



## Establishing the Diagnosis of Lung Cancer

### Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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**Background:** Lung cancer is usually suspected in individuals who have an abnormal chest radiograph or have symptoms caused by either local or systemic effects of the tumor. The method of diagnosis of lung cancer depends on the type of lung cancer (small cell lung cancer or non-small cell lung cancer [NSCLC]), the size and location of the primary tumor, the presence of metastasis, and the overall clinical status of the patient. The objective of this study was to determine the test performance characteristics of various modalities for the diagnosis of suspected lung cancer.

**Methods:** To update previous recommendations on techniques available for the initial diagnosis of lung cancer, a systematic search of the MEDLINE, Healthstar, and Cochrane Library databases covering material to July 2011 and print bibliographies was performed to identify studies comparing the results of sputum cytology, conventional bronchoscopy, flexible bronchoscopy (FB), electromagnetic navigation (EMN) bronchoscopy, radial endobronchial ultrasound (R-EBUS)-guided lung biopsy, transthoracic needle aspiration (TTNA) or biopsy, pleural fluid cytology, and pleural 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 (see the article “Methodology for Development of Guidelines for Lung Cancer” in this guideline), and reviewed by all members of the Lung Cancer Guideline Panel prior to approval by the Thoracic Oncology NetWork, the Guidelines Oversight Committee, and the Board of Regents of the American College of Chest Physicians.

**Results:** Sputum cytology is an acceptable method of establishing the diagnosis of lung cancer, with a pooled sensitivity rate of 66% and a specificity rate of 99%. However, the sensitivity of sputum cytology varies according to the location of the lung cancer. For central, endobronchial lesions, the overall sensitivity of FB for diagnosing lung cancer is 88%. The diagnostic yield of bronchoscopy decreases for peripheral lesions. Peripheral lesions < 2 or > 2 cm in diameter showed a sensitivity of 34% and 63%, respectively. R-EBUS and EMN are emerging technologies for the diagnosis of peripheral lung cancer, with diagnostic yields of 73% and 71%, respectively. The pooled sensitivity of TTNA for the diagnosis of lung cancer was 90%. A trend toward lower sensitivity was noted for lesions < 2 cm in diameter. TTNA is associated with a higher rate of pneumothorax compared with bronchoscopic procedures. In a patient with a malignant pleural effusion, pleural fluid cytology is reported to have a mean sensitivity of about 72%. A definitive diagnosis of metastatic disease to the pleural space can be established with a pleural biopsy. The diagnostic yield for closed pleural biopsy ranges from 38% to 47% and from 75% to 88% for image-guided closed biopsy. Thoracoscopic biopsy of the pleura carries the highest diagnostic yield, 95% to 97%. The accuracy in differentiating between small cell and non-small cell cytology for the various diagnostic modalities was 98%, with individual studies ranging from 94% to 100%. The average false-positive and false-negative rates were 9% and 2%, respectively. Although the distinction between small cell and NSCLC by cytology appears to be accurate, NSCLCs are clinically, pathologically, and molecularly heterogeneous tumors. In the past decade, clinical trials have shown us that NSCLCs respond to different therapeutic agents based on histologic phenotypes and molecular characteristics. The physician performing diagnostic procedures on a patient suspected of having lung cancer must ensure that adequate tissue is acquired to perform accurate histologic and molecular characterization of NSCLCs.

**Conclusions:** The sensitivity of bronchoscopy is high for endobronchial disease and poor for peripheral lesions < 2 cm in diameter. The sensitivity of TTNA is excellent for malignant disease, but TTNA has a higher rate of pneumothorax than do bronchoscopic modalities. R-EBUS and EMN bronchoscopy show potential for increasing the diagnostic yield of FB for peripheral lung cancers. Thoracoscopic biopsy of the pleura has the highest diagnostic yield for diagnosis of metastatic pleural effusion in a patient with lung cancer. Adequate tissue acquisition for histologic and molecular characterization of NSCLCs is paramount. *CHEST* 2013; 143(5)(Suppl):e142S–e165S

**Abbreviations:** ACCP = American College of Chest Physicians; ALK = anaplastic lymphoma kinase; CT-ANPB = CT scan-guided Abrams needle pleural biopsy; EBUS = endobronchial ultrasound; EBUS-NA = endobronchial ultrasound-guided needle aspiration; EGFR = epidermal growth factor receptor; EMN = electromagnetic navigation; EUS-NA = endoscopic ultrasound-guided needle aspiration; FB = flexible bronchoscopy; FN = false-negative; FNA = fine needle aspiration; NSCLC = non-small cell lung cancer; PICO = patient, intervention, comparison, outcomes; PLL = peripheral lung lesion; R-EBUS = radial endobronchial ultrasound; SCLC = small cell lung cancer; TBNA = transbronchial needle aspiration; TTNA = transthoracic needle aspiration; TUS = thoracic ultrasound

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## SUMMARY OF RECOMMENDATIONS

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### *General Approach to Diagnosis*

