the tumor. Bronchoscopic debridement is best suited for intraluminal tumor growth and not applicable for therapy of extrinsic compression. Rigid bronchoscopy is best accomplished under general anesthesia or deep IV sedation. The major complication of simple bronchoscopic debridement is the bleeding associated with tumor resection.

Balloon Dilatation: Bronchoscopic balloon dilatation has a limited role in the treatment of major airway obstruction by malignant tumors.[81,82] This technique is a preparatory procedure to dilate the obstructed airway prior to placement of stents. Balloon dilatation through either the flexible or rigid bronchoscope is best suited for stenoses that are short in length.[83] Complications are few; excessive dilatation has the potential to cause airway rupture.

Laser: Bronchoscopic laser therapy is useful in relieving obstruction caused by intraluminal lesions. It has no role in treatment of obstruction caused by extraluminal tumors. Either rigid or flexible bronchoscopy can be used for application of laser energy, even though the former accomplishes this more quickly.[84] Rigid bronchoscopy is recommended for the management of large tumors in the trachea and mainstem bronchi. Once the laser accomplishes the coagulation of the tumor, a rigid bronchoscope itself or large forceps can be deployed to rapidly remove the obstructing tissue. If significant bleeding is encountered during the procedure, a rigid bronchoscope can provide quick control of this problem by tamponading the bleeding source as well as permitting suctioning of large quantities of blood from the airway. Currently, various types of lasers are available for treatment of endobronchial tumors. These include Nd-YAG, potassium titanyl phosphate, and CO_2 laser units. The Nd-YAG laser is the most commonly employed type of laser to treat malignant

lesions of major airways. Immediate relief of airway occlusion and obstructive symptoms can be expected in > 90% of patients. Laser therapy also helps in preparing the airway for insertion of airway stents as well as brachytherapy catheters. Complications from laser therapy include endobronchial fire, severe hemorrhage, perforation of the airway, pneumothorax, and pneumomediastinum.[85–88]

Electrocautery: Electrocautery application through either a rigid or flexible bronchoscope employs alternating electrical current to produce coagulation and vaporization of endobronchial lesions.[89–94] The result from electrocautery technique is similar to that achieved with laser therapy. Immediate relief of dyspnea can be achieved with electrocautery in 55 to 75% of patients.[90,93,95–97] A prospective study[98] evaluated the impact of bronchoscopic electrosurgery on the need for bronchoscopic Nd-YAG laser in patients with symptomatic airway lesions and observed that of the 47 bronchoscopic electrosurgery procedures, 42 procedures (89%) were successful in alleviating the obstruction, thus eliminating the need for laser. All procedures were performed in the outpatient bronchoscopy suite with the patient under conscious sedation (morphine and midazolam) and topical anesthesia with 2% lidocaine.[98] The advantages of electrocautery include less-expensive equipment (compared to laser) and the ease of use through flexible or rigid bronchoscope. Complications are similar to those encountered in laser ablation, and inadvertent delivery of electrical shock to the operator or patient.

APC: APC applies a technique to achieve noncontact electrocoagulation of viable tissue. APC utilizes electrically conductive argon plasma as a medium to deliver high-frequency current via a flexible probe to coagulate tissue. APC devitalizes tissue gradually by producing temperatures that coagulate and desiccate tissue. One retrospective study[99] of 60 patients with bronchogenic carcinoma (n = 43), metastatic tumors of airways (n = 14), or benign bronchial disease (n = 3) employed APC therapy via flexible bronchoscopy to control hemoptysis, symptomatic airway obstruction, or both obstruction and hemoptysis. Patients with endoluminal airway lesions had an overall decrease in mean obstruction of 18 ± 22%. All patients with obstructive lesions had symptom improvement, and symptom control was maintained during a median follow-up period of 53 days.[99] The advantages of APC include low cost (compared to laser), noncontact mode of therapy, easy portability of equipment, and ease of use. The noncontact feature of APC allows rapid coagulation with minimal manipulation of and mechanical trauma to the target tissue. Complications are similar to those described for laser and electrocautery.

Cryotherapy: Cryotherapy employs cryoprobes through either a rigid or flexible bronchoscope to apply extremely cold temperatures to tumor tissue so that malignant cells are devitalized and killed by repeated cycles of cold application followed by thawing. Nitrous oxide or liquid nitrogen is most commonly used to produce temperatures of − 80°C.[100–102] As is the case with laser and electrocautery, cryotherapy can be used to treat only intraluminal tumors. Subjective improvements have been observed in > 75% of patients with malignant airway lesions.[103,104] In a study[105] of 476 consecutive patients with obstructive airway tumors treated by cryotherapy, significant improvements in hemoptysis, cough, and dyspnea were observed in 76%, 69%, and 59%, respectively. In this study,[105] the overall complication rate was 3.5% and included bleeding, pneumothorax, respiratory distress, and cardiac events. Repeat bronchoscopy is needed for continued therapy in many patients. Cryotherapy equipment is less expensive and easier to use than laser therapy. The major disadvantage of treating large tumors in major airways is that cryotherapy requires repeated applications and far more time to relieve obstruction. Therefore, cryotherapy is not an ideal technique to acutely relieve dyspnea caused by major airway lesions.

Brachytherapy: Brachytherapy is the term used to describe intraluminal radiation therapy to treat malignant tumors within the airways. The flexible bronchoscope is used to insert and place the brachytherapy catheter into the affected airway lumen. Brachytherapy can be used to treat airway obstruction caused by intraluminal, luminal, as well as extraluminal cancer located immediately adjacent to the airway.[106–110] Usually, brachytherapy is aimed at palliating malignant airway lesions in patients who have already received a maximum dose of external-beam radiation. Brachytherapy can also be used as a stand-alone therapy or as complimentary or combined therapy following external beam radiation therapy, airway debulking (laser, mechanical removal), or after airway stent placement. Even though earlier experience demonstrated that brachytherapy alone resulted in adequate symptomatic relief in a considerable number of patients,[11,12,111–115] current evidence indicates that brachytherapy as a complimentary therapy provides better relief of dyspnea and other symptoms than brachytherapy alone.[112,116–123] Relief from dyspnea can be expected in > 60% of patients and can last for weeks to months. A phase II study[124] involving 30 patients with stage-III NSCLC treated with 60 Gy x-ray therapy also used brachytherapy and reported palliation rates of 80% for dyspnea and 43% for

cough. One prospective study[123] of 342 patients with endobronchial tumors treated by the combination of external-beam radiation therapy (30 to 60 Gy) and concomitant brachytherapy during weeks 1, 3, and 5 observed a response rate of 85% for cough and 86% for dyspnea. Major complications of brachytherapy include fistula formation between the airways and other thoracic structures in up to 8% of patients. The risk of massive hemoptysis increases dramatically when a fraction size of 15 Gy is used.[121]

Photodynamic Therapy: Photodynamic therapy (PDT) consists of deploying tumor-tagging compounds such as hematoporphyrin derivative and porfimer sodium. When tumor cells thus tagged are exposed to the light of the proper wavelength, chemical reactions cause death of malignant cells through production of toxic radicals. Patients with small (< 3 cm^2) epithelial cell malignancies are most likely to benefit from this therapy.[125] Complete response lasting for > 12 months has been observed in 50% of patients.[126,127] The effectiveness of PDT for symptom palliation, and survival benefit has been evaluated in patients with advanced inoperable bronchogenic cancer and endobronchial luminal obstruction. Among 100 such patients, 82% had received prior chemotherapy and/or radiotherapy. On an average, endoluminal obstruction diminished from 86 to 18%. This study suggests that PDT is effective in palliation of inoperable advanced lung cancer in a subset of patients. One study[128] has reported on the therapeutic efficacy of combined brachytherapy and PDT in patients with bulky endobronchial lung cancer. Another study[129] of 37 consecutive cases of inoperable cancer, either primary or metastatic to lung, used porfimer sodium as a primer before PDT and observed 32 complete or partial responders and five treatment failures.

When PDT alone is used, however, the relief from obstruction is slow[130]; because of this slow response, there is no major role for PDT in the treatment of obstructing lesions of central airways. In locally advanced and symptomatic lung cancer, PDT with or without radiotherapy can contribute to the relief of airway obstruction and hemoptysis, but it has not exhibited a survival advantage when compared with current treatments, such as Nd-YAG laser therapy or radiotherapy alone.[131] Complications from PDT include phototoxicity, hemoptysis, and obstruction of bronchi by thick necrotic material.

Stents: Airway prostheses or stents made of metal, silicone, or other materials can be used to relieve airway obstruction caused by malignant tumors.[132–137] Stent therapy is indicated in both intraluminal and extraluminal major airway obstructions. Stent therapy is more effective in patients with tracheal or main bronchial obstruction than in those with airway diseases that involve lobar and more distal bronchi. Either silicone or metallic stents can be used to treat malignant airway lesions. Malignancy involving the main carina is best treated with silicone stents designed for this anatomic location.[138] Uncovered metallic stents are not recommended in patients with malignant airway lesions because the growth of cancer through the wire mesh negates the benefits of stent placement.[139] After bronchoscopic debridement of tumor and laser therapy, stent placement should be considered to maintain long-term airway patency. Even though bronchoscopy is frequently used to deploy airway stents, tracheobronchial stent insertion can be accomplished using fluoroscopic guidance alone.[140]

In a report[136] on clinical experience over a 10-year period with 307 Gianturco metal stents placed via the flexible bronchoscope in 162 patients (144 primary lung tumors, 18 secondary malignancy), the average survival following stent insertion was less for primary lung cancer than for secondary disease (103 days vs 431 days, $p < 0.001$). In a study[141] of 22 patients with severe malignant strictures, 34 airway stents were implanted as a temporary measure before patients received irradiation or chemotherapy. Significant improvements of dyspnea and partial oxygen pressure were observed; and in 50% of patients, the stents were removed after successful tumor-specific therapy.[141] In another study,[77] among 34 patients with inoperable malignant airway stenosis, covered metallic stents were implanted on emergency basis in 19 patients (56%) because of life-threatening airway obstruction. Immediate relief of dyspnea was achieved in 82% of the patients, and significant improvements were observed in airway diameter, vital capacity, and peak expiratory flow.[77]

All silicone stents require rigid bronchoscopy for their insertion, manipulation, and removal,[142–144] whereas metal stents can be inserted with the aid of flexible bronchoscopy and/or fluoroscopic guidance. Frequently, multiple stents and multiple procedures will be necessary to maintain a satisfactory airway.[73] Complications from silicone stents include migration of stent and inspissations of thick mucus within the stent lumen. Metallic stents are more likely to promote growth of granulation tissue.

Surgery: Surgical resection of malignant tracheobronchial tumors should be considered when unusual types of malignant tumors are encountered. The types of tumors that are amenable to resection and anastomosis include carcinoid, cylindroma, and mucoepidermoid tumors. The length of involvement of trachea or major bronchus

should be short enough for the surgeon to resect the tumor so that the anastomotic site is free of malignant cells. Malignancy involving the main carina is usually deemed advanced and thus unresectable. Such patients, if symptomatic, benefit from the bronchoscopic techniques described above. In recent years, surgical resection and reconstruction of the main carina is being performed in patients who can tolerate surgery.[145–147]

Recommendations

12. For all lung cancer patients who complain of dyspnea, it is recommended that they be evaluated for potentially correctable causes, such as localized obstruction of a major airway, a large pleural effusion, pulmonary emboli, or an exacerbation of coexisting COPD or congestive heart failure. If one of these problems is identified, treatment with appropriate methods is recommended. Grade of recommendation, 1C

13. For all lung cancer patients whose dyspnea does not have a treatable cause, opioids are recommended. Also recommended are other pharmacologic approaches such as oxygen, bronchodilators, and corticosteroids. Grade of recommendation, 1C

14. For all lung cancer patients with dyspnea, it is recommended that nonpharmacologic and noninterventional treatments be considered, such as patient and family education, breathing control, activity pacing, relaxation techniques, fans, and psychosocial support. Grade of recommendation, 2C

Palliation of Cough

Cough is a frequent and distressing symptom in patients with lung cancer. Cough can be dry or associated with sputum production. Involvement of any part of the respiratory system can lead to cough. Among the initial symptoms of lung cancer, cough is present in $> 65\%$ and productive cough in $> 25\%$ of patients.[148] Cough can be the presenting or leading symptom of lung cancer. It is more likely among patients with lung cancer originating in the airways. As in the treatment of dyspnea, the principal cause of the cough needs to be identified and treated appropriately (such as pleural involvement by the tumor, and infection). Other factors can contribute, such as esophageal reflux, coexisting COPD, or congestive heart failure, and should be addressed.[7]

Even if complete cessation of cough is not possible, significant control of cough may help patients enjoy cough-free periods. In late stage cancer when no specific therapy can address the cancer itself, control of bothersome cough becomes a problem. The following commentary is a brief summary of methods available to manage cough in the setting of lung cancer; a more detailed review was recently published as part of the American College of Chest Physicians evidence-based clinical practice guidelines for cough.[7]

Pharmacologic Agents

Cough Suppressants: Nonopioid cough suppressants may work in a small group of patients with advanced lung cancer. Occasionally, even opioid-resistant cough may respond to agents such as the peripherally acting nonopioid drug benzonatate.[149]

Bronchodilators: Bronchospasm can cause or contribute to cough. If the patient with lung cancer also has underlying bronchospastic obstructive airways disease, then standard bronchodilator therapy may help alleviate the cough.

One study[150] tested the role of inhaled sodium cromoglycate in 20 patients with NSCLC and cough resistant to conventional treatment. The patients were randomized to receive, in a double-blind trial, inhaled sodium cromoglycate or placebo. The results showed that inhaled sodium cromoglycate reduced cough in all patients with NSCLC.

Opioids: Opioids are the best cough suppressants in patients with lung cancer. Codeine is the most widely used opioid for cough suppression. In advanced stages of lung cancer, standard nonopioid cough suppressants may not control the cough. Intractable or troublesome cough should be treated with opioid agents. Caution should be exercised in prescribing graduated doses of these drugs because of the risk of respiratory depression and hypoventilation.

A double-blind RCT[151] regarding the treatment of nonproductive cough was performed in 140 adults with primary lung cancer or metastatic cancer of the lungs. The therapeutic efficacy and the tolerability of a 7-day treatment with levodropropizine drops (75 mg tid) were evaluated in comparison with dihydrocodeine drops (10 mg tid). Efficacy was assessed on the basis of cough severity scores, number of night awakenings due to cough, and overall estimate of antitussive efficacy. Tolerability was evaluated by laboratory results, vital signs, and any adverse event occurring during the clinical trial, including the presence or absence of somnolence. Subjective cough severity was significantly reduced during treatment with levodropropizine and dihydrocodeine, the antitussive effect, and its time profile being similar for both drugs. Also, according to the investigator's evaluation, both levodropropizine and

dihydrocodeine produced a significant decrease in cough severity. Concurrently with the relief of cough, the number of night awakenings was decreased significantly by both drugs, with no difference between the two treatments. No change in laboratory test values was considered clinically relevant, and vital signs were not clinically affected. The number of patients reporting adverse events was similar in the levodropropizine (n = 6) and dihydrocodeine (n = 4) group. However, the percentage of patients with somnolence in the group receiving levodropropizine (8%) was significantly lower as compared with that of the dihydrocodeine group (22%). These results confirm the antitussive effectiveness of levodropropizine and suggest a more favorable benefit/risk profile when compared to dihydrocodeine.[151] However, levodropropizine is not available for use in the United States.

Corticosteroids: There are no studies on steroids specifically for cough in lung cancer. If cough is caused by radiation-induced lung problems, then high-dose corticosteroid therapy may relieve a significant degree of cough.

Lidocaine: There are no studies on the role of inhaled lidocaine on cough in patients with lung cancer.

Chemotherapy: Newer agents such as gemcitabine and cisplatin-based chemotherapy have been studied with regard to their specific effects on cough frequency and severity among patients with NSCLC. Gemcitabine reduces cough in 44% of subjects so treated, and moderate or severe cough was improved in 73%.[152,153] Treatment of SCLC patients with chemotherapy is reported to improve cough in 7 to 80%.[154–156]

Nonpharmacologic Treatment of Cough

Surgery: No systematic studies have addressed the effect of surgical resection of NSCLC on the specific symptom of cough, but clinical experience suggests that cough will improve when the cancer is resected. Palliative ipsilateral high intrathoracic vagotomy immediately below the origin of the recurrent laryngeal nerve was reported in a small case series[157] to improve cough when an exploratory thoracotomy was done but the cancer was not resectable.

Radiation Therapy: Two RCTs in the United Kingdom were designed to assess the effect of different external-beam radiation programs on specific symptoms, including cough.[158,159] The first study[158] was a comparison of a two-dose schedule (8.5 Gy each) to longer conventional external-beam multifractionated treatment; and the second study[159] was a comparison of two 8.5-Gy fractions to a single 10-Gy fraction. Relief of cough occurred in 48 to 95% of patients treated with one or another of these schedules.

Endobronchial Treatment Methods: Laser and electrocautery methods of endobronchial treatment are usually offered for the purpose of palliating dyspnea or hemoptysis. However, various series[91,111–113,116,122,160,161] that have reported on cough have noted improvement in 51 to 90% of patients. All such reports are case series; there are no RCTs that have specifically analyzed cough as an outcome variable for such methods of palliating symptoms. Brachytherapy is the one endobronchial treatment modality that specifically includes a mention of cough palliation.[106,111–113,116,122]

Recommendations

15. For all lung cancer patients who have troublesome cough, it is recommended that they be evaluated for treatable causes. Grade of recommendation, 1B

16. For all lung cancer patients who have troublesome cough without a treatable cause, it is recommended that opioids be used to suppress the cough. Grade of recommendation, 1B

Palliation of Bone Metastases

Metastatic lung cancer to bone is a manifestation of stage IV disease; thus, cure essentially is not possible, and care for the patient will be palliative in nature. Elimination or reduction of pain is the primary goal of treatment. There are no randomized prospective studies that directly compare radiation to pharmacotherapy for the management of pain due to bony metastases. If a metastasis occurs in a weight-bearing bone, prophylactic surgical stabilization should be considered before a pathologic fracture occurs.

Pain caused by bone metastases has multiple causes. Periosteal inflammation and elevation is the most common mechanism behind the pain from bone metastases. Lung cancer metastases to bone are predominantly lytic. After controlling pain with pharmacologic methods, treatment should be directed at managing the inflammation. External-beam radiation should therefore be considered as the initial nonpharmacologic method. This technique uses energy to diminish the local inflammatory response and thereby eliminates the source of the pain. Other nonpharmacologic methods to manage pain

from bone metastases include radioactive isotope infusion, supportive measures for pain management, and direct local management (such as surgery and nerve blocks).

A majority of patients with symptomatic bone metastases obtain some pain relief with a low-dose, brief course of palliative radiation therapy. One half of the responding patients may experience complete pain relief.[162] For short-term improvement in bone pain, 8 Gy in a single fraction is as effective as higher doses.[158,159] Single-fraction radiotherapy is less expensive than multiple-fraction radiotherapy, and it is more convenient from the patient's perspective. A systematic review and metaanalysis[163] of 11 randomized trials involving 3,435 patients treated with single-fraction radiotherapy vs multiple fraction radiotherapy was conducted in 2005. Although the trials included patients with painful bony metastases from multiple primary sites, the majority were from prostate, breast, and lung cancers. Lung cancers compromised 19.9% of the total. The overall response for relief of pain was 60% for patients treated with a single fraction, and 59% for patients treated with multiple fractions. Complete pain relief was accomplished in 34% of patients treated with a single fraction vs 32% for those treated with multiple fractions (odds ratio [OR], 1.11; 95% confidence interval [CI], 0.94 to 1.30). Although a single dose of radiation is effective, the duration of pain relief is less than with higher fractionated doses of radiation therapy. Retreatment was needed in 21.5% vs 7.4% for patients treated with multiple fractions (OR, 3.44; 95% CI, 2.67 to 4.43).[163] The pathologic fracture rate was 3% among patients treated with a single fraction, compared to 1.6% for those treated with multiple fractions (OR, 1.82; 95% CI, 1.06 to 3.11). If large fields are required, local inflammation and edema may be a problem with a high single dose. A high single dose is appropriate for small extremity fields, provided internal organs are not included, and for patients whose expected survival is only a few months.

Bisphosphonates have assumed an important role in the treatment of patients with bone metastases, especially since the introduction of zoledronic acid. Bisphosphonates prevent bone resorption at sites of bone remodeling. In three large randomized phase III trials[164] with $>$ 3,000 patients, 4 mg of zoledronic acid administered during a 15-min infusion was found to be a very effective treatment for bone metastases in patients with lung cancer, prostate cancer, and other solid tumors. Zoledronic acid is generally well tolerated, but it can be associated with increases in serum creatinine that require monitoring of renal function.[164] Zoledronic acid has also been shown to prevent skeletal related events (pathologic fractures, spinal cord compression, hypercalcemia, or pain requiring surgery).[165] In a multicenter RCT comparing zoledronic acid to placebo, there were 378 patients with NSCLC among the 773 subjects with solid tumors that had metastasized to bones. The incidence of skeletal related events was significantly reduced among patients treated with zoledronic acid ($p = 0.039$).[166]

Adjunctive therapy with disodium pamidronate has demonstrated good therapeutic response by itself, but more importantly when it is used in combination with radiotherapy for bony metastases. Response rates of 92% were seen in a randomized study[167] with external-beam radiation and pamidronate, vs radiation alone (83%), pamidronate alone (85%), or pamidronate in combination with chemotherapy (87%).

IV radioisotope infusion can also be used to manage pain from bony metastases, and it is especially useful for patients with widespread bony metastases. In a systematic review, Bauman et al[168] identified six randomized phase III trials, two randomized phase II trials, and one randomized crossover trial of ^{89}Sr. Another three randomized phase III trials and two randomized phase II trials of ^{153}Sm were part of their review, as were additional randomized trials of rhenium, ^{117m}Sn, and ^{32}P. As is true for most issues regarding the palliative management of a specific problem, the study groups contained mixtures of primary organ sites of the cancers. In these studies, only 5 to 10% of the patients had primary lung cancer, with the majority of other patients having breast or prostate primary sites. In most of these studies, pain relief in existing sites of metastases was significantly longer for patients treated with radiopharmaceuticals. This led to the conclusion that single-agent radiopharmaceuticals (^{89}Sr and ^{153}Sm) should be considered as a possible option for the palliation of multiple sites of bone pain from metastatic cancer, when pain control with conventional analgesic regimens is unsatisfactory, and when activity on a bone scan of the painful lesions is demonstrated.[168]

Pathologic fractures may occur when lung cancer metastasizes to bones. Fracture of long bones significantly impairs functional status and quality of life. The femur is at special risk because of its role in weight bearing, and surgical intervention may be needed. Other bones that may require palliative surgical intervention include the tibia, hip (proximal femur plus acetabulum), vertebrae, and the humerus.

Prophylactic surgery is recommended for the following situations when long bones are involved: persistent or increasing local pain despite the completion of radiation therapy; a solitary well-defined lytic lesion circumferentially involving $>$ 50% of the

cortex; involvement of the proximal femur associated with a fracture of the lesser trochanter; and diffuse involvement of a long bone.[169] Contraindications to surgical treatment of metastatic disease to long bones include a survival expectancy < 4 weeks and a poor general condition that is an obstacle to a safe operation.[170]

No randomized, prospective, controlled trials have compared surgery alone, surgery plus radiation therapy, or radiation therapy alone for metastatic long bone disease. Generally, however, postoperative radiotherapy is recommended regardless of the type of surgical procedure chosen for bony metastases.[171] All series that have analyzed operative intervention have included metastatic bone disease from multiple primary organ sites, with breast cancer as the most common. Lung cancer usually is the second most common primary site in reported series. A retrospective study[170] of 60 patients compared adjuvant surgery plus radiation therapy (35 sites) to 29 sites that were treated with surgery alone. Univariate analysis revealed that combined therapy ($p = 0.02$) and prefracture functional status ($p = 0.04$) were the only predictors of patients achieving a good functional status after surgery. On multivariate analysis, only postoperative radiation therapy was significantly associated with attaining a good level of function after surgery ($p = 0.02$).[170]

Intramedullary nailing is generally regarded as the preferred operative approach to deal with metastatic long bone disease. Standard total joint arthroplasty of the proximal femur is very useful for pathologic fractures of the femoral head and neck and for intertrochanteric fractures that have metastases in the neck and head of the femur.[171] Operative intervention for metastatic fractures of long bones provides a good functional result in approximately 80 to 85% of patients; a good analgesic effect is accomplished in nearly all patients.

In summary, pain relief is complete after radiotherapy for bony metastases in only one-third of patients. An approach to the management of bony metastases that is multifactorial (radiotherapy, bisphosphonates, and radioisotopes) coupled with analgesics is recommended. Because such combination approaches are usually successful, older methods of treatment (calcitonin, percutaneous ethanol injection into metastatic lesions, and embolization of the bone tumor vasculature) have not been reported extensively in recent years.

Recommendations

17. For patients with lung cancer who have pain due to bone metastases, external radiation therapy is recommended for pain relief. A single fraction of 8 Gy is as effective as higher fractionated doses of external radiation therapy for immediate relief of pain. Grade of recommendation, 1A

18. For patients with lung cancer who have pain due to bone metastases, higher fractionated doses of radiation therapy provide a longer duration of pain relief, less frequent need for retreatment, and fewer skeletal-related events than does a single fraction. Grade of recommendation, 1A

19. For patients with lung cancer who have painful bone metastases, bisphosphonates are recommended together with external radiation therapy for pain relief. Grade of recommendation, 1A

20. For patients with lung cancer who have painful bone metastases refractory to analgesics, radiation, and bisphosphonates, radiopharmaceuticals are recommended for pain relief. Grade of recommendation, 1B

21. In patients with lung cancer who have painful bone metastases to long and/or weight-bearing bones and a solitary well-defined lytic lesion circumferentially involving > 50% of the cortex and an expected survival > 4 weeks with satisfactory health status, surgical fixation is recommended to minimize the potential for a fracture. Intramedullary nailing is the preferred approach, especially for the femur or the humerus. Grade of recommendation, 1C

Palliation of Brain Metastases

Brain metastases are more common from lung cancer than from any other primary site. Brain metastases from NSCLC occur in approximately one third of patients.[172] They are the presenting clinical problem in 10% of SCLC patients at the time of diagnosis, and the reported cumulative incidence in SCLC at 2 years is > 50%.[173] If patients with brain metastases are not treated, neurologic deterioration occurs quickly.[174,175] Brain metastasis has generally been considered as one manifestation of the terminal stage of cancer. This view holds true in many cases. However, patients with limited numbers of metastatic lesions have a considerably longer survival, particularly when the systemic cancer is controlled. The methods available to treat patients with metastatic lung cancer to the brain include the following: (1) systemic glucocorticoids, used to ameliorate the brain edema that typically accompanies intracranial metastases; (2) whole-brain radiation therapy (WBRT); (3) surgical resection of the metastasis; (4) stereotactic

radiosurgery; (5) chemotherapy; and (6) a judicious combination of these treatments.

Corticosteroids: Systemic glucocorticoids are known to improve neurologic function only for a short time (maximum, 1 month).[176] Two thirds of patients will have improvement in neurologic signs and symptoms with the use of glucocorticoids.[177] Dexamethasone is the most commonly used glucocorticoid because it has minimal mineralocorticoid activity as compared with other steroids. Conventional dosing with dexamethasone for brain tumor edema is ≥ 16 mg/d.[178–180] When dexamethasone is used in these doses for > 1 month, serious side effects are common.[181] Two consecutive, randomized, double-blind, prospective, controlled trials of patients with brain metastases and Karnofsky scores ≤ 80 compared dexamethasone at 8 mg/d or dexamethasone at 4 mg/d to dexamethasone at 16 mg/d.[182] Lower doses of dexamethasone were equally effective for improvement in quality of life as compared with patients treated with 16 mg/d, with significantly fewer toxic side effects (cushingoid facies, peripheral edema, steroid-induced myopathy) than in the 16 mg/d group ($p < 0.03$). One other study[183] (nonrandomized and nonblinded) also reported on the effect of lower doses of dexamethasone; there were similar benefits from lower doses and fewer toxic side effects. In a small pilot study,[184] 12 patients with intracranial metastases were initially administered 24 mg of dexamethasone IV q6h for 48 h, and then randomized to receive either 4 mg dexamethasone po q6h for approximately 2 weeks during brain irradiation or no further dexamethasone during the radiotherapy. Withholding steroids during the radiotherapy did not result in pronounced deterioration of general performance status or neurologic function at the conclusion of treatment or in reduction in overall survival. A multiinstitutional, prospective trial is needed to perform adequate statistical evaluation of patients regarding the role of steroid therapy in managing intracranial metastases. Until such a study is done, the consensus of opinion holds that dexamethasone at 16 mg/d should be administered for 4 weeks, during the time of WBRT, and that it should then be rapidly tapered and discontinued.

WBRT: Because of the frequency with which brain metastases occur in patients with SCLC, prophylactic cranial irradiation (PCI) is routinely indicated in patients with limited-stage disease who achieve either a complete or a near-complete response in the thorax following combined radiation and chemotherapy. In seven RCTs[185,186] of PCI for SCLC patients, the survival advantage at 3 years was 5.4%, and brain metastases were reduced by 25.3% at 3 years in patients who had achieved a complete remission with chemotherapy. Quality of life data were not collected in any of these trials, but it is likely that there was some improvement in quality of life. When intracranial metastases are known to be present with small cell lung cancer, WBRT is again the primary method for palliating symptoms.

Patients with multiple intracranial metastases from NSCLC are generally treated with WBRT. Median survival with this approach is 3 to 7 months, depending on prognostic factors.[187] Oligometastatic disease (fewer than three metastases) may be treated with surgical resection or radiosurgery followed by WBRT. Four randomized controlled trials[188] have compared PCI with no PCI in NSCLC patients who were treated with the intent to cure. While PCI did reduce the incidence of brain metastases in three of these trials, none of them was associated with a survival advantage of PCI over no PCI.[188] There were no good quality of life data in any of the trials, and toxicity was poorly reported.

Surgical Resection of Brain Metastases: Currently, there are three treatment options available for patients with a known NSCLC and a solitary intracranial metastasis: surgical resection, external-beam WBRT, and stereotactic radiosurgery[189] (see chapter on "Special Treatment Issues") Most often, some combination of these methods of treatment is preferable. Almost all studies of patients with solitary intracranial metastases that have compared two or more methods of treatment have included patients with tumors from a variety of primary sites, not solely lung cancer. Lung cancer is almost always the most common primary site in these studies; SCLC is usually an exclusion criterion. Whereas data analyses are done on the group as a whole, it is reasonable to apply the conclusions to the subset of NSCLC patients with solitary intracranial metastases.

Two randomized, prospective, controlled trials[190,191] have demonstrated a better outcome for a combination of WBRT plus surgical resection of a solitary metastasis over WBRT alone. Surgery is appropriate for a solitary metastasis in patients with good functional status and a surgically accessible lesion. Median survival for the patients treated with combination therapy was significantly better in both studies as compared with WBRT alone. A third randomized trial[192] failed to show a survival benefit from surgery, but more patients with active systemic disease were included in this study. In one[191] of the two studies that showed a significant difference in median survival for the combined approach, the differences were most pronounced for patients with stable extracranial disease.

The rationale for adding WBRT to surgical resection in the setting of a solitary brain metastasis is based on the notion that micrometastases cannot

reliably be detected with current technology. A randomized, prospective, controlled trial[193] that compared postoperative WBRT plus surgical resection to surgery alone demonstrated that recurrence of tumor anywhere in the brain was less frequent in the WBRT group than in the observation group (18% vs 70%, $p < 0.001$). The time to any brain recurrence was also significantly longer in the WBRT group. Overall survival was not different between the two groups; thus, postoperative radiotherapy prevented death due to neurologic causes, but death due to systemic cancer was more frequent.