**2.3.1. In patients suspected of having small cell lung cancer (SCLC) based on the radiographic and clinical findings, it is recommended that the diagnosis be confirmed by the least invasive method (sputum cytology, thoracentesis, fine needle aspiration [FNA], bronchoscopy including transbronchial needle aspiration [TBNA]), as dictated by the patient's presentation (Grade 1C).**

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**2.3.2. In patients suspected of having lung cancer, who have extensive infiltration of the mediastinum based on radiographic studies and no evidence of extrathoracic metastatic disease (negative PET scan), it is recommended that the diagnosis of lung cancer be established by the least invasive and safest method (bronchoscopy with TBNA, endobronchial ultrasound-guided needle aspiration [EBUS-NA], endoscopic ultrasound-guided needle aspiration [EUS-NA], transthoracic needle aspiration [TTNA], or mediastinoscopy) (Grade 1C).**

**2.3.3. In patients suspected of having lung cancer who have a solitary extrathoracic site suspicious of a metastasis, it is recommended that tissue confirmation of the metastatic site be obtained if a FNA or biopsy of the site is feasible (Grade 1C).**

**2.3.4. 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 least invasive method (Grade 1C).**

**2.3.5. 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 1C).**

*Remark:* Ultrasound-guided thoracentesis improves the success rate and decreases the rate of pneumothorax and therefore ultrasound is recommended for performing diagnostic thoracentesis.

**2.3.6. In patients suspected of having lung cancer who have an accessible pleural effusion, if pleural fluid cytology is negative, pleural biopsy**

(via image-guided pleural biopsy, medical or surgical thoracoscopy) is recommended as the next step (Grade 1C).

*Remark:* If the CT scan of the chest shows pleural thickening or pleural nodules/masses, image-guided needle biopsy may be considered as the first step to obtain a biopsy of the pleura.

*Remark:* If pleural cytology is negative after the first thoracentesis, a second thoracentesis has been shown to increase the diagnostic yield of pleural fluid cytology. Depending on preferences and values (a simpler and less invasive test vs a more definitive test) a second thoracentesis may be considered before proceeding to biopsy of the pleura.

#### *Diagnosis of the Primary Tumor*

**3.1.2.1. In patients suspected of having lung cancer, if sputum cytology is done but is negative for carcinoma, it is recommended that further testing be performed (Grade 1C).**

*Remark:* Sputum cytology is an acceptable method of establishing the diagnosis. However, the sensitivity or sputum cytology varies by location of the lung cancer, and with the frequency and processing of the sputum at the center.

**3.2.2.1. 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 non-diagnostic and suspicion of lung cancer remains (Grade 1B).**

*Remark:* In recent years a number of complementary tools including radial endobronchial ultrasound and electromagnetic navigation have been added to flexible bronchoscopy to aid in the diagnosis of peripheral lung lesions.

**3.3.2.1. In patients suspected of having lung cancer, who have a peripheral lung nodule, and a tissue diagnosis is required due to uncertainty of diagnosis or poor surgical candidacy, radial EBUS is recommended as an adjunct imaging modality (Grade 1C).**

*Remark:* Radial EBUS can confirm in real time the ideal location of bronchoscopic sampling and increase the diagnostic yield over conventional bronchoscopy for peripheral nodules.

**3.4.2.1. In patients with peripheral lung lesions difficult to reach with conventional bronchos-**

**copy, electromagnetic navigation guidance is recommended if the equipment and the expertise are available (Grade 1C).**

*Remark:* The procedure can be performed with or without fluoroscopic guidance and it has been found complementary to radial probe ultrasound.

*Remark:* If electromagnetic navigation is not available, TTNA is recommended.

**3.5.2.1. In patients suspected of having lung cancer who have a peripheral lesion, and who require tissue diagnosis before further management can be planned, TTNA is a diagnostic option. However, it is recommended that further testing be performed if TTNA results are non-diagnostic and suspicion of lung cancer remains (Grade 1B).**

**3.6.2.1. In patients suspected of having lung cancer, the diagnosis of non-small cell lung cancer made on cytology (sputum, TTNA, bronchoscopic specimens, or pleural fluid) is reliable. However, it is recommended that adequate tissue be obtained to accurately define the histologic type and to perform molecular analysis when applicable (Grade 1B).**

*Remark:* It is critical to obtain adequate tissue to characterize a lung cancer. Within an institution, effective communication between those obtaining the biopsies, those interpreting them, and those delivering the treatment must be in place so that collectively, the members of various subspecialties involved in the care of the lung cancer patient can decide how best to obtain and optimally use the tissue. If specimens are not adequate for histologic and molecular characterization then obtaining a second biopsy is acceptable given the importance of accurate tumor characterization.