There are no significant differences among various conventional radiation therapy fractionation schemes (20 Gy in 5 fractions, 30 Gy in 10 fractions, 40 Gy in 20 fractions). A common dose of radiation therapy used is 30 Gy administered at 3 Gy per fraction in 10 fractions. A more protracted schedule is used for patients who have limited or no evidence of systemic disease, or those who have undergone resection of a single brain metastasis, because these patients have the potential for long-term survival or even cure.[194,195] Because of the potential side effects of WBRT in the long-term survivors, the role of WBRT also has been questioned because there has been no overall survival benefit when combined with other treatment modalities. However, the concept of omitting WBRT after focal therapy (*ie*, surgery or radiosurgery), in the hopes of decreasing the number of patients with cognitive decline after radiation therapy, leads to decreased control of intracranial metastases and is not associated with a survival advantage. Treatment with WBRT that uses 3 Gy daily fractionation is not associated with a substantial increase in the long-term risk of dementia.[196]

Stereotactic Radiosurgery: Stereotactic radiosurgery utilizes a stereotactic fixation system and noncoplanar convergent beams that create a very sharp peripheral dose fall-off along the edge of the target. Thus, the surrounding normal tissues are spared while the radiation kills the tumor cells; accordingly, a single large fraction of ionizing radiation can be administered, making this method of treatment an attractive alternative to treat lesions whether surgically accessible or not. Stereotactic radiosurgery is usually restricted to lesions < 3 cm in diameter. Larger lesions, particularly those in the posterior fossa, are a relative contraindication for radiosurgery. The most recent randomized study was to test the role of radiosurgery with or without WBRT.[197] Patients with one to three newly diagnosed brain metastases were randomly allocated either WBRT alone or WBRT followed by a stereotactic radiosurgery boost. There was a survival advantage in the WBRT and stereotactic radiosurgery group for patients with a single brain metastasis. In addition to the survival benefit for patients with a single brain metastasis, data from this study also showed improved performance in all patients with one to three brain metastases who had radiosurgery boost, with or without previous craniotomy and within reasonable size constraints. Thus, WBRT and stereotactic radiosurgery should also be considered for patients with two or three brain metastases.[197] Stereotactic radiosurgery is of special value for patients with a single surgically inaccessible lesion and for patients who are unable to tolerate surgery.

Sneed et al[198] found from a retrospective review that median survival did not differ for patients with brain metastases who were treated with stereotactic radiosurgery alone or stereotactic radiosurgery followed by WBRT (8.2 months vs 8.6 months). When WBRT was added to stereotactic radiosurgery, however, there was a reduction in progression of brain metastases. With the addition of WBRT, only 7% of patients needed salvage brain therapy as compared with 37% if stereotactic radiosurgery was administered by itself ($p < 0.00001$).

No randomized, prospective trials have compared stereotactic radiosurgery to surgery. Many studies[199–203] of stereotactic radiosurgery for patients with intracranial metastases have reported similar median survival times to surgery as reported by others. A retrospective study[204] has demonstrated equal local tumor control rates and equal neurologic death rates between surgery and stereotactic radiosurgery. A prospective but nonrandomized study[205] of patients with lung cancer (both SCLC and NSCLC) demonstrated significantly longer median survival for stereotactic radiosurgery plus WBRT over WBRT alone (10.6 months and 9.3 months vs 5.7 months, $p < 0.0001$). A randomized study[206] of WBRT alone vs WBRT plus stereotactic radiosurgery in patients with two to four intracranial metastases showed significantly improved local control with a trend toward increased survival for WBRT plus stereotactic radiosurgery. Stereotactic radiosurgery can be performed after brain recurrence in patients who previously have had WBRT, surgical excision of a metastasis, or both. Median survival in a case series of lung cancer patients whose brain metastases were treated with stereotactic radiosurgery alone was 13.9 months, 14.5 months for stereotactic radiosurgery plus WBRT, and 10 months for patients treated with stereotactic radiosurgery for recurrent brain metastases.[207]

It is thought that surgical resection is preferred when rapid relief of increased intracranial pressure is needed. The general trend is toward less invasive treatment but improved intracranial tumor control.

Although there has been no randomized study for direct comparison of the local tumor control using surgical resection or radiosurgery, many institutions use radiosurgery for oligometastatic (up to three to four) brain metastases without WBRT. This is because of the potential for long-term side effects of WBRT.

Chemotherapy: The notion that chemotherapeutic agents do not cross the blood-brain barrier is no longer thought to be true for patients with cancers metastatic to the brain, and evidence has indicated that chemotherapeutic agents that are active elsewhere also may be associated with a response of metastatic brain lesions.[208–210] Platinum-based doublet therapy has been reported to produce a 20 to 21% overall objective intracranial response.[211] Another study[212] that included a variety of platinum-based doublet chemotherapy treatment arms after WBRT reported a median survival for the chemotherapy arm of 58.1 weeks vs 19 weeks in the no-chemotherapy arm ($p < 0.001$). Temozolomide is able to cross the blood-brain barrier, and it has been studied as a monotherapeutic agent for treatment of brain metastases. In a study[213] of 134 patients with brain metastases, 82% of whom had lung cancer, response rates for temozolomide plus WBRT were 53% vs 33% for WBRT alone ($p = 0.039$). More data are needed from randomized, prospective trials of chemotherapy for brain metastases before firm recommendations can be made.

In summary, there are many different options for brain metastases based on prognostic factors developed by the Radiation Therapy Oncology Group.[214] Steroids only are recommended for hospice care; WBRT for multiple brain metastases for those with a poor prognosis; for patients with a limited number of metastases in a favorable prognostic group, surgical resection for symptomatic lesions or radiosurgery with or without WBRT can be offered. Newer chemotherapy agents are showing some promise in the treatment of patients with brain metastases from lung cancer.

Recommendations

22. In patients with lung cancer who have symptomatic brain metastases, dexamethasone at 16 mg/d is recommended during the course of definitive therapy with a rapid taper and discontinuation within 6 weeks of completion of definitive therapy (either surgery or radiation therapy). Grade of recommendation, 1B

23. Patients with NSCLC and an isolated solitary brain metastasis should be considered for a curative resection of the lung primary tumor as long as a careful search for other distant metastases or mediastinal lymph nodes has been performed and results are negative. Grade of recommendation, 1C

24. In patients with no other sites of metastases and a synchronous resectable N0,1 primary NSCLC, resection or radiosurgical ablation of an isolated brain metastasis should be undertaken (as well as resection of the primary tumor). Resection of the isolated solitary brain metastases should be followed by WBRT. Grade of recommendation, 1B

Palliation of Spinal Cord Compression

Spinal cord compression by epidural tumor is an important complication for many patients with lung cancer, with an estimated frequency of 5% based on autopsy data.[215] Spinal cord compression can be classified anatomically as intramedullary, leptomeningeal, and extradural. No studies focus on functional results of treating intramedullary or leptomeningeal compression of the spinal cord; paraplegia and death occur rapidly in almost all such cases, and treatment is merely supportive. Epidural spinal cord compression is defined as compression of the dural sac and its contents (spinal cord and/or cauda equina) by an extradural tumor mass. The minimum radiologic evidence for cord compression is indentation of the theca at the level of clinical features, which include any or all of the following: pain (local or radicular), weakness, sensory disturbance, and/or evidence of sphincter dysfunction.

Early detection of epidural metastases with compression of the spinal cord and prompt treatment appears to favorably affect outcome. Back pain is usually present for weeks or months before the onset of neurologic dysfunction. Approximately 60% of cancer patients with the new onset of back pain but with a normal neurologic examination will have spinal metastases that can be detected by radiologic studies.[216] Because the consequences of cord compression are so severe (paraplegia with its attendant complications and altered functional status), sagittal T1-weighted MRI of the entire spine should be done initially in known lung cancer patients with the new onset of back pain. This is the most rapid and cost-effective means of diagnosing spinal cord compression; other studies such as plain films, bone scans, or CT myelograms should be bypassed because they delay the process of a definitive diagnosis.[217]

Corticosteroids: There is good evidence to support the use of high-dose dexamethasone (96 mg/d) for patients with malignant extradural spinal cord compression.[218] This recommendation was based on a systematic review of studies that compared high-

dose dexamethasone to no dexamethasone in malignant spinal cord compression treated with radiation therapy alone. In an RCT,[219] 81% of patients in the high-dose dexamethasone treatment arm who were ambulatory before treatment remained ambulatory after treatment, compared with 63% in the control arm. In patients who are paretic or paraplegic before treatment, there is a lesser likelihood that gait function will be regained, but the addition of dexamethasone appears to improve the probability of regaining the ability to ambulate. A review of the evidence in 2004 led to the conclusion that the optimal dose of dexamethasone was not known.[218]

Significant side effects occur in 11% of those who receive high-dose dexamethasone. High-dose dexamethasone is recommended, however, as an adjunct to radiation therapy and/or surgery to retain or restore ambulation after treatment. The amount of dexamethasone may need to be reduced in the setting of uncontrolled diabetes mellitus or other intolerance of higher-dose therapy.

Radiation Therapy: The evidence for radiation therapy for patients with spinal metastases but no epidural spinal cord compression is fair, and radiation therapy without surgery should be the first line of treatment for patients who are ambulatory and do not have compression of the spinal cord. A combination of high-dose steroids plus radiation should be administered for patients who are not paretic and who are ambulatory.[220]

In a systematic review[163] of three RCTs, 1.9% of 1,102 patients with bony spinal metastases treated with a single fraction of radiotherapy had spinal cord compression, vs 1.4% of 1,104 patients treated with multiple fractions ($p = 0.3$). Among the 739 patients with spinal metastases, cord compression was again not significantly different in the single-fraction groups (5.6%) vs the multiple-fraction groups (4%) [$p = 0.3$].[163] Stereotactic radiosurgery is a combination of stereotactic localization of the treatment site so that multiple radiation beams of equal intensity can deliver a high dose of radiation without exposing normal tissues to excessive doses. In the few centers where stereotactic approaches are utilized, one or two treatment sessions with 8 to 18 Gy are given.[221,222] Most lesions that do not compress the spinal cord can be managed with nonoperative aggressive treatment aimed at shrinking tumor size and halting growth of the tumor.[163]

Surgery: Until recently, surgical intervention was limited to specific indications that included spinal instability, progressive neurologic deterioration from bony collapse and compression, intractable pain, and failure of conservative treatment.[220] Posterior laminectomy alone was once the surgical intervention of choice, but it was associated with a high rate of spinal instability and inferior ambulatory outcomes compared with radiation therapy alone. An anterior approach to the vertebral body with removal of tumor, immediate circumferential decompression of the spine, and reconstruction with stabilization of the spine has the advantage of maintaining the structural integrity of the spine and removing the bulk of bony disease. Reconstruction (cement or prosthesis) is often needed.[223] In several case series,[224–226] a minimally invasive approach with vertebroplasty or kyphoplasty has been satisfactory, and this is most often done by interventional radiologists. Patchell et al[227] performed a randomized multi-institutional nonblinded study of patients with spinal cord compression caused by metastatic cancer that has led to a recent change in the approach to patients with metastatic epidural spinal cord compression. Surgery followed by radiation was compared to radiotherapy alone. Both treatment groups received radiotherapy in 10 3-Gy fractions. Using the ability to walk after treatment as the primary end point, 84% (42 of 50 patients) of the surgery group were ambulatory after treatment compared to 57% (29 of 51 patients) in the radiation group ($p = 0.001$) [OR, 6.2; 95% CI, 2.0 to 19.8]. In addition, the ability to ambulate was sustained for a longer period of time in the surgery group than the radiation group (122 days vs 13 days, $p = 0.003$), with additional benefits for the surgery group that included maintenance of continence, muscle strength, functional ability, survival time, reduction in the use of corticosteroids, and opioid requirements. Thus, patients with metastatic epidural spinal cord compression and generally good performance status should be treated with direct surgical decompression followed by radiation because this will allow most patients to remain ambulatory for the rest of their lives. Good performance status patients with metastatic epidural spinal cord compression who are treated only with radiation and no surgical decompression will become paraplegic for a substantial portion of the rest of their lives, and they will not live as long if surgical intervention is not done initially.[227] However, there are also patients who have symptomatic cord compression who are not going to be surgical candidates due to the extent of their other disease (such as performance status) relative to the extent of surgery required.

Recommendations

25. For cancer patients with lung cancer who have the new onset of back pain, sagittal T1-weighted MRI of the entire spine is recom-

mended for diagnostic purposes. Other diagnostic studies such as plain radiographs, bone scans, or CT myelograms are not recommended. Grade of recommendation, 1C

26. For patients with lung cancer and epidural spinal cord metastases who are not paretic and ambulatory, prompt treatment with high-dose dexamethasone and radiotherapy is recommended. Grade of recommendation, 1B

27. When there is symptomatic radiographically confirmed compression of the spinal cord, neurosurgical consultation must be sought and, if appropriate, surgery should be performed immediately and should then be followed by radiation for patients with metastatic epidural spinal cord compression and generally good performance status. Grade of recommendation, 1A

Hemoptysis

Hemoptysis (expectoration of blood) is the presenting symptom in 7 to 10% of lung cancer patients. Approximately 20% will have hemoptysis some time during their clinical course, with 3% having terminal massive hemoptysis.[2,4,6,228] In contrast to other respiratory symptoms, hemoptysis is usually interpreted as serious by patients.[229] Hemoptysis is more likely in malignant lesions involving the airways than in cancers located in the peripheral lung parenchyma. The mechanisms responsible for hemoptysis include growth of new blood vessels (neovascularization) in and around the neoplasm, exfoliation of surface tumor with exposure of underlying blood vessels, tumor necrosis, trauma from cough and iatrogenic procedures (such as bronchoscopy), and formation of airway-vascular fistula. Minor episodes of hemoptysis do not usually require bronchoscopic therapy. However, significant hemoptysis may call for interventional procedures including therapeutic bronchoscopy, bronchial or pulmonary angiography followed by therapeutic embolization, and surgery. For patients with significant hemoptysis caused by a surgically resectable tumor, surgical resection of the bleeding lobe or the entire lung may be appropriate.

Massive hemoptysis, which most commonly requires intervention, has a broad definition as expectoration of at least 200 mL of blood in 24 h. Massive hemoptysis due to lung cancer has a much poorer prognosis than hemoptysis of other etiologies. The mortality rate of massive hemoptysis may be as high as 59 to 100% in patients with bronchogenic carcinoma.[230] Surgery, a more definitive therapeutic modality, is not on the algorithm for intervention because most lung cancer patients with massive hemoptysis have advanced disease and are already nonsurgical candidates. When surgical therapy is deemed futile or not feasible, less-invasive forms of therapy are considered.

Treatment of significant or massive hemoptysis requires securing and maintaining an adequate airway and optimal oxygenation.[231–233] This usually necessitates endotracheal intubation, and a single-lumen cuffed endotracheal tube is generally more beneficial than a double-lumen endotracheal tube. Selective right or left mainstem intubation can be performed to protect the nonbleeding lung. Double-lumen endotracheal tubes are more difficult to place and position, have smaller lumens, and do not permit a therapeutic bronchoscope to be passed through each side of the tube. This makes it difficult to further control and/or suction the airways.[234] Since blood clot formation obstructing the airways is the most common cause of respiratory insufficiency from massive hemoptysis, it is essential to place an endotracheal tube with a larger diameter so that bronchoscopic suctioning and removal of large obstructing clots can be accomplished quickly.

Bronchoscopy is used for both diagnostic and therapeutic purposes in patients with massive hemoptysis.[235] Bronchoscopic visualization will provide the following information: anatomic site and side of bleeding, nature of the bleeding source, severity of bleeding, and therapeutic feasibility. When no direct source of bleeding is found, as in bleeding from a peripheral tumor, bronchoscopic management begins with tamponade of the segment by tightly inserting the tip of the bronchoscope into the bronchus, followed by bronchoscopic instillation of iced saline solution to constrict the blood vessels.[236,237] This alone may stop the bleeding in many patients. If the bleeding is brisk, instillation of vasoactive agents like epinephrine is unlikely to help. Bronchial blockade balloons can be used to tamponade the bronchus. It may be necessary to leave the balloons in place for 24 to 48 h to allow tamponade of hemoptysis.[238–242] A study[242] reported that of the 57 patients who had persistent endobronchial bleeding despite bronchoscopic wedging technique, cold saline solution lavage, and instillation of regional vasoconstrictors, bronchoscopy-guided topical hemostatic tamponade therapy using oxidized regenerated cellulose mesh immediately arrested hemoptysis in 56 of 57 patients (98%). All patients thus treated remained free of hemoptysis for the first 48 h.

If these measures are unsuccessful, consideration should be given to bronchial artery embolization to temporize the bleeding. Most reports[243–246] of bronchial artery embolization are limited by the few cases of lung cancer managed in almost all studies.

Bronchoscopically visualized lesions that are responsible for the bleeding can be treated with one of

the following techniques described above, namely Nd-YAG laser coagulation, electrocautery, or APC. Nd-YAG laser coagulation has shown a therapeutic response rate of 60%.[84,247] Electrocautery should produce similar results, but its use to control hemoptysis has thus far been anecdotal. APC has provided resolution of hemoptysis in 100% of patients with a 3-month follow-up.[99] Cryotherapy, PDT, and stent insertion have no role in the treatment of massive hemoptysis.

When bronchoscopy reveals that insignificant or nonmassive hemoptysis is caused by a bronchoscopically visible or invisible, unresectable lung cancer, external beam radiation should be the next consideration.[162] Bronchoscopic techniques should be available if bleeding increases or becomes massive.

Recommendation

28. For all lung cancer patients with large-volume hemoptysis, bronchoscopy is recommended to identify the source of bleeding, followed by endobronchial management options such as APC, Nd-YAG laser, and electrocautery. Grade of recommendation, 1C

Malignant Pleural Effusions

Malignant pleural effusions occur in 7 to 15% of lung cancer patients.[248–250] In the United States, > 156,000 new cases of malignant pleural effusion are estimated to occur each year, with lung and breast cancers responsible for 75% of them.[251] The discussion and recommendations in this section apply to malignant pleural effusion caused by lung cancer and cancers from other sites with the exception of malignant mesothelioma.

Dyspnea is the most common presenting symptom when a malignant pleural effusion is present, and > 50% of patients with malignant pleural effusion have dyspnea.[252] Other symptoms caused by malignant pleural effusion include orthopnea, cough, chest discomfort, and pain. The mechanism of dyspnea with pleural effusions is unclear. Mechanical factors influencing the chest wall, depression of the ipsilateral diaphragm, mediastinum and its contents, pleural space, and the lung itself all may contribute to the dyspnea.[8,251,253–258] Palliation of a malignant pleural effusion is to relieve dyspnea and respiratory distress. Removal and prevention of reaccumulation of malignant pleural effusion does not treat or cure the underlying malignancy. Complete success of palliation is dependent on the long-term relief of symptoms related to the malignant effusion, with absence of fluid reaccumulation on chest radiographs until death.[251]

It is essential to recognize that there are multiple causes of dyspnea in patients with lung cancer, and removal of the pleural fluid may or may not provide adequate relief of dyspnea. If the lung is trapped because of parenchymal or pleural disease, there will be minimal relief of dyspnea and the lung will not re-expand after thoracentesis. The steps in the diagnosis of malignant pleural effusion are discussed in another section. (See "Initial Diagnosis of Lung Cancer" chapter in this guideline.)

Once the presence of symptomatic pleural effusion is confirmed by clinical examination and appropriate imaging techniques, therapeutic thoracentesis should be performed in virtually all dyspneic patients with malignant pleural effusions to determine its effect on dyspnea, as well as the rate and degree of reaccumulation of pleural fluid.[251] If bilateral pleural effusions are present, the larger accumulation is drained first. In patients with massive effusions and resultant respiratory distress, immediate hospitalization for chest tube drainage is prudent. If the initial thoracentesis provides relief of dyspnea and the lung re-expands on a postprocedure chest radiograph, reaccumulation of fluid can be managed by one or more of the following techniques (Table 2): (1) intermittent therapeutic thoracentesis; (2) insertion of a chest tube to completely evacuate the pleural fluid; (3) chest tube drainage followed by chemical pleu-

Table 2—*Intrapleural Pleurodesis Agents and Their Reported Complete Response Rates*

Pleurodesis Agent	Success, %	Dose*
Talc (poudrage or slurry)	60–95	2.5 to 10 g
Tetracycline	45–70	500 mg, or 20 to 35 mg/kg†
Doxycycline	50–75	500 mg†
Bleomycin	54–70	15 to 240 U (usual, 1 U/kg)
Chemotherapy agents‡	35–100	Varied
Quinacrine (mepacrine)	65–86	500 mg†
Corynebacterium parvum	60–76	3.5 to 14 mg
Other chemical agents§	30–95	Varied
Pleural catheter	85–95	Drainage‖
Surgical pleurodesis	75–100	Thoracoscopy, thoracotomy

*Wide variation in dosages reported in publications.

†Sometimes in repeated doses.

‡Agents other than bleomycin have included doxorubicin, adriamycin, cisplatin, cytarabin, mitomycin C, 5-fluorouracil, etoposide, mitoxantrone, combined intrapleural, IV chemotherapy, and pulmonary irradiation, and others.

§Minocycline, fibrinolytic agents (streptokinase and urokinase), fibrinogen solution, saline solution, silver nitrate, iodoprovidone, interleukin-2, ß-interferon, tumor necrosis factor, methylprednisolone, collagen powder, batimastat (matrix metalloproteinase inhibitor).

‖Duration of drainage has varied from 2 days to 6 mo; pleuroperitoneal catheters have been left in place for prolonged periods.

rodesis; (4) long-term chest tube drainage; (5) pleuroperitoneal shunting; (6) surgical pleurodesis; or (7) systemic therapy. The American Thoracic Society and the British Thoracic Society have published guidelines on the management of malignant pleural effusion.[8,251]

Therapeutic Thoracentesis: Repeated thoracentesis using topical anesthetic may suffice in some patients. In such patients, if the need for repeated procedures is too frequent, discomfort and inconvenience may persuade the patient to seek more definitive therapy. Repeated thoracentesis also increases the risk of pneumothorax, loculated effusions, and empyema. Ultrasound-guided thoracentesis is reported to be safer and to reduce the risk of pneumothorax. The volume of fluid removed with the initial thoracentesis should be no more than 1 to 1.5 L, stopping earlier should the patient experience dyspnea, chest pain, or cough. Removal of larger amounts of pleural fluid may be associated with re-expansion pulmonary edema, particularly if there is coexisting endobronchial obstruction.[251] Interventional bronchoscopy to open the obstructed airway before the thoracentesis may minimize the risk of re-expansion pulmonary edema and help assess for the presence of a trapped lung at the time of the diagnostic or therapeutic thoracentesis.[259,260] Repeated therapeutic thoracentesis is an option for patients with poor performance status or with advanced disease, and a very short life expectancy.[8,251]

Chest Tube Drainage: If repeated thoracentesis is not an option, insertion of a chest tube to drain the pleural fluid can be considered. This procedure can be accomplished under topical anesthesia and mild IV sedation. After the pleural space is completely drained of fluid, and if fluid does not reaccumulate, then the tube can be removed. Currently, however, chest tube drainage is almost always followed by intrapleural instillation of a chemical agent to produce pleurodesis (see below). Since the recurrence rate at 1 month after fluid drainage alone is close to 100%, chest tube drainage without pleurodesis is not recommended.[8]

Long-term Indwelling Pleural Catheters: One of the options is to place a smaller tunneled long-term pleural drainage catheter to drain the fluid on a long-term basis.[261–267] This technique is effective in controlling recurrent and symptomatic malignant effusions in selected patents. After the placement of the catheter under fluoroscopic or CT guidance, the patient is instructed to drain the fluid from the collecting bag. In a randomized and controlled study,[268] long-term indwelling pleural catheter was compared with doxycycline pleurodesis via a standard intercostal tube. Spontaneous pleurodesis was observed in 42 of the 91 patients in the catheter group. A late failure rate (*ie*, accumulation of pleural fluid) of 13% was reported, compared with 21% for the doxycycline group. The complication rate was higher (14%) in the catheter group and included local cellulitis and tumor seeding of the catheter tract. A retrospective analysis[265] of 250 sequential tunneled long-term pleural drainage catheter insertions in 223 patients during a 3-year period observed complete symptom control in 39%, partial relief in 50% of the procedures, and no relief in 4%. Spontaneous pleurodesis occurred in 103 of the 240 successful procedures (43%). Catheters stayed in place for a median period of 56 days.[265]

Chemical Pleurodesis: This technique involves drainage of pleural fluid by chest tube followed by intrapleural instillation of a sclerosant. Various agents have been used to bring about pleurodesis (Table 2). The overall complete response rate to chemical pleurodesis is 64%.[251,269] Further analysis according to the type of agent used reveals that sclerosant agents as a group are associated with a 75% complete response rate. Antineoplastic agents are less often successful, with a reported complete response of 44%.[269,270] However, some reports[271,272] indicate a success rate $>90\%$ for antineoplastic agents such as bleomycin and the antiparasitic (antimalarial) drug quinacrine. Interferon α or β, biological response modifiers, have been administered intrapleurally to treat malignant pleural effusions, with reported success rates ranging from 21 to 100%.[270,273–276] Intrapleural corticosteroid has been used to delay reaccumulation of malignant pleural effusion. However, a double-blind, randomized, placebo-controlled trial[277] in 67 patients comparing methylprednisolone to saline solution showed that intrapleural methylprednisolone did not delay reaccumulation of symptomatic pleural effusion compared to placebo.

Tetracycline derivatives, quinacrine, silver nitrate, iodopovidone, and other talc preparations such as facial talc have been used to produce pleurodesis.[278] All chemical pleurodesis and intrapleural therapy agents that are available have common as well as their own unique complications and constraints for use, which should be reviewed before a specific agent is chosen. In a study[279] of 49 patients who were enrolled into a randomized study, malignant pleural effusion was initially drained by chest tube, and 25 patients received 5 g of talc diluted to a total volume of 50 mL with saline solution, 24 patients received 20 mL of 0.5% silver nitrate through the chest tube, and

the results indicated that silver nitrate is as effective as talc for producing a pleurodesis.

Talc Pleurodesis: Talc remains the most effective agent for pleurodesis. Asbestos-free talc is an inexpensive agent now commonly used to treat malignant pleural effusions. The two favored methods of intrapleural talc administration are talc poudrage and talc slurry. Talc poudrage is accomplished under thoracoscopic guidance, and the technique consists of complete pleural fluid drainage, complete collapse of the lung, followed by spraying talc (approximately 5 g) evenly over the pleural surfaces. A 24 to 32F chest tube is inserted for progressive suction and re-expansion of lung. Talc slurry is prepared by thoroughly mixing talc (5 g) with normal saline solution (50 to 250 mL). The slurry is instilled through the chest tube, which then is clamped for 1 h afterwards. This is followed by drainage of the pleural fluid, and the chest tube is removed when the 24-h tube drainage is $<$ 100 to 150 mL. Intrapleural topical anesthetic (lidocaine), systemic analgesia, and sedation are recommended before talc pleurodesis is performed.

An overall success rate (complete and partial response) for talc pleurodesis is $>$ 90% (range, 88 to 100%).[269,280–285] The Cochrane Database Systemic Review (metaanalysis)[286] of 36 RCTs with 1,499 subjects (1980 to June 2002) reported that compared to different sclerosants, talc was most efficacious for pleurodesis. The relative risk of death was 1.19 (95% CI, 0.08 to 1.77) for talc compared to bleomycin, tetracycline, mustine and tube drainage alone based on six studies of 186 subjects.[286] However, the risk of respiratory failure as a result of talc pleurodesis has been debated.[282,287–292] Also debated is the difference in results and complications following talc poudrage and talc slurry therapy. One prospective study[293] of video-assisted thoracoscopic talc poudrage was no better than talc slurry. Another prospective, randomized trial[294] also compared thoracoscopy with talc insufflation to thoracostomy and talc slurry in patients with malignant pleural effusions. The results showed no difference between patients with successful 30-day outcomes (78% vs 71%). This study also noted that both methods of talc delivery are similar in efficacy. However, respiratory failure was observed in 8% of patients who underwent thoracoscopy with talc insufflation, and in 4% of patients who received talc slurry, and accounting for six deaths and five deaths, respectively.[294] The etiology and incidence of respiratory complications from talc pleurodesis need further exploration.

Pleuroperitoneal Shunting: This is an alternative technique to manage malignant pleural effusions refractory to chemical pleurodesis.[294–300] It may also benefit patients with trapped lung, particularly those with lungs trapped by visceral pleural carcinomatosis.[300] All studies of pleuroperitoneal shunting are case series. The device consists of a valved chamber containing two unidirectional valves, with fenestrated pleural and peritoneal catheters attached at either end. The insertion of the shunt is facilitated by thoracoscopy or a minithoracotomy. The device is pressure activated but many patients with malignant pleural effusions lack the ability to actively utilize the pumping device, which must be pushed at least 100 times or so daily to overcome the positive peritoneal pressure. In a report[301] on 368 patients who were treated for malignant pleural effusions, 160 patients (44%) had a pleuroperitoneal shunt inserted. Follow-up in 88% of patients showed a median survival of 7.7 months. Shunt complications occurred in 21 patients (15%), and included shunt occlusion, skin erosion, infection, breakage of a shunt limb, and malignant seeding at the site of shunt insertion.[301] Some of the complications require revision or shunt removal. The presence of pleural infection, multiple pleural loculations, and inability to compress the pump chamber are contraindications to pleuroperitoneal shunting.

Intrapleural Fibrinolysis: In patients who have dyspnea due to multiloculated malignant effusions that are resistant to simple drainage, instillation of an intrapleural fibrinolytic agent has been recommended.[8,302,303] Reports have shown that instillation of intrapleural streptokinase or urokinase with multiloculated or septated malignant effusions, leads to increased pleural fluid drainage and radiographic improvement and palliation of symptoms. The published studies on the topic have included small numbers of patients. In one study,[302] 10 consecutive patients with malignant multiloculated pleural effusions were administered intrapleural streptokinase, 250,000 IU bid, after the standard chest tubes failed to drain the effusions. All 10 patients responded to between 500,000 and 1,500,000 IU of streptokinase, and radiographic improvement was seen in all. There were no hemorrhagic or allergic complications. One patient died of unrelated septicemia.[302]

Systemic Therapy: The treatment of choice for malignant effusions due to SCLC is systemic chemotherapy. Many patients will respond with resolution of pleural effusions and the associated dyspnea.[304] There is little role for administration of external radiation therapy to the pleural surfaces. If the malignant pleural effusion is caused by mediastinal lymphadenopathy as in lymphoma, mediastinal radiation may be useful.[305] Combined intrapleural and

IV chemotherapy, and pulmonary irradiation have been tried to treat malignant pleural effusion.[306]

Surgical Pleurodesis: Thoracoscopic drainage of pleural fluid followed by pleural decortication/abrasion and instillation of chemical agents is perhaps the most definitive invasive procedure to prevent reaccumulation of malignant pleural effusion. However, these procedures should be reserved for patients who have failed to respond to other forms of treatment.[283,307–315] In the comparison of thoracoscopic vs medical pleurodesis, the Cochrane Database Systemic Review (metaanalysis) of 36 randomized controlled trials with 1499 subjects (1980 to June 2002) reported that thoracoscopic pleurodesis was more effective. The relative risk of nonrecurrence of effusion is 1.19 (95% CI, 1.04 to 1.36) in favor of thoracoscopic pleurodesis compared with tube thoracostomy pleurodesis utilizing talc as the sclerosant based on two studies with 112 subjects.[286] Currently, thoracoscopic drainage of pleural fluid with talc poudrage is an effective and popular technique controlling malignant effusions with a success rate $> 90\%$.[314,316,317]

Palliation of Pleurodesis-Associated Complications

Pleurodesis is not innocuous, and the discussion above describes some of the complications associated with the procedure. The most commonly reported adverse effects are pain and fever.[269] Intrapleural instillation of sclerosing agents is associated with chest pain and discomfort in up to 40% of patients.[318,319] Preinstillation of lidocaine and premedication with analgesics and sedative should be considered to alleviate anxiety and pain associated with pleurodesis.[8]

Paramalignant Pleural Effusion: Paramalignant effusions are pleural effusions that are not the direct result of malignant involvement of the pleura but are still related to the primary tumor.[251] Common causes include postobstructive pneumonia complicated by parapneumonic effusion; chylothorax due to obstruction of the thoracic duct, pulmonary embolism and infarction, radiation therapy, and chemotherapy. In addition, patients with lung cancer may also have pleural effusions that are due to concurrent nonmalignant disorders (congestive heart failure, renal failure, hypoproteinemia). Definitive and palliative therapy should address the cause of the pleural effusion.

Recommendations

29. In lung cancer patients with symptomatic malignant pleural effusions, thoracentesis is recommended as the first drainage procedure for symptom relief. Grade of recommendation, 1C

30. In lung cancer patients with symptomatic pleural effusions that recur after thoracentesis, chest tube drainage and pleurodesis are recommended. Grade of recommendation, 1B

Palliation of SVC Obstruction

Obstruction of the SVC is usually caused by malignancies, the majority of which are due to lung cancer.[320] Typically, the lung cancer spreads by lymph node metastases into the right paratracheal or precarinal lymph nodes, although some cancers cause obstruction of the SVC by direct extension. Impending obstruction of the SVC may be identified by CT imaging before development of symptoms associated with SVC obstruction.[321] At the time of diagnosis, SVC obstruction is present in 10% of patients with SCLC and 1.7% of patients with NSCLC.[322]

While SVC obstruction may not be symptomatic, SVC syndrome develops in 10% of patients with right-sided malignant intrathoracic lung cancers.[323] SVC syndrome includes symptoms that may be severe and debilitating, including neck swelling, swelling of one or both arms, and swelling of the face and eyelids. Collateral veins of the neck and anterior chest wall become engorged, and dyspnea is often present. Headache from cerebral venous hypertension is common with SVC syndrome; hoarseness of the voice and cyanosis are less frequent. Typically, lifestyle is significantly impaired with SVC syndrome.