**3.6.2.2. 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 be performed to establish a definitive cell type (Grade 1B).**

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Approximately 75% to 80% of newly diagnosed lung cancers are non-small cell lung cancers (NSCLCs) (adenocarcinoma, large cell carcinoma, or squamous cell carcinoma). The clinical presentation and the findings on CT scan and/or fluoro<sup>18</sup>-2deoxyglucose-PET scan of the chest usually allow the physician evaluating a patient with suspected lung cancer to presumptively make a diagnosis of lung cancer and

differentiate between NSCLC and small cell lung cancer (SCLC). Massive lymphadenopathy and direct mediastinal invasion, or masses in or adjacent to the hilum, are particular radiographic characteristics of SCLC, reported in about 78% of cases.<sup>2,3</sup> Not infrequently, SCLC presents with paraneoplastic syndromes,<sup>4</sup> which include the syndrome of inappropriate antidiuretic hormone, ectopic adrenocorticotrophic hormone production, and the Lambert-Eaton syndrome. If SCLC is suspected, the diagnosis should be established 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, bronchoscopy with or without transbronchial needle aspiration [TBNA] of mediastinal nodes, or submucosal process). If the diagnosis of SCLC is established based on a biopsy of the primary lesion, the distinction between limited or extensive disease is then made radiographically.

In patients suspected of having NSCLC, the method of achieving a diagnosis is usually dictated by the presumed stage of the disease. NSCLC can present with extensive infiltration of the mediastinum, defined as a mass that infiltrates and encases the mediastinal structures and where no discrete mediastinal lymph nodes are visible. In such patients, the diagnosis should be established by the method that has the most favorable risk-benefit ratio. Bronchoscopy with TBNA for cytologic or histologic examination of mediastinal lymph nodes has been shown to be a safe procedure.<sup>5-8</sup> Technical aspects that are frequently emphasized as 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.<sup>9-11</sup> The overall sensitivity of TBNA is 76%, and the specificity is 96%.<sup>5-8,11-14</sup> Endobronchial ultrasound (EBUS)-guided needle aspiration (EBUS-NA) has emerged as a minimally invasive procedure for sampling mediastinal lymph nodes or masses, with a diagnostic yield of 93% (95% CI, 91%-94%) and a specificity of 100% (95% CI, 99%-1%).<sup>15</sup> (The reader is referred to Silvestri et al<sup>16</sup> in the American College of Chest Physicians (ACCP) Lung Cancer Guidelines for a more detailed review of the performance characteristics of TBNA and EBUS-NA for staging the mediastinum). The negative predictive value of TBNA (71%) is not high enough to obviate the need for further confirmation of negative results. Mediastinoscopy is warranted in patients with nondiagnostic results.

Transthoracic (CT scan-guided) needle aspiration (TTNA) of mediastinal masses or nodes (nodes >1.5 cm) can be performed safely.<sup>17</sup> The role of TTNA in patients with extensive mediastinal disease (defined as such extensive mediastinal tumor that discrete

lymph nodes can no longer be discerned) is usually to confirm SCLC; in patients with NSCLC, its role is to determine those who are not surgical candidates because of the extent of their mediastinal disease.

Patients with metastatic NSCLC (stage IV disease) usually present with constitutional symptoms (fatigue, weight loss) or with organ-specific symptoms (bone pain, neurologic symptoms). In many of these patients, FNA or needle biopsy of a site of metastasis represents the most efficient way to both make a diagnosis and confirm the stage. In some cases, however, the metastatic site may be in a location in which it is difficult to perform a 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 establish a diagnosis of the primary lung lesion by whatever method is easiest for the patient (sputum cytology, bronchoscopy, or TTNA). This decision must be made by weighing the technical considerations involved in each approach and the reliability of diagnosing an extrathoracic lesion as a site of metastasis based on radiographic appearances alone (see Silvestri et al<sup>16</sup> in the ACCP Lung Cancer Guidelines).<sup>16</sup> A joint decision among a radiologist, a pulmonologist, and a medical or radiation oncologist is the desirable approach.

In the case of a small (<3 cm), solitary, peripheral lung lesion (PLL) 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 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, surgical excision performed via thoracoscopy is the most definitive method of establishing a diagnosis and determining treatment. In nodules with an indeterminate likelihood of malignancy, sampling via TTNA or bronchoscopy with or without guidance technology (radial EBUS [R-EBUS] or electromagnetic navigation [EMN]) may be considered. (For a more detailed review on the diagnostic approach to the solitary pulmonary nodule, the reader is referred to Gould et al<sup>18</sup> in the ACCP Lung Cancer Guidelines.)

## 1.0 METHODS

This article updates previous ACCP Lung Cancer Guidelines.<sup>19,20</sup> The data from these previous editions were included and updated as described later. Where new technology or procedures became available, new data summaries were developed. In addition, because of the increasing importance of distinguishing the cell type of NSCLC in the identification of genetic mutations, a discussion of how this impacts diagnostic procedures has been included.

In collaboration with an ACCP methodologist, the writing committee carried out a systematic search of the MEDLINE, Healthstar, and Cochrane Library databases, covering July 2004 (to



overlap with the search for the second edition of the guidelines) to July 2011. The searches were limited to English-language and human studies of at least 50 patients with suspected lung cancer, and only studies that provided information on test parameters with an adequate definition of final true results were included (ie, histologic confirmation or radiographic follow-up of at least 1 year). Both prospective and retrospective studies were included; because of the nature of the subject (diagnostic test), randomized studies were generally not appropriate or were unavailable. Details of the searches for the specific topics are described in the particular section; full details of the searches are available from the ACCP upon request.

To structure the literature search, the following patient, intervention, comparison, outcomes (PICO) questions were selected as the most relevant (see Table S1):

1. How do the test performances of closed, image-guided pleural biopsy and thorascopic pleural biopsy compare for evaluating pleural effusions for malignancy in patients with known or suspected lung cancer?
2. What are the performance characteristics of sputum cytology for the diagnosis of lung cancer, with special consideration for the location of the tumor?
3. What are the performance characteristics of flexible bronchoscopy (FB) and its ancillary procedures for the diagnosis of central (endobronchial) as opposed to peripheral tumors and peripheral tumors < 2 and > 2 cm in size?
4. What are the performance characteristics of R-EBUS as a diagnostic modality for peripheral lung cancer?
5. What are the performance characteristics of EMN in the diagnosis of a PLL?
6. What are the performance characteristics of TTNA as a diagnostic modality, with particular emphasis on the size and location of the suspected cancer?
7. What is the diagnostic error when differentiating between NSCLC and SCLC generated by various diagnostic techniques (bronchoscopy, TTNA, and sputum cytology)?

Data were abstracted and combined with data from previous guideline editions. From the assembled literature and data tables, recommendations were developed. The manuscript and recommendations underwent iterative revisions, and were then discussed, revised, and approved by the entire ACCP Lung Cancer Guidelines Panel, as outlined in Lewis et al.<sup>1</sup> The manuscript then underwent a multilevel internal and external review process, similar to that for all the lung cancer guidelines articles.<sup>1</sup>

## 2.0 DIAGNOSIS OF PLEURAL ABNORMALITIES

### 2.1 Thoracentesis

Patients with suspected lung cancer who present with a pleural effusion should undergo thoracentesis. Cytologic examination of the pleural fluid is a quick and minimally invasive way 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 has particular clinical relevance because the finding of malignant cells in the pleural fluid alters the stage of the cancer and the treatment of the particular patient.

Performing thoracentesis under ultrasound guidance improves the rate of successful pleural aspiration

and reduces the incidence of iatrogenic pneumothorax, independent of the size of the effusion.<sup>21-29</sup> In one study,<sup>28</sup> the incidence of pneumothorax following thoracic ultrasound (TUS)-guided thoracentesis was 0% compared with 29% following conventional thoracentesis. Ultrasound features can distinguish malignant from benign effusions. In a study of 52 patients with suspected malignant pleural effusion who underwent TUS and contrast-enhanced CT scanning, TUS correctly diagnosed malignancy in 26 of 33 patients. Pleural thickening > 1 cm, pleural nodularity, and diaphragmatic thickening > 7 mm were highly suggestive of malignant disease.<sup>29</sup> The overall sensitivity of TUS in the differentiation of malignant from benign effusions was 79% (95% CI, 61%-91%) and the specificity was 100% (95% CI, 82%-100%). TUS compared favorably with CT scanning and is an important adjunct in the diagnostic pathway of a patient with an undiagnosed pleural effusion.<sup>29</sup> In addition, TUS-guided thoracentesis has been shown to significantly decrease the incidence of iatrogenic pneumothorax following thoracentesis, independent of the size of the effusion.<sup>22-24</sup>

Because pleural metastases are more common in the visceral pleura<sup>30</sup> and tend to be focal when there is involvement of the parietal pleura, pleural fluid cytology is a more sensitive diagnostic test than percutaneous pleural biopsy. Studies examining the diagnostic yield for malignancy of pleural cytology have reported a mean sensitivity rate of about 72% (range, 49%-91%)<sup>31-37</sup> when at least two pleural fluid specimens are submitted (Fig 1). When the first pleural fluid analysis is nondiagnostic, a second specimen is reported to yield a diagnosis of cancer in about 25% to 28% of cases.<sup>34,35</sup> The yield from examining more than two specimens of pleural fluid taken on different occasions is low. In one study, pleural fluid cytology had a diagnostic yield of 65% from the first specimen, a further 27% yield from a second specimen, but only a 5% yield from the third.<sup>34</sup>

Opinion on the volume of fluid needed for cytologic evaluation varies among facilities and operators. In a prospective study to define the volume of pleural fluid adequate for maximal yield of cytologic diagnosis, large-volume (range, 250-1,800 mL) specimens were compared with 50-mL specimens in 44 patients. The authors reported that pleural fluid cytology was positive in 55% of cases and the submission of more than 50 mL of pleural fluid did not increase the diagnostic yield.<sup>38</sup> The diagnostic yield for malignancy depends on sample preparation (there is a higher yield when both a cell block and a smear are prepared from the collected sample), the experience of the cytologist, and the tumor type, with the highest diagnostic yields retrieved in patients with adenocarcinoma.<sup>35</sup>

FIGURE 1. [Section 2.1] Sensitivity of pleural fluid cytology.