Obstruction of the SVC with SVC syndrome has historically been considered a medical emergency. Systemic corticosteroids are usually administered to relieve swelling associated with radiation therapy, although data to support the efficacy of steroids are missing.[320] A randomized trial is needed to discern the value of steroid therapy when radiation is administered. In the era when treatment for SVC syndrome was considered an emergency, SCLC patients were administered chemotherapy and NSCLC patients were administered external-beam radiation. Since the outcome of treatment is not related to the duration of symptoms, emergency treatment is no longer believed to be needed.[324,325]

As the need for emergent treatment is no longer considered mandatory, it is prudent to obtain a histologic diagnosis before treating patients with SVC syndrome. SCLC patients are managed well with chemotherapy.[326] After treatment with chemotherapy, objective and subjective responses of SVC syndrome are seen in 68% and 77% of SCLC patients, respectively.[327] Whereas chemotherapy for SCLC may improve the symptoms associated with

SVC syndrome, radiation therapy is usually a part of treating SCLC with SVC obstruction. Relief of SVC symptoms is nearly equal for SCLC patients treated with either chemotherapy (77%) or radiation therapy (78%) or both chemotherapy and radiation therapy (83%).[322] In one nonrandomized observational study,[18] patients with SCLC and SVC syndrome undergoing concurrent treatment with chemotherapy and radiation therapy had paradoxically improved 5-year survival (15 ± 7%) compared with SCLC patients without SVC syndrome (9 ± 2%; $p = 0.008$). Similarly, a metaanalysis[328] of SCLC patients with SVC obstruction showed a median survival of 16.1 months compared to 13.7 months for SCLC patients without SVC obstruction. Relapse of SVC syndrome after treatment for SCLC occurs in 17%.[322]

A histologic diagnosis is also needed for patients with NSCLC because the choice of appropriate antineoplastic drugs is different from the treatment of SCLC. Reported response rates for relief of SVC obstruction in NSCLC are 59% (chemotherapy), 63% (radiation therapy), and 31% for synchronous chemoradiation.[322] Relapses after treatment with chemotherapy and/or radiation therapy are seen in 19% of patients with NSCLC.[322]

Symptom relief from SVC syndrome is more rapidly achieved by stenting.[326] Headache may disappear immediately,[329] and swelling of the face and arms are reported to abate within 24 h and 72 h, respectively.[330,331] Overall response rates of 94 to 95% with stent insertion are reported from a variety of case series, with an 11% recurrence rate.[322] Multiple authors of case series[332–346] of stenting advocate for stents as the initial treatment of SVC syndrome because symptom relief is more rapid and there is a low incidence of complications. The need to place a stent soon after the onset of SVC syndrome is not clearly established, however, because chemotherapy and/or radiation therapy are almost always offered in the setting of symptomatic SVC obstruction. Stent placement also has been demonstrated to be effective in relieving symptoms in patients who fail to respond to radiation therapy.[344]

It is sometimes necessary to enlarge the vascular lumen by way of balloon angioplasty in order to properly place a stent. Occasionally it may not be possible to insert a stent because a tumor has grown directly into the SVC.[329] When thrombosis occurs as a complication of SVC syndrome, local thrombolytic therapy may be of value to re-establish patency and subsequently to allow insertion of a stent. The use of thrombolytics and anticoagulants after stenting patients with SVC obstruction is associated with an increased frequency of complications attributable to bleeding. The need for long-term anticoagulation has not been established.

Recommendations

31. In patients with SVC obstruction from suspected lung cancer, definitive diagnosis by histologic or cytologic methods is recommended before treatment is started. Grade of recommendation, 1C

32. In patients with symptomatic SVC obstruction due to SCLC, chemotherapy is recommended. Grade of recommendation, 1C

33. In patients with symptomatic SVC obstruction due to NSCLC, stent insertion and/or radiation therapy are recommended. Stents are also recommended for SCLC or NSCLC symptomatic patients with SVC obstruction who fail to respond to chemotherapy or radiation therapy. Grade of recommendation, 1C

Palliation of Malignant Tracheoesophageal Fistula

Tracheoesophageal fistulas (TEFs) are uncommon complications of lung cancer. TEFs are more common with esophageal cancers than primary lung cancers. Because patients with TEF have repeated aspiration of food, gastric contents, and saliva into the lungs, they have cough, shortness of breath, and recurrent pneumonia with the potential for sepsis. These phenomena lead to a markedly reduced survival of 1 to 7 weeks. Patients frequently lose weight and become dehydrated because they cannot tolerate oral intake. Even with abstinence from eating and drinking most patients have difficulty with controlling their own secretions.

Curative resection of the involved tracheal-bronchial and/or esophageal segments in face of a malignancy is inappropriate; most such patients are near the end of their lives and palliation should be the primary treatment objective. Likewise, esophageal bypass procedures can be considered, but they have very high morbidity and mortality rates and are inappropriate as palliative tools in advanced lung cancer. The goals of therapy are to restore patency of the trachea, bronchi, and/or esophagus to prevent spillage of further material into the lung and ensure that the patient receives nutrition and fluid.

Double stenting of the tracheobronchial tree and the esophagus appears to be the procedure that yields the best overall results for symptomatic relief for patients with this condition. All reports are case series; there are no controlled trials that study any of these endoscopic treatment methods.

Clinical series have attempted either esophageal

or tracheobronchial stenting with mixed results. Most reports[347–351] with higher success rates use a double-stenting technique. If stents are not placed into both the esophagus and the trachea at the same operative setting, the tracheal stent should be placed first because an esophageal stent alone may compress the trachea and lead to respiratory distress or failure. The addition of percutaneous enterogastric tube placement can ensure proper nutrition and fluid management for patients with a TEF. Patients may be able to eat soft foods once double stenting is performed, but maintaining adequacy of fluid status and nutrition is often difficult.

Recommendation

35. For patients with malignant TEF or bronchoesophageal fistula, stenting of esophagus, airway, or both should be considered for symptomatic relief. Attempts at curative resection or esophageal bypass of the involved airway and/or the esophagus are not recommended. Grade of recommendation, 1C

Depression, Fatigue, and Other Symptoms

Lung cancer patients can have a variety of symptoms from the time of the diagnosis through the treatment and possible progression of their disease, and each needs to be addressed. Two studies in newly diagnosed patients revealed that fatigue, pain, loss of appetite, coughing, and insomnia were common.[28] A study[28] of patients with advanced disease admitted to a palliative medicine service revealed that they had a median of nine symptoms, with pain, dyspnea and anorexia being the most common. All of these symptoms can impact their quality of life and therefore need to be addressed. This is best done by gathering information about symptoms directly from the patient because family caregivers tend to rate the symptom distress as more severe than the patient, and physicians tend to underrate the severity.[28]

Depression is common and can be persistent in lung cancer patients. A study[352] of self-rated depression in 987 patients with inoperable lung cancer revealed that 33% had depression before entering a palliative medicine treatment trial, and it persisted in 50% of them. SCLC patients had a threefold-greater prevalence of depression. Functional impairment was the most important risk factor for depression.

The caregiver must guard against assuming that the patient receiving a diagnosis of lung cancer is in itself depressing, and therefore miss assessing the patient for depression.[353] Various screening tools can be used to identify patients in need of specific treatment. The Hospital Anxiety and Depression Scale is commonly used.[354] Clinicians sometimes feel that there is insufficient time for medications to improve the depression in a patient with advanced lung cancer who may have an abbreviated life span. However, randomized studies reveal an improvement of symptoms with antidepressants. Cognitive, behavioral and psychosocial interventions also show benefit.[355]

Fatigue is a common symptom among patients with lung cancer as well, particularly those with advanced disease.[356] One study[357] of 227 cancer patients and 98 control subjects reported that the prevalence of severe fatigue was 15% among patients with recently diagnosed breast cancer, 16% among patients with recently diagnosed prostate cancer, 50% among patients with inoperable NSCLC, and 78% among patients receiving specialist inpatient palliative care. Fatigue was significantly associated with the severity of psychological symptoms (anxiety and depression) and with the severity of pain and dyspnea.[357]

Fatigue and anemia commonly coexist and can be treated with RBC transfusions and/or erythropoietic agents, including epoetin alfa and darbepoetin. Studies[355] reveal that patients with hemoglobin ≤ 10 g/dL treated with either of these agents revealed an improvement in fatigue and quality of life.

Insomnia is common in many patients with a chronic illness, including lung cancer, and is associated with other symptoms that can decrease quality of life. Treatment includes modalities used for the treatment of chronic insomnia, including addressing symptoms that are disturbing the patient's sleep (*eg*, pain, dyspnea), instructing the patient in proper sleep hygiene and behavior modification techniques (*eg*, guided imagery, relaxation), and supplementing them with the periodic use of a hypnotic agent chosen to address the patient's insomnia complaint.

Anorexia cachexia syndrome is characterized by loss of appetite, weight loss, wasting of muscle mass and adipose tissue, anemia and asthenia. It is a common problem in advanced cancer and can impact quality of life and survival. Various pharmacologic treatments have been tried, including the use of megestrol acetate and cannabinoids.[355]

Recommendation

36. It is recommended that all patients with lung cancer be evaluated for the presence of depression and, if present, treated appropriately. Grade of recommendation, 1C

Conclusion

The majority of patients with lung cancer will have one or more symptoms or complications from met-

astatic disease. These symptoms will severely alter the patient's quality of life. It is important for clinicians who care for lung cancer patients to be familiar with these many different symptoms and complications of the disease, and to utilize the many available methods that are designed to palliate these problems and improve the patient's life quality.

Summary of Recommendations

1. All lung cancer patients and their families must be reassured that pain can be relieved safely and effectively. All patients should be questioned regularly about their pain, using the patient's self-report of pain and a simple rating scale as the primary source of assessment. Grade of recommendation, 1A

2. For all patients individualize medications that are used to control pain. Administer medications regularly and treat pain appropriately. Document the effectiveness of pain management at regular intervals during treatment. Grade of recommendation, 1A

3. For all patients with mild-to-moderate pain, manage the pain initially with acetaminophen or an NSAID, assuming there are no contraindications to their use. Use opioids when pain is more severe or when it increases. Grade of recommendation, 1B

4. For any patient, if it is anticipated that there will be a continuous need for opioid medication, meperidine is not recommended. It has a short duration of action, and its metabolite normeperidine is toxic and can cause CNS stimulation resulting in dysphoria, agitation, and seizures. Grade of recommendation, 1B

5. For patients whose pain is not controlled by pure analgesic medications, adjunctive medications such as tricyclic antidepressants, anticonvulsants, and neuroleptic agents will often augment the effects of pure analgesic medications. Grade of recommendation, 1C

6. For all patients, administer medications by mouth because of convenience and cost-effectiveness. In patients with lung cancer who cannot take pain medications by mouth, rectal and transdermal administration are recommended. Administration of analgesics by the IM route is not recommended because of pain, inconvenience, and unreliable absorption. Grade of recommendation, 1C

7. For all patients receiving opioids, because constipation is common, anticipate it, treat it prophylactically, and constantly monitor it. Grade of recommendation, 1B

8. Encourage all patients to remain active and to care for themselves whenever possible. Avoid prolonged immobilization whenever possible. Grade of recommendation, 1B

9. In patients who have pain associated with muscle tension and spasm, it is recommended that complimentary methods for pain relief such as cutaneous stimulation techniques (heat and cold applications), acupuncture, psychosocial methods of care, and pastoral care be incorporated into the pain-management plan, but not as a substitute for analgesics. Grade of recommendation, 1C

10. For patients with advanced lung cancer, provide palliative radiation therapy to control pain. Palliative chemotherapy to decrease pain and other symptoms is recommended even though the increase in survival may be only modest. Grade of recommendation, 1B

11. In patients with lung cancer who have pain unresponsive to standard methods of pain control, referral to a specialized pain clinic or palliative care consultant is recommended. Grade of recommendation, 1C

12. For all lung cancer patients who complain of dyspnea, it is recommended that they be evaluated for potentially correctable causes, such as localized obstruction of a major airway, a large pleural effusion, pulmonary emboli, or an exacerbation of coexisting COPD or congestive heart failure. If one of these problems is identified, treatment with appropriate methods is recommended. Grade of recommendation, 1C

13. For all lung cancer patients whose dyspnea does not have a treatable cause, opioids are recommended. Also recommended are other pharmacologic approaches such as oxygen, bronchodilators, and corticosteroids. Grade of recommendation, 1C

14. For all lung cancer patients with dyspnea, it is recommended that nonpharmacologic and noninterventional treatments be considered, such as patient and family education, breathing control, activity pacing, relaxation techniques, fans, and psychosocial support. Grade of recommendation, 2C

15. For all lung cancer patients who have troublesome cough, it is recommended that they be evaluated for treatable causes. Grade of recommendation, 1B

16. For all lung cancer patients who have troublesome cough without a treatable cause, it is recommended that opioids be used to suppress the cough. Grade of recommendation, 1B

17. For patients with lung cancer who have pain due to bone metastases, external radiation therapy is recommended for pain relief. A single fraction of 8 Gy is as effective as higher fractionated doses of external radiation therapy for immediate relief of pain. Grade of recommendation, 1A

18. For patients with lung cancer who have pain due to bone metastases, higher fractionated doses of radiation therapy provide a longer duration of pain relief, less frequent need for retreatment, and fewer skeletal-related events than does a single fraction. Grade of recommendation, 1A

19. For patients with lung cancer who have painful bone metastases bisphosphonates are recommended together with external radiation therapy for pain relief. Grade of recommendation, 1A

20. For patients with lung cancer who have painful bone metastases refractory to analgesics, radiation and bisphosphonates, radiopharmaceuticals are recommended for pain relief. Grade of recommendation, 1B

21. In patients with lung cancer who have painful bone metastases to long and/or weight-bearing bones and a solitary well-defined lytic lesion circumferentially involving > 50% of the cortex and an expected survival > 4 weeks with satisfactory health status, surgical fixation is recommended to minimize the potential for a fracture. Intramedullary nailing is the preferred approach, especially for the femur or the humerus. Grade of recommendation, 1C

22. In patients with lung cancer who have symptomatic brain metastases, dexamethasone, 16 mg/d, is recommended during the course of definitive therapy with a rapid taper and discontinuation within 6 weeks of completion of definitive therapy (either surgery or radiation therapy). Grade of recommendation, 1B

23. Patients with NSCLC and an isolated solitary brain metastasis should be considered for a curative resection of the lung primary tumor as long as a careful search for other distant metastases or mediastinal lymph nodes has been carried out and is negative. Grade of recommendation, 1C

24. In patients with no other sites of metastases and a synchronous resectable N0,1 primary NSCLC, resection or radiosurgical ablation of an isolated brain metastasis should be undertaken (as well as resection of the primary tumor). Resection of the isolated solitary brain metastases should be followed by WBRT. Grade of recommendation, 1B

25. For patients with lung cancer who have new onset of back pain, sagittal T1-weighted MRI of the entire spine is recommended for diagnostic purposes. Other diagnostic studies such as plain radiographs, bone scans, or CT myelograms are not recommended. Grade of recommendation, 1C

26. For patients with lung cancer and epidural spinal cord metastases who are not paretic and ambulatory, prompt treatment with high-dose dexamethasone and radiotherapy is recommended. Grade of recommendation, 1B

27. When there is symptomatic radiographically confirmed compression of the spinal cord, neurosurgical consultation must be sought and, if appropriate, surgery should be performed immediately and followed by radiation for patients with metastatic epidural spinal cord compression and generally good performance status. Grade of recommendation, 1A

28. For all lung cancer patients with large-volume hemoptysis, bronchoscopy is recommended to identify the source of bleeding, followed by endobronchial management options such as APC, Nd-YAG laser, and electrocautery. Grade of recommendation, 1C

29. In lung cancer patients with symptomatic malignant pleural effusions, thoracentesis is recommended as the first drainage procedure for symptom relief. Grade of recommendation, 1C

30. In lung cancer patients with symptomatic pleural effusions that recur after thoracentesis, chest tube drainage and pleurodesis are recommended. Grade of recommendation, 1B

31. In patients with SVC obstruction from suspected lung cancer, definitive diagnosis

by histologic or cytologic methods is recommended before treatment is started. Grade of recommendation, 1C

32. In patients with symptomatic SVC obstruction due to SCLC, chemotherapy is recommended. Grade of recommendation, 1C

33. In patients with symptomatic SVC obstruction due to NSCLC, stent insertion and/or radiation therapy are recommended. Stents are also recommended for SCLC or NSCLC symptomatic patients with SVC obstruction who fail to respond to chemotherapy or radiation therapy. Grade of recommendation, 1C

35. For patients with a malignant TEF or bronchoesophageal fistula, stenting of esophagus, airway, or both should be considered for symptomatic relief. Attempts at curative resection or esophageal bypass of the involved airway and/or the esophagus are not recommended. Grade of recommendation, 1C

36. It is recommended that all patients with lung cancer be evaluated for the presence of depression and, if present, treated appropriately. Grade of recommendation, 1C

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Palliative Care Consultation, Quality-of-Life Measurements, and Bereavement for End-of-Life Care in Patients With Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Objective: **To develop clinical practice guidelines for application of palliative care consultation, quality-of-life measurements, and appropriate bereavement activities for patients with lung cancer.**

Methods: **To review the pertinent medical literature on palliative care consultation, quality-of-life measurements, and bereavement for patients with lung cancer, developing multidisciplinary discussions with authorities in these areas, and evolving written guidelines for end-of-life care of these patients.**

Results: **Palliative care consultation has developed into a new specialty with credentialing of experts in this field based on extensive experience with patients in end-of-life circumstances including those with lung cancer. Bereavement studies of the physical and emotional morbidity of family members and caregivers before, during, and after the death of a cancer patient have supported truthful communication, consideration of psychological problems, effective palliative care, understanding of the patient's spiritual and cultural background, and sufficient forewarning of impending death.**

Conclusion: **Multidisciplinary investigations and experiences, with emphasis on consultation and delivery of palliative care, timely use of quality-of-life measurements for morbidities of treatment modalities and prognosis, and an understanding of the multifaceted complexities of the bereavement process, have clarified additional responsibilities of the attending physician.**

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Key words: bereavement; cultural competence; end-of-life care; lung cancer; palliative care consultation; quality-of-life measurements

Abbreviations: CAPC = Center to Advance Palliative Care; EORTC-QLQ-30 = European Organization for Research and Treatment of Cancer core 30-item quality of life questionnaire; EPEC = Educating Physicians in End-of-Life Care; FACT-L = functional assessment of cancer therapy–lung cancer; HR-QOL = health-related quality of life; LCSS = Lung Cancer Symptom Scale; SDS = symptom distress scale; SF-36 = 36-item short-form health survey

Specific areas of interest were identified as important for the creation of American College of Chest Physicians guidelines for end-of-life care in patients with lung cancer.[1] After a review of the medical literature revealed few prior guidelines, the improvement of communication between members of the health-care team and their patients and families was identified as essential. It was recommended that clinicians increase their focus on the patient's experience of illness to improve congruence of treatment with goals and preferences of the patient. Education was considered inadequate at all levels of training despite an increasing availability of important information in this area. Effectiveness of advance directives was measured after examination of their legal development, and was found often to be

lacking in critical medical situations, or inconsistent in their application. It was recommended that such instruments, valid and well understood by patients with lung cancer, should be present and applied as a physician responsibility. The hospital ethics committee was evaluated as to its clarification of ethical and legal matters, and assistance in resolution of difficulties between clinicians, their patients, their families and surrogates; although now available by requirement and sophisticated in its membership, the assistance of this group is seldom requested. The role of the critical care specialist in end-of-life care for patients with lung cancer was examined, including contributions to the treatment of reversible complications or comorbidity, and to palliative care. The role of the hospice environment for end-of-life care was measured and could be recommended as an appropriate choice in the longitudinal planning and care for these patients. Realization of the majority request for death in the home setting, the application of quality-of-life considerations, and satisfaction with the palliative care provided by the multidisciplinary team have resulted in progressively greater use of this environment.

Methodology

To evaluate the role of palliative care consultation, quality-of-life measurements, and to broaden caregiver understanding of the bereavement process, a detailed examination of the English-language medical literature on these end-of-life care topics from a computerized database (MEDLINE) was performed by clinical researchers in these fields, covering the period of 1965 to 2005 identifying a majority of references in the past 10 years, but with use of classic psychosocial studies from other noncomputerized sources from earlier times. Additionally in 2006, several cancer-care Web sites were searched for even more recent unpublished pertinent information. Also, the authors of this chapter participated in extensive discussions of the experience of experts from multiple medical centers relative to these end-of-life topics. Recommendations were then developed by the writing committee, graded by the standardized method (see section on "Methods and Grading") and reviewed by all members of the lung cancer panel, prior to approval by the Thoracic Oncology Network, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.

Role of Palliative Care Consultation for Patients With Lung Cancer

Throughout the various stages of lung cancer, the needs of patients and their families are complex, with distress of all forms—physical, psychological, social, and spiritual—typically intensifying as the disease advances. Discussion of care goals as well as of symptom and treatment issues in the context of progressive illness is required. Arrangements for an appropriate care setting and adequate care giving support at the end of life require knowledge of available alternatives, and an experience-based understanding of how best to match needs and services. Many specialists in pulmonary disease are experienced in end-of-life care for patients with lung cancer, and appropriately consider this care to be an integral part of their work. However, the field of palliative medicine is emerging as a discrete specialty and a strong source of support for clinicians, for patients with serious and life-threatening illness, and their families. A growing body of evidence suggests that input from specialists in palliative medicine can improve the quality of patient care and reduce costs. Major professional organizations and consumer advocacy groups have called for better access to palliative care for patients with serious illness.[2–4]

Defining Palliative Care

Palliative care is interdisciplinary care to relieve suffering and improve quality of life for patients with advanced illness and their families.[5] The patient need not be imminently dying, or even certain to die of the illness, for this care to be appropriate and beneficial. Nor is palliative care a mutually exclusive alternative to curative care. In fact, effective palliation may be essential to enable the optimal delivery of aggressive, cure-oriented treatment. Increasing data document associations between symptom distress in lung cancer and other unfavorable outcomes including shorter survival[6–10] and suggest, conversely, that effective palliative treatment is associ-

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ated with favorable outcomes of cancer and other diseases.[11–14] Ideally, palliative care is initiated at the time of diagnosis of lung cancer or any serious or life-threatening illness, regardless of prognosis, and is integrated—"integrative palliative care"[15]—with restorative or life-prolonging treatments that are expected to benefit the patient. It is unfortunate, therefore, that many patients with severe illness including lung cancer still receive only repeated episodes of short-term, life-prolonging efforts, followed in the last weeks by a short period of end-of-life care in hospice or another setting.[16,17]

Integrative palliative care is both patient centered and family centered. It is comprehensive, encompassing expert management of all forms of distress, communication about treatment plans and care goals, and facilitation of smooth transitions between care settings. The emphasis is on functional independence and quality of life at every stage of serious disease. Regular, formal assessment is used to identify problematic issues in a timely way, and an interdisciplinary team approach addresses the spectrum of needs of patients and families. This kind of care provides management throughout the course of serious illness, up to and including the end of life.

Growth of Palliative Care Programs in the United States

The past decade has been a time of explosive growth for the field of palliative medicine. A study[18] found that larger hospitals, academic medical centers, not-for-profit hospitals, and Veteran's Affairs hospitals were significantly more likely to have a palliative care program. This development has been supported by growth in the numbers of certified palliative medicine professionals: physicians numbered nearly 2,000 and nurses numbered $> 5{,}500$ in 2005.[19] Between 2000 and 2005, the number of postgraduate fellowships in palliative medicine more than tripled.[19,20] This period has also seen significant increases in the number of specialty journals and publications, and in research funding for palliative medicine.[21] Following recent co-sponsorship by seven major specialty boards, it is expected that palliative medicine will soon be formally recognized as a specialty of the American Board of Medical Specialties.[22]

Benefits of Palliative Care

Where palliative care is available, evidence suggests that involvement of this team will provide benefit to patients, families, clinicians, and health-care systems. Systematic reviews and metaanalysis of hospital palliative care programs showed improvement in symptoms and patient and family satisfaction, as well as lower rates of in-hospital death and shorter hospital length of stay.[23–26] A high rate of implementation of palliative care consultant recommendations, including symptom treatment, goal setting, and advance care and discharge planning, has been reported.[27] In addition, studies[28,29] suggest that as compared to conventional care, palliative care can achieve substantial reductions in direct and indirect hospital costs. These results have been observed across a range of hospital settings and clinical service delivery models. However, empirical studies to date were generally limited to single sites or programs, and lacked power to detect clinically significant differences in certain important outcomes including symptom management, analgesic prescribing, and service utilization. Many studies failed to use optimal statistical techniques to adjust for confounding variables and reduce bias in observational designs. Further research is needed to confirm benefits found in past studies of palliative care programs, and to define the essential components of successful interventions, so that existing and future programs can stand on a stronger evidentiary foundation.

Some institutions that do not have palliative care consultation services offer resources such as ethics services that may serve some palliative needs and achieve other favorable outcomes. In a large, multicenter, prospective, randomized controlled trial, Schneiderman et al[30] compared ethics consultation with usual care for ICU patients in whom value-laden treatment conflicts were imminent or manifest that could lead to incompatible courses of action. The consultations followed a general process model attending to relevant medical factors, the patient's known or inferred values and preferences, quality-of-life considerations, and other contextual factors. The consultant helped articulate consensus or disagreement and either facilitated implementing the consensus or facilitated ways to address and resolve the disagreement. Usual care in this study included family meetings or other conferences as judged appropriate by the health-care team. While mortality was not statistically different between the groups, length of stay for patients receiving ethics consultation was 3 days shorter in the hospital, and 1.4 days shorter in the ICU than for the usual-care patients. Nonsurviving patients in the intervention group also received fewer days of nonbeneficial life-sustaining treatment with mechanical ventilation. Patients, families, and clinicians found the consultations helpful in addressing treatment conflicts.

Defining a Role for Palliative Care Consultation

Input from palliative care consultants is not a substitute for close and continuing attention by

pulmonologists and other clinicians to basic palliative needs. Whether or not specialty services are available, every physician and nurse (as well as respiratory therapists and others) caring for patients with lung cancer should receive education in the fundamentals of palliative care. This was the goal of the Educating Physicians in End-of-Life Care (EPEC) project sponsored by the American Medical Association and the Robert Wood Johnson Foundation, which has been widely disseminated.[31] A comparable program for nurses, the End-of-Life Nursing Education Consortium Project, was created by a partnership of the American Association of Colleges of Nursing and the City of Hope National Medical Center.[32] Cancer-specific educational resources are also available.[33,34] Through a collaboration between EPEC and the American Society of Clinical Oncology, the original EPEC curriculum is being adapted as "EPEC-O" to meet the specific needs of medical, surgical, and radiation oncologists.[33] The National Comprehensive Cancer Network and American Society of Clinical Oncology have both developed guidelines for palliative care of cancer patients[33,34]; and the National Consensus Project for Quality Palliative Care,[35] a collaborative effort of five national palliative care organizations, has similar guidelines for patients with advanced chronic illnesses with or without malignancy. Readily accessible by the Internet, those recommendations can help to guide clinicians treating patients with all stages of lung cancer. As is the case for involvement of other specialists, palliative care consultation is most appropriate for complex or refractory problems. Conflict within families or between families and clinicians may require special skills and extended time for communication about care goals. Even without conflict, delivery of distressing news to patients and families in a clear and compassionate way is challenging for virtually all clinicians. Where multiple clinicians from different specialties are involved, palliative care consultants can facilitate consistent communication and care planning. Many physicians and others without specialized palliative care training find it difficult to coordinate the range of social and medical services required by patients with progressive disease and their families. Interdisciplinary palliative care teams provide assistance to clinicians and case managers as well as to patients and families in arranging appropriate transitions between care settings and engaging available services. Complicated grief or bereavement is also addressed by professionals with palliative care expertise.

Institution-specific factors including historical patterns, practices, and circumstances known as "culture" define different roles for palliative care services in different institutions.[16] Some teams function almost exclusively as consultants, providing advice, support, and education to the primary team. In other institutions, the palliative care team may assume comprehensive, primary patient care responsibilities. The value of its input and the success of the palliative care team overall will depend on flexibility and adaptation to this institutional culture both by referring clinicians and by consultants. It will also be important for referring clinicians to remain actively involved with the patient and family as well as with palliative care consultants in all-important aspects of treatment, communication, and planning.

Building a Palliative Care Team

Although a growing number of American hospitals now have palliative care programs, the majority still do not.[18] The benefits of these programs are demonstrable, but many palliative care services cannot fund themselves fully through clinical income and must rely to varying degrees on institutional and philanthropic support. Fortunately, excellent resources are available through the national Center to Advance Palliative Care (CAPC)[36] to support all phases of program development, including step-by-step assistance in formulation of a persuasive initial proposal to the institution and a preliminary business plan. In addition, the CAPC provides practical information and tools for individual clinicians as well as larger teams to use in patient assessment and management, family support, and billing for palliative care services. Intensive hands-on training followed by an extended period of mentorship are available through the CAPC at six exemplary Palliative Care Leadership Centers across the country.[19]

Composition of the Palliative Care Team

The hospital-based palliative care team functions best as an interdisciplinary service,[16] and Clinical Practice Guidelines of the National Consensus Project for Quality Palliative Care[34] provide that specialist-level palliative care is delivered by an interdisciplinary team. Following the model of hospice, early palliative care teams in hospitals often consisted solely of clinical nurse specialists, but today, the hospital team in a large, tertiary institution includes a physician and social worker as well as the nurse specialist. Chaplains, bereavement counselors, and therapists are members of many teams, which may also include pharmacists and nutritionists. The National Consensus Project Guidelines provide that the team includes palliative care professionals with the appropriate patient population-specific education, credentialing and experience, and ability to meet the physical, psychological, social, and spiritual needs of both patient and family. Of particular importance is

hiring physicians, nurses, and social workers who are appropriately trained and ultimately certified in hospice and palliative care.[34] Valuable members and skills/experience requirements of a palliative care team are shown in Table 1.

Maximizing the Benefit of Palliative Care Consultation

Patients appear to benefit most from care that combines appropriate life-prolonging treatment with palliation of symptoms, clear and sensitive communication, functional optimization, and caregiver support, across the trajectory of disease. Although direct empirical data are not yet available, clinical experience, expert opinion, and accumulating evidence suggest that the benefit of palliative care consultation is maximized by early engagement. This will require that referring clinicians as well as patients and families consider from the beginning the real prospect—always present in the context of lung cancer—of progressive disease and death. It will also require that they understand palliative care and curative/life-prolonging treatments as mutually enhancing rather than mutually exclusive. Traditionally, palliative interventions are often deferred until restorative treatment has clearly failed and death is imminent. This has also resulted in the use of burdensome and costly life-prolonging treatments when they are no longer beneficial, and in preventable suffering for patients at all stages of lung cancer. It is never too early for palliative care, and no patient or family facing lung cancer is "not ready yet."

Recommendations

1. For all patients with advanced lung cancer (and their families), it is recommended that palliative care be integrated into their treatment, including those pursuing curative or life-prolonging therapies. Grade of recommendation, 1C

2. For patients with advanced lung cancer, it is recommended that palliative and end-of-life care include involvement of a palliative care consultation team, which should be made available. Grade of recommendation, 1C

Table 1—*The Palliative Care Consultation Team*

Key interdisciplinary team members
Physician
Nurse (specialist)
Social worker
Other valuable team members
Pastoral care representative
Bereavement counselor
Pharmacist
Physical therapist
Nutritionist
Skills/experience
Physical/psychological symptom management
Communication
Spiritual support
Coordination of transitions between care settings
Sophisticated discharge planning
Bereavement support

Health-Related Quality-of-Life Measurements and Assessment of Outcome

Most lung cancers in adults are diagnosed at an advanced stage of disease when antineoplastic options are limited and palliative care assumes a central role.[37] Palliative care aims to reduce symptoms, suffering and enhance health-related quality of life (HR-QOL) for patients and their caregivers.[5,38] These goals are pertinent for adults with advanced lung cancer and their health-care providers because the overall median survival is approximately 6 months despite advances in disease-oriented treatment.[39] Thus, ongoing measurements of symptom distress and HR-QOL may provide assistance to clinicians in the following: (1) early recognition of problems, (2) identification of changes in symptoms over time in response to medical treatments and other interventions, (3) delineation of subgroups that may have unexpected worsening of symptoms and decreased HR-QOL, and (4) promoting discussion among clinicians, patients with lung cancer, and their caregivers, in making decisions about disease-oriented treatment, and about initiating appropriate palliative care services. This overview of the symptom experience and the associated effects on HR-QOL in patients with lung cancer discusses the role of symptom and HR-QOL assessment in the clinical setting, identifies the most common assessment instruments for use in adults with lung cancer, and reviews studies that have evaluated the effectiveness of symptom and HR-QOL assessment on improving clinical outcomes.