First Author	No. of patients	No. of patients with cancer	% Positive on 1 <sup>st</sup> sample	% Positive on 2 <sup>nd</sup> sample	Total % diagnosed by cytology
Bielsa <sup>35</sup>	1,427	466	49	29	77
Johnson <sup>36</sup>	472	427	91	-	91
Prakash <sup>33</sup>	414	281	58	-	58
Hirsch <sup>37</sup>	300	117	54	-	54
Nance <sup>32</sup>	385	109	71	-	71
Garcia <sup>34</sup>	215	105	65	27	92
Salyer <sup>31</sup>	271	95	53	12	65
<b>Total</b>	<b>3,484</b>	<b>1,600</b>	<b>63</b>	<b>22</b>	<b>72</b>

Inclusion criteria: studies of cytologic yield of malignant pleural effusion in > 50 patients with lung cancer up to December 2011.

When a patient with known or suspected lung cancer has a pleural effusion and has undergone thoracentesis without a definitive diagnosis, the physician caring for the patient must decide on the next diagnostic test to confirm malignant pleural disease. Diagnostic options include closed pleural biopsy, image-guided biopsy, and thoracoscopic biopsy.

## 2.2 Pleural Biopsy

*2.2.1 Key Question 1: How Do the Test Performances of Closed, Image-Guided Pleural Biopsy and Thoracoscopic Pleural Biopsy Compare for Evaluating Pleural Effusions for Malignancy in Patients with Known or Suspected Lung Cancer?*<sup>9</sup> A biopsy specimen of the pleura can be obtained via blind or closed percutaneous needle biopsy, image-guided needle biopsy, medical thoracoscopy, or video-assisted thoracoscopic biopsy. A review of 2,893 closed pleural biopsies performed using the Abrams needle reported a diagnostic yield for malignancy of only 57%.<sup>39</sup> The diagnostic yield for malignancy increased by only 7% to 27% over the yield from pleural fluid cytology.<sup>32,33</sup> When evaluating a patient with known or suspected lung cancer, a contrast CT scan of the chest often provides information that helps differentiate between benign and malignant pleural diseases. Without knowledge of the clinical history or pathologic results, Leung and colleagues<sup>40</sup> reviewed the CT scan findings in 74 consecutive patients with proven diffuse pleural disease (39 malignant and 35 benign). Features that were helpful in distinguishing malignant from benign pleural disease were (1) circumferential pleural thickening (sensitivity 41%, specificity 100%), (2) nodular pleural thickening (sensitivity 51%, specificity 94%), (3) parietal pleural thickening > 1 cm (sensitivity 36%, specificity 94%), and (4) medias-

tinal pleural involvement (sensitivity 56%, specificity 88%). Twenty-eight of the 39 malignant cases (sensitivity 72%, specificity, 83%) were identified correctly by the presence of one or more of these criteria.<sup>40</sup> Clinical and radiographic predictors of malignancy, including chronic symptoms (dyspnea, weight loss, and anorexia), chest pain, blood-tinged pleural fluid, and CT scan findings suggestive of cancer, have also been reported to better indicate the need for pleural biopsy in patients with undiagnosed pleural effusions.<sup>41</sup>

Because a percutaneous image-guided cutting needle allows the biopsy of a focal area of abnormality under direct visualization, it has been shown to be superior to the percutaneous blind Abrams needle biopsy approach in the diagnosis of malignant pleural disease. In four studies involving 215 patients with pleural effusions and diffuse pleural thickening, percutaneous image-guided pleural biopsy had a sensitivity of 84% (76%-88%) and a negative predictive value of 75% to 80%.<sup>41-44</sup> Two of these were randomized studies, in which image-guided pleural biopsy performed better than blind Abrams needle pleural biopsy (sensitivity of Abrams biopsy, 47%; negative predictive value, 44%).<sup>42,44</sup> The rate of pneumothorax following image-guided pleural biopsy has been reported to be about 5%.<sup>42</sup>

Thoracoscopic biopsy of the pleura, which can be performed with a semirigid instrument under local anesthesia (medical thoracoscopy) or by video-assisted thoracoscopic surgery, is safe and can provide a definitive diagnosis with a high degree of accuracy and minimal risk to the patient. The reported sensitivity rate ranges from 80% to 99%, the specificity rate ranges from 93% to 100% and the negative predictive value ranges from 93% to 96%.<sup>45-51</sup> False-negative (FN) results are more common in cases of mesothelioma

than in cases of primary lung carcinoma.<sup>47</sup> A systematic review of five randomized studies to determine the accuracy of medical thoracoscopy in the diagnostic workup of 154 patients with undiagnosed pleural effusions revealed that medical thoracoscopy resulted in a pooled sensitivity of 97% (95% CI, 92% to 99%) and a pooled specificity of 100% (95% CI, 69%-100%), without major complications reported.<sup>45</sup> In a prospective randomized study of 124 patients with cytology-negative exudative pleural effusions and CT scan evidence of pleural thickening or pleural nodules, no statistically significant difference in the diagnostic yield between CT scan-guided Abrams needle pleural biopsy (CT-ANPB) and medical thoracoscopy was identified.<sup>46</sup> The overall diagnostic yield and the diagnostic yield of malignant pleural effusion due to lung cancer for CT-ANPB were 88% and 93%, respectively, compared with 94% and 100%, respectively, for medical thoracoscopy. The authors concluded that CT-ANPB should be used as the primary method of diagnosis in patients with pleural thickening on the CT scan, whereas thoracoscopy should be the primary diagnostic method in patients with pleural fluid only on the CT scan.<sup>46</sup>