Several studies[40–42] have identified that patients with lung cancer experience more symptom severity and distress as compared with other samples of cancer patients. Elderly patients with lung cancer had a greater number of additional symptoms as compared to those with breast, colon, or prostate cancer.[42] Adults with lung cancer had higher levels of symptom distress as compared with women with breast cancer, or men with genitourinary cancer in an ambulatory oncology setting.[41]

Adults with lung cancer often experience multiple symptoms that cluster and change with various disease-oriented treatments and over time.[43–47] The most common symptoms in patients with newly diagnosed lung cancer are fatigue, pain, cough, lack

of appetite, and insomnia. Although many symptoms improve over time, fatigue and pain often remain as persistent symptoms. These two symptoms may also predict the number of other symptoms that patients experience. Of 841 elderly patients with breast, colon, lung, or prostate cancer, patients who reported both pain and fatigue had an average of 6.3 other symptoms, whereas those with fatigue alone had an average of 4.4 symptoms, those with pain alone had 3.8 other symptoms, and those with neither symptom had an average of 2.5 other symptoms.[42] The most common symptoms experienced in adults with lung cancer near the end of life are presented in Table 2.[48–50]

Patients with progressive lung cancer have a high prevalence of uncontrolled symptoms. Kreech and colleagues[51] found a median of nine symptoms among 100 adults with advanced lung cancer. Pain, fatigue, dyspnea, and anorexia were most common. The incidence and severity of dyspnea were highest in the lung cancer sample as compared to other advanced cancer patients.[52] These findings suggest that most lung cancer patients suffer from multiple, dynamic symptoms that may benefit from ongoing assessment.

Similar to symptom distress, high rates of psychological distress and depression have been noted among adults with lung cancer. Zabora and colleagues[53] determined the prevalence of psychological distress among 4,496 cancer patients with 14 different cancer diagnoses. The prevalence rate ranged from a high of 43.4% among adults with lung cancer to 29.6% for adults with gynecologic cancers. Depression has also been reported at higher rates than the general population among persons with lung cancer, especially those with advanced stage disease,[54–56] and has been linked to decreased survival.[57]

Uncontrolled symptoms are associated with decreased HR-QOL and shortened survival.[6,41,10,58] Increased symptom distress was strongly associated with greater psychological distress and reduced quality of life in 243 cancer patients.[59] In elderly adults with lung cancer, increased symptom severity was associated with increased levels of depression and a loss of physical and social functioning.[6,58] Multiple studies[10,41] have shown a link between symptom distress and length of survival. In 53 patients with inoperable lung cancer followed up for 3.5 years, postdiagnosis symptom distress was found to be the most important predictor of survival after adjusting for age, functional status, and personality traits.[10] A subsequent study[41] with 5-year follow-up confirmed these results, finding that increased baseline symptom distress scores in newly diagnosed lung cancer patients predicted decreased survival.

Similar to symptom distress, quality of life has also been shown to be a predictor of survival. Ganz et al[60] found that quality of life was related to length of survival in patients with advanced lung cancer. Median survival was 24 weeks for those reporting a high quality of life, compared to 11.9 weeks for those reporting a low quality of life. Montazeri and colleagues[61] also found that prediagnosis global quality of life was the most significant predictor of length of survival in adults with lung cancer, even after adjusting for age and extent of disease.

In order to enhance clinical outcomes in this population of patients, the use of standardized questionnaires may be useful to monitor symptoms, enhance communication, and improve HR-QOL. The symptom experience is based on symptom occurrence, and distress.[62–64] Symptom occurrence includes frequency, duration, and severity of the symptom, whereas symptom distress is the degree of discomfort as reported by the patient in response to the specific symptom being experienced. To understand the complexity of the symptom experience among adults with lung cancer, multidimensional symptom assessment instruments may be useful, but instrument burden is an issue in certain settings. If a single symptom assessment measure is preferred, symptom distress will provide the most useful information.[65]

HR-QOL assessment is defined as the evaluation of health by using questionnaires that measure various domains, which include patient perception of symptoms, mental health, social factors, and functional status.[66] Increasingly, spirituality is also considered an essential component of HR-QOL in those with advanced disease.[67–70] Desired characteristics of HR-QOL assessment questionnaires include ease of self-administration, multiple dimensions, adequate psychometric properties, and efficacy in the particular patient population and setting in which they will be used.[71]

Table 2—*Highly Distressing Symptoms in Lung Cancer Patients Within 90 Days of Death*

Symptoms*	Patients Reporting High Distress, %
Fatigue	93
Decreased appetite	62
Frequency of pain	55
Cough	55
Insomnia	48
Dyspnea	43
Worried outlook about the future	41
Bowel problems	38
Difficulty concentrating	33
Nausea	30

*Defined as symptoms score ≥ 3 on the SDS (n = 42).

Because symptoms and quality of life are subjective experiences, patient self-reporting is the preferred method of assessment. Evidence suggests that disparity exists between patient and health-care provider perceptions of the patient's symptom status and overall HR-QOL. Physicians tend to underestimate the severity of patient symptoms especially as severity of symptoms increase.[72] Similarly, physicians tend to underestimate overall quality of life in those with advanced cancer.[73]

For comprehensive assessment, it is recommended that at least three domains of HR-QOL be used. Several types of questionnaires are available to measure HR-QOL: generic, disease specific, cancer-site specific, and domain specific.[68,74] Selection of a HR-QOL questionnaire depends on what one wants to measure and how one wants to use the results. Generic measures are not specific to any population and are useful when one wants to compare HR-QOL across populations. Disease-specific measures are designed for a certain group of patients such as those with cancer, cancer site-specific measures focus on a particular type of cancer, whereas domain-specific measures assess particular domains within the overall concept of HR-QOL. Disease-, cancer site-, and domain-specific measures are useful when one wants to monitor changes in an individual over time. A standardized pain questionnaire can help to monitor changes in an individual's pain over time. The combined use of the various types of measures yields greater information about HR-QOL than any one type alone.

Advances have been made in the development and testing of HR-QOL questionnaires. Despite the fact that many of these instruments are brief, reliable, valid, and easy to use and score, the routine use of these questionnaires in clinical practice remains uncommon.[75,76] One problem limiting the use of symptom and HR-QOL assessment questionnaires in the practice setting may be the vast array of instruments that are available. Over 50 instruments have been used to measure quality of life in lung cancer studies.[77] The instruments that have been used most often in adults with lung cancer are the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), the European Organization for Research and Treatment of Cancer Core-30 Item Quality of Life Questionnaire (EORTC-QLQ-30), Functional Assessment of Cancer Therapy-Lung Cancer (FACT-L), Lung Cancer Symptom Scale (LCSS), and the Symptom Distress Scale (SDS).[37,78,79] The SF-36 is a generic measure, the EORTC-QLQ-30 and FACT-L are disease-specific measures but also have cancer site-specific modules, the LCSS is cancer-site specific, and the SDS is domain specific (Table 3).[80–84] Other symptom assessment questionnaires that have been used in adults with cancer are the Memorial Symptom Assessment Scale, Rotterdam Symptom Checklist, Edmonton Symptom Assessment Scale, and Hospital Anxiety and Depression Scale.[85–88]

The development of questionnaires to measure HR-QOL in palliative care and end of life has received increased attention.[69,71,89,90] HR-QOL questionnaires that are used for patients receiving active treatment have several limitations when used in the care of those who have progressive disease and are dying. HR-QOL questionnaires that are used for cancer clinical trials often give increased weight to physical domains of functioning, whose salience may be decreased at the end of life. Moreover, many questionnaires used for clinical trials do not capture the existential and spiritual domain that often increases in importance as death approaches. To address some of these limitations, several questionnaires were designed to specifically measure HR-QOL at the end of life, which include the McGill Quality of Life Questionnaire, Hospice Quality of Life Index, and Missoula-VITAS Quality of Life Index (Table 4).[91–94] A tool kit of instruments to measure end of life care is available and can be accessed at http://www.cher.brown.edu/pcoc/Quality.htm.[89] For more in-depth discussion of the psychometric properties of these instruments, readers are referred to other sources of information.[80–83,95–98]

Use of Symptom and HR-QOL Assessment Questionnaires

In a review of the cancer literature, symptom and HR-QOL assessment interventions were defined as studies that administered a patient self-reporting HR-QOL questionnaire with the intent of using the results to improve clinical care. The growing number of studies[99–118] show that the use of these questionnaires is feasible in the clinical setting, and that both patients and clinicians have found them to be of potential value in enhancing the clinical encounter. Collective results showed that HR-QOL assessment improved some clinical outcomes but not others. Overall symptom distress and patient/health-care provider communication improved, but patient satisfaction and clinical management were not responsive to change.[119] It appears that the systematic use of these questionnaires may be more effective for certain subgroups of patients (*eg*, cancer patients who were moderately to severely depressed at baseline had improved outcomes at 6 months).[110] In another study,[114] the explicit use of HR-QOL data and discussion of pain and role function were associated with clinically significant improvement in HR-QOL.

Table 3—*Comparison of Key Characteristics of HR-QOL Measures for Patients With Lung Cancer

Characteristics	FACT-L	LCSS	EORTC-QLQ-C30/ EORTC-QLQ-LC13	SDS
Focus	Generic with site-specific modules	Site specific	Disease-specific with site-specific modules	Domain specific
No. of items	27 items for core module; 7 or 9 items for lung cancer module (option of not scoring 2 items)	9 items for patient scale; 6 items for observer scale	30 items for core module; 13 items for lung cancer module	13 items
Scale type	5-point Likert scale	Visual analogue scale: patient scale; categorical scale: observer scale	4-point Likert scale	5-point Likert scale
Reliability and validity data	Reliable: yes; valid: yes	Reliable, yes; valid, yes	Reliable: yes; Valid: yes	Reliable, yes; valid, yes
Quality-of-life domains	1, physical; 2, functional; 3, emotional; 4, social/ family	1, physical; 2, functional; 3, global quality of life	1, global quality of life; 2, functional scales: physical, role, emotional, cognitive, and social; 4, symptoms; 5, financial impact	1, physical; 2, emotional
Symptom domains	Core module: general side effects of treatment, insomnia, lack of energy, nausea, pain, sexuality; lung module: appetite, breathing, chest tightness, cognition, cough, weight loss	Appetite, cough, dyspnea, fatigue, general symptoms, hemoptysis, pain	Core module: appetite loss, constipation, diarrhea, dyspnea, fatigue, insomnia, nausea and vomiting, pain; lung module: alopecia, cough, dysphagia, dyspnea, hemoptysis, neuropathy, pain, sore mouth	Appearance, appetite, bowel function, concentration, cough, dyspnea, fatigue, insomnia, nausea, outlook, pain

*EORTC-QLQ-LC13 = European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-Lung Cancer.

Only three studies[110,112,113] addressed the use of these questionnaires as an intervention in lung cancer patients. Although encouraging, studies conducted to date have used quasiexperimental designs or have had small sample sizes, so larger, more rigorous studies are needed to evaluate the efficacy of systematic assessment within this group. Questionnaires may be especially helpful among lung cancer patients, who often experience higher rates of symptoms and psychological distress. Cooley and colleagues[101] found that outpatients with advanced cancer undergoing specific treatment preferred symptom assessment questionnaires (*ie*, Symptom Distress Scale and Hospital Anxiety and Depression Scale), and disease-specific questionnaires (*ie*, FACT-L or European Organization for Research and Treatment of Cancer-Lung). The frequency of using the standardized assessment intervention varied from patients completing the questionnaire only once to completing it at every clinic visit.[110,112,114] Studies[109,112,114] that administered the standardized assessment questionnaire on at least three consecutive clinic visits or on a monthly basis had significant improvement in patient outcomes.

Barriers to Implementation of Standardized Assessment in the Clinical Setting

Challenges exist in widespread adoption with recent evidence that HR-QOL assessment rarely occurs in clinical practice within the United States.[76] Potential problems that may limit their use are lack of provider knowledge about application of HR-QOL data, lack of knowledge about the interpretation of HR-QOL scores, and logistical problems in data collection and recording.[120] Now the SF-36 has extensive information about normative values, and data from adults with lung cancer can be compared with these values to understand the context and meaning for scores. Data have also been gathered about the use of the FACT, European Organization for Research and Treatment of Cancer, LCSS, and SDS questionnaires in adults with lung cancer, and reference values for symptom and HR-QOL domains are available.[80,84,98,121–123] Also, progress is being made in identifying a clinically meaningful change in scores. Cella and colleagues[124] determined that a 2- to 3-point change in the lung cancer subscale and a 5- to 6-point change in the treatment

Table 4—*Comparison of Key Characteristics of HR-QOL Measures for Patients With Progressive Disease/End of Life*

Characteristics	McGill Quality of Life Questionnaire	Hospice Quality of Life Index	Missoula-VITAS Quality of Life Index	Edmonton Symptom Assessment System
Population	Palliative care, hospice, cancer, HIV	Hospice Cancer	Advanced, incurable disease, hospice, long-term care, end-stage renal disease	Palliative Care Cancer
No. of items	16 items	28 items	25-item or 15-item versions	9 items
Scale type	11-point Likert scale	11-point Likert scale	Each item consists of single statement with agree/disagree anchors; respondent chooses one of five responses indicating amount of agreement between the two anchors	11-point numerical rating scale Visual analogue scale Graph
Reliability and validity data	Reliability, yes; validity, yes	Reliability, yes; validity, yes	Reliability, yes; validity, yes	Reliability, yes; validity, yes
Quality-of-life domains	1, physical; 2, physical symptoms; 3, psychological; 4, existential; 5, support; 6, global quality of life	1, physical; 2, psychological; 3, social	1, symptoms; 2, function; 3, interpersonal; 4, well-being; 5, transcendent	1, physical; 2,emotional
Symptom domains	Write in three most troublesome symptoms	Fatigue, insomnia, dyspnea, appetite, constipation, nausea, sexuality	General assessment of symptoms, satisfaction with symptom control, and level of physical distress	Pain, fatigue, nausea, depression, anxiety, drowsy, well-being, dyspnea, other problems

outcome index of the FACT-L questionnaire constituted a clinically meaningful change in patients with advanced non-small cell lung cancer receiving chemotherapy during a clinical trial.

Another challenge is minimizing the logistical barriers with clinical resources often stretched to the limit in the current health-care environment. Successful strategies for implementation have been identified in feasibility studies. Wright and colleagues[108] found that integrating these measures into the routine care of the clinic setting was successful, resulting in higher rates of patient completion over time. Automated data collection solved many of the logistical barriers. Patient acceptance of these methods of HR-QOL data collection was high. For further improvement, increased attention to the principles of effective dissemination, new information infrastructures and technologies, in combination with redesign of care[76] are advocated.

Recommendation

3. For patients with advanced lung cancer, it is recommended that standardized evaluations with symptom assessment and abbreviated disease-specific HR-QOL questionnaires should be administered by the responsible member of the health-care team at the appropriate frequency. Grade of recommendation, 1B

Bereavement

The emotional pain of grief and bereavement has physical dimensions, particularly when the loss is sudden and unexpected, with survivors possibly experiencing substantial morbidity or mortality. Grief is the quintessential mind-body problem[125]; the nature of grief is that of a multidimensional loss.[126] Even our terminology about death and bereavement creates a sensation of separation, loss, and change.

In caring for a person who has died, a physician's role continues beyond the death itself.[127] That patient is a member of a family unit, and in compassionate care for the dying patient, the physician is also caring for the family. This should not end abruptly when the patient dies.[128]

Emotional tasks for someone who has been left behind include making sense of the death, finding

meaning, restoring integrity, managing affect, managing emotions, and realigning relationships, including the relationship with the deceased.[129–132] How the survivor fares in their grief experience is related to how their loved one died, who the deceased was, who the survivor is, and what the relationship was. There is no medical literature specific to families of lung cancer victims, but the assumption is that there are elements of the survivor's experience of grief that are common regardless of the diagnosis. As to closure, the sense is that the adjustment to grief must proceed at its own pace and, particularly for close family members, may be a life-long process.[130,133,134]

Loss-attachment theory is commonly used to describe the emotional experience of bereavement.[129] The survivor must revise internal models, and plans must change. Status, power, and control are often lost, and one's very identity alters.[129,131] The survivor must accept the reality of the loss on both intellectual and emotional levels, and adjust to an environment in which the deceased is missing.[135]

Engel[136] saw the process of mourning as a process of healing. In a small observational series[137] of survivors with high risk factors for dysfunctional grief, several associations were noted that potentially contributed to personal growth as an outcome of grief. Such adaptive grief characteristics include the ability to see some good resulting from the death, having a chance to say goodbye, intrinsic spirituality, and spontaneous positive memories of the decedent.

Clinicians may be able to assist patients and families grieve in a more normal or "healthier" manner if they are able to facilitate adaptive grief by the following:

- Giving sufficient forewarning for all parties that death is pending, providing the opportunity to at least begin to process the experience rather than being forced to face it suddenly. Anticipatory grief has not been shown to modify the experience of actual grief.[129,131] This is rather a kindly warning to take special time together, to perhaps enable a discussion about life and death, which may give comfort to survivors.[129,138]
- Providing adequate notice of imminent death so they can be present if possible because inability to be present at the death may lead to guilt.[130,134,135,139,140]
- Making available palliative care to include focus on existential issues where appropriate[141] because problems in death experience can be associated with problems for the survivors.[142]
- Honoring and respecting the cultural and religious practices of the patient and family because open-minded attitudes from clinicians can make the experience of death for survivors less traumatic.[143,144]
- Following up with survivors as a manifestation of caring, and to assess for any problems with the grieving process because some normal experiences of bereavement might in other situations be interpreted as signs of mental illness.[129,130,132,135,145]

Sufficient Forewarning

Having a chance to say goodbye appears to be very important to survivors, and those who lose their loved ones suddenly and unexpectedly may show less resilience in recovery, and more anger and pain.[130,134,135,139,140] Forewarning appears to improve adjustment during bereavement, particularly for widows.[146,147] The critical amount of forewarning necessary appears to be approximately 2 weeks.[130,146]

Forewarning creates some space for joint processing of the experience. Of parents in Sweden who had lost a child to cancer, none of the 147 parents who had talked with their child about death regretted it, but 27% of parents who did not discuss this regretted not having done so.[138]

Deaths that are expected are less likely to give rise to lasting psychological problems in the bereaved than those that are unexpected. In 2 years of follow-up of a series of sudden deaths, survivors who had no warning of potential loss subsequently had more sick days and larger number of psychiatric diagnoses than did a group of survivors with advanced warning.[139]

Psychiatric Difficulties and the Range of Normal

Both grief and clinical depression are syndromes that share constitutional symptoms such as sleep and appetite disturbance, as well as intense sadness, but in a grief reaction there is not the loss of self esteem that is associated with depression.[135] Pharmacotherapy is useful for symptoms of true depression in survivors.[148] Formal grief counseling is not always helpful and should probably be reserved for those bereaved who truly appear to be dysfunctional.[149,150]

The range of normal in bereavement embraces experiences that under other circumstances might be considered pathologic, and it may be helpful to reassure that these events are actually normal for the situation.[129] Survivors may have a sense of the presence of the deceased (*eg*, many children feel watched over by their deceased parent for up to 2 years).[135] Transient hypnagogic hallucinations in which the deceased are seen or heard are reported by up to 50% of widows and may be misinterpreted as signs of mental illness.[129] During this phase of yearning and searching, environmental cues can be perceived and interpreted as the actual presence of the deceased.[132] Hearing or seeing a vision of a dead partner is culturally associated, and is mostly a

pleasant experience.[130] Of 14 men and 36 women in their early 70s during the first year of bereavement, a third of subjects experienced episodes of seeing the deceased, and half had illusions of feeling the presence of and of hearing and talking to the deceased.[146]

Existential Well-being

Nurture of spirituality may improve both the experience of death for the dying person and the bereavement experience of survivors. For Swedish parents discussing death with their dying children, discussion of existential issues such as the idea of life after death, affected quality of the dying experience for the family unit.[138] Spirituality, as well as but distinct from religious beliefs,[141] may contribute to well-being and coping strategies.[151]

Successful palliative care enables a dying person to adapt to the situation and find quality in the existential, spiritual, psychological, and social domains despite the decline in physical and functional domains. The assumption is that improved patient adaptation to the experience of dying may help the survivor in adaptation to the loss. In two small studies of terminally ill cancer patients, scores of existential well-being correlate with physical well-being and psychological symptoms despite physical pain,[151] and depression and hopelessness were inversely related to spiritual well-being.[152] In a group of 1,610 ethnically diverse cancer patients, spirituality was shown to have a positive association with quality of life affecting it as much as physical well-being.[70]

Spiritual beliefs have been shown to be important in predicting clinical outcome for dying patients,[153] in management of death distress,[154] and in occurrence of end-of-life despair.[155] The presence of religious beliefs may reduce dependence on health professionals by cancer patients as they are dying.[156] One study[157] looked at how spiritual beliefs in survivors may assist in adaptation to loss, but no study has yet examined how nurturing spiritual belief and existential comfort in the dying patient might help the survivor.

Rituals for Death and Dying

Culture influences the meaning and experience of death and dying as well as mourning practices.[158] For the sake of both the deceased and the survivors, religious rituals of death should be honored.[159] Physicians need to maintain a nonjudgmental attitude toward unfamiliar beliefs and practices and be willing to negotiate and compromise when world views conflict.[143] Mourning is culture based, what Parkes[129] called "the social face of grief." Customs, rituals, and how that family functions as a subunit of its culture all introduce variables.[159] Misunderstandings can develop from the simplest differences in body language, custom, or address. Human touch demonstrates respect for grieving Latino individuals,[159] but Chinese do not usually like to be touched.[160] Sending cut flowers is not part of the Jewish tradition.[159] Laotian elders believe that their "death date" is predestined; if you talk about death, you are tempting fate, a taboo that is common to all Southeast Asian cultures,[161] yet is in direct conflict with the recommendation that the clinician be open and honest about impending death. Several countries believe that each person has several souls, regional variation ranging from 3 to 32 souls.[158]

In a study by the Connecticut Coalition to Improve End of Life Care, 95 participants identified 10 domains that characterize the quality of the death experience, and only 1 domain related to physical distress. Minority participants were concerned that spiritual aspects of dying are not adequately addressed currently, that there is insufficient respect and tolerance for cultural and religious differences, and that respect for each death as a unique and individual phenomenon is lacking.[144]

Bereavement is a family developmental process that unfolds in cultural context.[162] Prevailing North American attitudes toward practices of other cultures can be very narrow minded, particularly the attitude that recovery is associated with successful detachment from the dead.[162] Geissler[160] notes that concepts of health, illness, and care cannot readily be separated from general cultural values, beliefs, and practices; many of the tenets of conventional medicine and role expectations during the patient-provider encounter are derived from a Northern European world view that espouses individualism, independence, paternalism, reductionism, and belief in the scientific methods of finding truth.

Historically, Freud's[163] work in 1917 compared the emotions experienced in mourning to those of melancholia, and Lindemann[164] in 1944 described the experience of 101 bereaved who had lost their loved one in a night club disaster, coining the concept of morbid grief characterized by somatic distress, preoccupation with the image of the deceased, guilt, hostility, and loss of patterns of conduct.

The identification of pathologic, complicated, morbid, or traumatic grief may be difficult due to a wide spectrum that probably qualifies as normal grief,[6,43] which is a self-limiting process consisting of sadness, longing for the deceased person, somatic complaints, and subsequent recovery.[134]

Physicians should not impose their own notions about what is healthy or unhealthy grief but should reference the assumptions of the culture/subcultures about good and bad, and health and sickness.[162]

Although there is no specific time frame for failure to adapt to loss that signals impaired grief, specific symptoms may be used as discriminators to identify abnormal reactions to loss[134]: negative perceptions of self, functional impairment, profound depression, suicidal ideation, and pervasive feelings of worthlessness. In 112 participants after bereavement, Ott[165] identified 29 participants with complicated grief as early as 6 months after loss; this group had more additional life stressors, perceived less social support, and achieved less improvement. Survivors with previous psychiatric histories, low self esteem or poor coping skills, high levels of dependency on the deceased, and abuse/trauma histories are high risk. There is also a category of "high distress" that may be identified early in bereavement: high levels of depressive, anxiety, anger, or rumination symptoms are associated with high intensity of grief reaction at the outset and correlate with poor 2-year outcome.[149] A randomized controlled trial[166] in treatment techniques for individuals with complicated grief indicates that combining techniques for treatment of posttraumatic stress disorder with standard interpersonal therapy techniques used for depression may improve grief scores to a greater degree and with faster response times than use of techniques to treat depression alone.

There may be physical as well as psychological morbidity, such as increased morbidity in cardiac events, hypertension, cancer, suicidality, changes in food, alcohol and tobacco intake, and constitutional complaints at the 6-month point following loss.[167,168] Palliative care and hospice care services may not only help the dying patient but may also improve both psychological[147] and physical[169] bereavement outcomes.

Medical Morbidity of Grief

There appears to be an overall increased risk of premature death for survivors in the years immediately following the death of a spouse.[127,170] The bereaved are probably at greater risk of death especially in the first year of their loss, and men are at greater risk, but the risk remains small in absolute terms.[131,171–179] Christakis and Allison[170] have shown that not only is there increased risk of death following death of a spouse, there is even increased risk following hospitalization of a spouse. Caregiving itself, during the patient's illness and decline, is an increased risk factor for mortality, particularly when the caregiver experiences strain.[180]

The physiologic stress created by the impact of loss has been associated with altered autonomic, immune, and endocrine response.[181–184] The connection between disrupted sleep and depression of the immune system was made by Irwin et al.[185] Normal sleep patterns at 6 months following loss of a spouse correlate with better emotional health and energy a year later.[186] Consistent exercise at least once a week and consistent attention to appropriate caloric intake correlate with better health in survivors as well.[186] One of the goals in future research about bereavement is to develop a stronger identification of possible cause-and-effect relationship between the experience of loss and physiologic immune and/or neuroendocrine changes that may alter medical outcome.[125]

Practitioner Intervention

Practitioners can contribute to the recovery of bereaved family and friends of their dying patients in a number of different ways:

- Make decisions early about how to face impending death, notifying the patient and family that hopes need to be altered and changing circumstances need to be adapted to.
- Provide the patient as much support in the dying process as possible: access to the support systems that are provided may help family as well as patient.
- Provide the opportunity for family to be at the bedside when death occurs if possible.
- Focus on the family as well as the patient during the death.[129]
- Enquire into cultural rituals and beliefs in death and dying.[158–160,187]
- Accept as normal those experiences of survivors that entail visitations of the departed.
- Identify those survivors at risk for correct referral because among many studies of interventions with positive outcomes there have been observations of treatment-associated deterioration.[149,150]
- Encourage maintenance of healthy lifestyle during the period of caregiver burden as well as during bereavement.[186]

The Institute of Medicine in 1984 indicated its belief that health professionals, having become involved with the families of dying patients prior to the death, have some obligations to these families after the death.[127] Follow-up or some condolence contact by caregivers appears to be a particularly comforting note for the bereaved.[133,134,140,188–190] Failure to communicate conveys a lack of concern about the loss.[190] Follow-up also enables diagnosis of potentially maladaptive mourning.[128] Some follow-up is indicated, even if purely for social-emotional reasons.[191] There may be unanswered questions.[140] Contact after death reassures the survivor that something more than mechanical medicine had been given.[130]

In a study[146] of 78 widows and 41 widowers, physicians of lost spouses had disappointed 33% of widows and 27% of widowers. Primary issues were allegations of failure to be honest; avoiding the family; lacking gentleness; having a poor bedside manner; being cold, impersonal, or unconcerned; and misdiagnosing the disease. Characteristics of physicians who offered great help to surviving spouses included honesty, compassion, availability, and an unhurried and comforting manner.[146]

The clinical tools to avoid such disappointment are basic communication skills such as active listening, joint reflection, empathy, setting limits, and clarification of the emotions being experienced.[134] In particular, the clinician can provide reassurance about the normality of grief or simple explanations of any symptoms.[129]

Clinician

The grief experience of clinicians is similar to that of loved ones, in quality if not in severity,[192] but the term *disenfranchised* has been applied to the grief of clinicians because it seems somehow less legitimate than the grief of family and friends.[193] There are additional challenges that involve issues of professional maturity,[194] competence, integrity, and interprofessional friction that may contribute to special difficulties for clinicians.[195] Of particular note is the tendency of clinicians to blame themselves for imagined failures; grief may be more intense if it is believed that the death was preventable.[195]

For oncology nurses, work stresses influence nursing burnout.[194,196] Nurses who face their own mortality and recognize their own reactions without defensiveness can cope constructively.[196] Informal surveys of bereavement workshops suggests that most nurses feel they manage their own grief more effectively if they help the patient die a good death.[194]

In a study of the physician's emotional reactions to the death of a patient in two US academic hospitals, 74% of physicians reported satisfying experiences in the care of 68 dying patients.[197] Women physicians and those physicians who had cared for their patients for a longer period of time tended to have stronger emotional reactions to the death of their patient. Less than one fourth of interns and residents found that their faculty were helpful in providing them emotional support.

It is as important for physicians as it is for family members to accept the normalcy of their own feelings of bereavement. Physicians should be alert to their own emotional reactions and take care to name and embrace their strong feelings because failure to do so may promote distress, disengagement, burnout, and poor medical judgment.[198] It has been shown that strong personal reaction may be deleterious in emotionally charged situations.[199]

With respect to death and dying issues, lack of self-awareness by clinicians regarding their own feelings about life-sustaining medical technology, death, and disability may contribute to inappropriate prescription of such technology; there may be failure to face the difficult decisions directly about appropriateness, particularly if there are high levels of ambiguity and uncertainty.[198]

If a physician has emotional discomfort with end-of-life issues, it may also inhibit effective handling of patient and family interchanges on death, dying, and bereavement issues. Physicians may feel awkward in discussing emotionally charged topics of such an existential nature, but learning how to respond effectively to the patient's and family's religious and spiritual concerns may help everybody, including the clinician, to find comfort and closure.[200,201]

Burnout, however, can be associated also with insufficient training in communication.[202] If, through practice and experience in caring for the dying and their families, specific rewards can be identified by the practitioner, distress caused by grieving for a patient's death can become more acceptable[191,203] and become a source of professional reward.[191]

Clinicians must develop a delicate balance between emotional involvement and detachment. Considering the multidimensional impact in the loss of a patient, Parkes[129] suggests that we examine our own mortality by asking ourselves, "Is today a good day to die?"

Recommendations

4. It is recommended that clinicians of patients who die from lung cancer should extend communication with the bereaved family and friends after death. Grade of recommendation, 1C

5. For patients with lung cancer, proactive interventions, such as those listed below, are recommended to improve grief outcomes: (1) informing the patient and family of foreseeable death within weeks; (2) forewarning family of impending death; and (3) enabling effective palliative care, focused on spiritual, existential, physical, and practical concerns. Grade of recommendation, 1C

6. It is recommended that clinicians of dying patients with lung cancer encourage caregivers to maintain a healthy lifestyle during the period of caregiver burden, as well as during bereavement. Grade of recommendation, 1C

7. It is recommended that clinicians of patients dying from lung cancer honor rituals of death and mourning in a culturally sensitive manner. Grade of recommendation, 1C

Conclusion

Palliative care consultation and expertise should be available for patients with lung cancer from the time of diagnosis and planning of primary modes of attempted curative therapy until their demise. This multidisciplinary team should be utilized for the application of supportive care modalities for the patient, family, and caregivers. The leader of this team could be a newly recognized and credentialed subspecialist in internal medicine. HR-QOL measurements are of clinical importance in the continuous assessment of symptomatic distress in these patients throughout the course of their disease, which permits the earliest and most beneficial application of specific palliative therapy. Bereavement identifies an additional attending physician responsibility in considering the physical and emotional needs of family members and caregivers before, during, and after the death of their loved one.

Summary of Recommendations

1. For all patients with advanced lung cancer (and their families), it is recommended that palliative care be integrated into their treatment, including those pursuing curative or life-prolonging therapies. Grade of recommendation, 1C

2. For patients with advanced lung cancer, it is recommended that palliative and end-of-life care include involvement of a palliative care consultation team, which should be made available. Grade of recommendation, 1C

3. For patients with advanced lung cancer, it is recommended that standardized evaluations with symptom assessment and abbreviated disease-specific HR-QOL questionnaires should be administered by the responsible member of the health-care team at the appropriate frequency. Grade of recommendation, 1B

4. It is recommended that clinicians of patients who die from lung cancer should extend communication with the bereaved family and friends after death. Grade of recommendation, 1C

5. For patients with lung cancer, proactive interventions, such as those listed below, are recommended to improve grief outcomes: (1) informing the patient and family of foreseeable death within weeks; (2) forewarning the family of impending death; and (3) enabling effective palliative care, focused on spiritual, existential, physical, and practical concerns. Grade of recommendation, 1C

6. It is recommended that clinicians of dying patients with lung cancer encourage caregivers to maintain a healthy lifestyle during the period of caregiver burden, as well as during bereavement. Grade of recommendation, 1C

7. It is recommended that clinicians of patients dying from lung cancer honor rituals of death and mourning in a culturally sensitive manner. Grade of recommendation, 1C

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