## 2.3 Recommendations

**2.3.1. In patients suspected of having SCLC based on the radiographic and clinical findings, it is recommended that the diagnosis be confirmed by the least invasive method (sputum cytology, thoracentesis, FNA, bronchoscopy including TBNA), as dictated by the patient's presentation (Grade 1C).**

**2.3.2. In patients suspected of having lung cancer, who have extensive infiltration of the mediastinum based on radiographic studies and no evidence of extrathoracic metastatic disease (negative PET scan), it is recommended that the diagnosis of lung cancer be established by the least invasive and safest method (bronchoscopy with TBNA, EBUS-NA, EUS-NA, TTNA, or mediastinoscopy) (Grade 1C).**

**2.3.3. In patients suspected of having lung cancer who have a solitary extrathoracic site suspicious of a metastasis, it is recommended that tissue confirmation of the metastatic site be obtained if a FNA or biopsy of the site is feasible (Grade 1C).**

**2.3.4. 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 least invasive method (Grade 1C).**

**2.3.5. 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 1C).**

*Remark:* Ultrasound-guided thoracentesis improves the success rate and decreases the rate of pneumothorax and therefore ultrasound is recommended for performing diagnostic thoracentesis.

**2.3.6. In patients suspected of having lung cancer who have an accessible pleural effusion, if pleural fluid cytology is negative, pleural biopsy (via image-guided pleural biopsy, medical or surgical thoracoscopy) is recommended as the next step (Grade 1C).**

*Remark:* If the CT scan of the chest shows pleural thickening or pleural nodules/masses, image-guided needle biopsy may be considered as the first step to obtain a biopsy of the pleura.

*Remark:* If pleural cytology is negative after the first thoracentesis, a second thoracentesis has been shown to increase the diagnostic yield of pleural fluid cytology. Depending on preferences and values (a simpler and less invasive test vs a more definitive test) a second thoracentesis may be considered before proceeding to biopsy of the pleura.

## 3.0 DIAGNOSIS OF PRIMARY TUMOR

A variety of techniques (sputum cytology, FB, EMN bronchoscopy, R-EBUS, TTNA) are available as methods to establish a definitive diagnosis. The main goals in selecting a specific diagnostic modality are (1) to 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. For the first edition of the ACCP Lung Cancer Guidelines, key questions were formulated to determine the test performance characteristics of various modalities for the diagnosis of lung cancer. The following diagnostic modalities were considered: sputum cytologic examination (expectorated or aspirated, spontaneous or induced), flexible bronchoscopy (including biopsy, brushing, washing, TBNA, or BAL), and TTNA. A systematic search of the MEDLINE, Healthstar, and Cochrane Library databases to covering data 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. Studies were required to report sufficient data to permit completion of a 2-by-2 table comparing test results with a reference standard diagnosis. If too few studies met this criterion, 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 first edition of the ACCP Lung Cancer Guidelines in 2003.<sup>19</sup> An updated literature review from July 2001 to July 2004 that compared the results of sputum cytology, bronchoscopy, and TTNA with histologic reference standard diagnoses among at least 50 patients with suspected lung cancer was performed and the data were compiled to generate updated tables. Recommendations based on a critical review of the updated evidence were published in the second edition of the ACCP Lung Cancer Guidelines in 2007.<sup>20</sup>

A literature review from July 2004 to July 2011 that compared the results of sputum cytology, flexible bronchoscopy, and TTNA was performed for this third edition of the guidelines. Where applicable, the existing evidence-based tables and recommendations were updated. Key questions were formulated to determine the test performance characteristics of pleural biopsy and newer diagnostic modalities, such as R-EBUS and EMN, that can be added to conventional flexible bronchoscopy. The ACCP performed a systematic search of the MEDLINE, Healthstar, and Cochrane Library databases to July 2011. Studies of at least 50 patients with suspected lung cancer, or radiographic follow-up of at least 1 year, were selected and results were reported in this third edition of the guidelines.

### 3.1. Sputum Cytology

**3.1.1 Key Question 2: 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 depends on rigorous specimen sampling (at least three specimens) and preservation techniques, as well as on the location and size of the tumor (central vs peripheral). Unfortunately, many institutions do not have an established program for sputum collection and processing,

and therefore their data have 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 bloody sputum, low FEV<sub>1</sub> values, large lung tumors (> 2.4 cm), centrally located tumors, and squamous cell cancers.<sup>52</sup>

Sputum cytology is particularly useful in patients who present with centrally located tumors (ie, SCLC or squamous cell carcinoma) and in those who present with hemoptysis. Sampling of sputum specimens should certainly be the first step in a patient who presents with a central lesion ± radiographic evidence of metastatic disease, in whom a semi-invasive procedure such as bronchoscopy or TTNA might pose a higher risk. The previously published systematic reviews<sup>19,20</sup> provided summary data on the performance characteristics of sputum cytology for the diagnosis of suspected lung cancer (Fig 2).<sup>53-69</sup> Sensitivity ranges from 42% to 97%; specificity ranges from 68% to 100%. The pooled sensitivity is 66%, and the pooled specificity is 99%. The single study conducted in patients evaluated for suspected lung cancer<sup>54</sup> had a sensitivity of 87% and a specificity of 90%. When all studies were pooled, regardless of indication for sputum testing, the false-positive rate was 8% and the FN rate was 10%.

Some of the bronchoscopy studies included under key question 3 describe the sensitivity of prebronchoscopy sputum examination. These studies have an advantage in that all patients were suspected of having lung cancer, and thus more closely approximated the population of interest.<sup>19</sup> Eight studies<sup>70-77</sup> provided data on the sensitivity of prebronchoscopy sputum and revealed a sensitivity ranging from 10% to 74%, with an average sensitivity of 22%.

The effect of location (central vs peripheral) of lung nodules or masses on the sensitivity of sputum cytology has been described in 17 studies.<sup>53,54,59-61,67,73,78-87</sup> Most studies showed decreased sensitivity for peripherally located masses, but a few showed no such difference. On average, sensitivity was 71% for central lesions and 49% for peripheral lesions. Böcking et al<sup>53</sup> showed 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 68% for a single specimen, to 78% for two specimens, to 85% to 86% for three or more specimens.

Studies of the accuracy of sputum cytology in diagnosing lung cancer are difficult to summarize because of a variety of methodologic problems.<sup>19</sup> The studies show highly variable estimates of sensitivity but 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



FIGURE 2. [Section 3.1.1] Test performance characteristics of sputum cytology for diagnosis of bronchogenic carcinoma.

First Author	Year	No. of Patients	Indication	Prevalence	Sensitivity	Specificity	FP Rate <sup>a</sup>	FN Rate <sup>a</sup>
Dahlgren <sup>61</sup>	1972	121	Mixed	83	42	95	2	(76) <sup>b</sup>
Kern <sup>55</sup>	1988	1289	Mixed	57	97	68	20	6
Gagnetten <sup>59</sup>	1976	506	Mixed	50	57	99	1	30
Liebow <sup>68</sup>	1948	108	Mixed	45	43	95	12	33
Hinson <sup>63</sup>	1963	528	Mixed	43	60	97	6	24
Allen <sup>65</sup>	1960	254	Mixed	41	90	100	0	6
Rosa <sup>60</sup>	1973	1003	Mixed	38	71	100	1	15
Jay <sup>54</sup>	1980	224	Lung mass	31	87	90	21	6
Koss <sup>66</sup>	1958	607	Mixed	24	60	98	7	11
Risse <sup>56</sup>	1985	1830	Mixed	17	60	98	(11) <sup>b</sup>	8
Koss <sup>62</sup>	1964	1307	Mixed	17	71	98	(12) <sup>b</sup>	6
Russell <sup>64</sup>	1963	3440	Mixed	13	51	100	(2) <sup>b</sup>	7
Böcking <sup>53</sup>	1992	1888	Mixed	12	86	100	(4) <sup>b</sup>	2
Erkilic <sup>69</sup>	2003	697	Lung mass	12	69	99	(4) <sup>b</sup>	4
Yoneyam <sup>58</sup>	1978	547	Mixed	12	83	100	(4) <sup>b</sup>	2
Spujt <sup>67</sup>	1955	4933	Mixed	9	53	100	(0) <sup>b</sup>	4
Johnston <sup>57</sup>	1981	9892	Mixed	5	44	100	(3) <sup>b</sup>	3
<b>Total<sup>c</sup></b>		<b>29,245</b>		<b>0.15</b>	<b>66</b>	<b>99</b>	<b>8</b>	<b>10</b>

Inclusion criteria: studies reporting the performance characteristics of sputum cytology for > 100 patients with suspected lung cancer, up to December 2011. Studies not having a true gold standard (ie, histologic confirmation or follow-up of  $\geq 1$  y) were excluded.

FN = false negative, FP = false positive.

<sup>a</sup>False-positive rate is 1 minus the positive predictive value of the test; false-negative rate is 1 minus the negative predictive value of the test. These parameters are affected by the prevalence of disease, especially at high or low prevalence.

<sup>b</sup>False-negative rate excluded from calculations if prevalence is > 80% and false-positive rate excluded if prevalence is < 20% because these results become increasingly affected by the prevalence.

<sup>c</sup>Excluding values in parentheses.

sensitivity of the technique, but there is insufficient detail about these features to determine whether these factors explain the heterogeneity of the test accuracy results.

### 3.1.2 Recommendation

#### 3.1.2.1. In patients suspected of having lung cancer, if sputum cytology is done but is negative for carcinoma, it is recommended that further testing be performed (Grade 1C).

*Remark:* Sputum cytology is an acceptable method of establishing the diagnosis. However, the sensitivity or sputum cytology varies by location of the lung cancer, and with the frequency and processing of the sputum at each individual center.

### 3.2 Flexible Bronchoscopy

#### 3.2.1. Key Question 3: What Are the Performance Characteristics of FB and its Ancillary Procedures for

*the Diagnosis of Central (Endobronchial) as Opposed to Peripheral Tumors and Peripheral Tumors < 2 and > 2 cm in Size?*<sup>9</sup> 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<sup>19</sup> to determine the sensitivity of FB for the diagnosis of bronchogenic carcinoma. Studies with < 50 patients and those that reported exclusively on interoperator performance variability or that focused on technical aspects (eg, needle size, cytology preparation, and so forth) were excluded. Forty-four studies<sup>5,70-77,88-122</sup> met the inclusion criteria. Nine additional studies<sup>123-131</sup> using the same inclusion criteria were found during the updated literature review.<sup>20</sup> 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 as to whether to pursue a diagnostic bronchoscopy for a lesion that is suspicious for lung cancer largely depends on the location of the lesion (central or peripheral). A central lesion can present as an exophytic endobronchial mass, submucosal spread, or a peribronchial tumor causing extrinsic compression. Thirty-five studies of patients with central disease were identified (Fig 3).<sup>5,70-75,77,88-109,123-127</sup> Among

a total of 4,507 patients, the overall sensitivity of FB was 88%. Direct forceps biopsy of visible central lesions is the technique used most frequently, and the sensitivity of this test by itself was 74%. At least three forceps biopsies of the visible lesion are recommended. The sensitivities from washings and brushings are somewhat lower (48% and 59%, respectively), but these tests are often combined with forceps biopsies. The addition of endobronchial needle aspiration to obtain cytology or histology samples when

FIGURE 3. [Section 3.2.1] Sensitivity of flexible bronchoscopic diagnostic procedures for central bronchogenic carcinoma.

First Author	Year	No. of Patients <sup>a</sup>	Sensitivity (%)				
			All Methods	Endobr Biopsy	Brush	Wash	EBNA/TBNA
Buccheri <sup>96</sup>	1991	708	-	80	35	31	-
Jones <sup>127</sup>	2001	514	89	72	72	48	-
Oswald <sup>77</sup>	1971	434	-	61	-	-	-
Lam <sup>102</sup>	1983	329	94	82	74	76	-
Pilotti <sup>73</sup>	1982	286	-	-	78	-	-
Gellert <sup>104</sup>	1982	218	-	78	-	-	-
Zavala <sup>109</sup>	1975	193	94	97	93	-	-
Govert <sup>94</sup>	1996	177	85	81	48	43	-
Mak <sup>98</sup>	1990	125	87	76	52	50	-
Saita <sup>100</sup>	1989	105	-	48	30	-	-
Popp <sup>97</sup>	1991	99	-	93	79	-	-
Karahalli <sup>126</sup>	2001	98	90	83	68	32	69
Chaudhary <sup>74</sup>	1978	95	-	76	53	78	-
Schenk <sup>72</sup>	1987	91	71	56	40	29	45
Utz <sup>5</sup>	1993	88	-	-	-	-	36
Win <sup>124</sup>	2003	78	85	61	27	45	42
Stringfield <sup>107</sup>	1977	78	-	85	-	-	-
Wagner <sup>71</sup>	1989	72	67	58	39	35	36
McLean <sup>92</sup>	1998	71	-	82	-	-	-
Kvale <sup>108</sup>	1976	71	-	71	77	63	-
Bilaceroglu <sup>93</sup>	1997	68	96	-	66	-	90
Govert <sup>91</sup>	1999	57	95	74	-	63	82
Sing <sup>70</sup>	1997	53	-	-	64	-	-
Gay <sup>99</sup>	1989	53	-	-	-	-	23
Chopra <sup>75</sup>	1977	51	-	66	72	51	-
Zisholtz <sup>103</sup>	1983	51	73	67	65	44	-
Gaber <sup>125</sup>	2002	39	90	79	74	54	-
Castella <sup>95</sup>	1995	39	-	-	-	-	87
Cox <sup>101</sup>	1984	33	94	84	83	76	-
Dasgupta <sup>90</sup>	1999	32	97	-	-	-	78
Hsu <sup>123</sup>	2004	24	-	-	-	-	71
Bungay <sup>89</sup>	2000	24	92	-	-	-	-
Baaklini <sup>88</sup>	2000	22	82	-	-	-	-
McDougall <sup>105</sup>	1981	16	-	50	23	-	-
Radke <sup>106</sup>	1979	15	87	-	-	-	-
<b>Summary</b>		<b>4,507</b>	<b>88</b>	<b>74</b>	<b>61</b>	<b>47</b>	<b>56</b>

Inclusion criteria: studies reporting results of bronchoscopy in patients suspected of having lung cancer with central lesions, up to December 2011. EBNA = endobronchial needle aspiration; TBNA = transbronchial needle aspiration.

<sup>a</sup>Maximal number included in sensitivity calculations for any one method.

there is submucosal tumor spread or peribronchial tumor causing extrinsic compression increases the sensitivity of bronchoscopy.<sup>132,133</sup>

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 is the case for central lesions. Thirty-four studies reported on the sensitivity of FB for peripheral lesions (Fig 4).<sup>70,73,76,77,88,95-99,101,102,105-122,125-131</sup> Transbronchial biopsies provided the highest sensitivity (57%, 21 studies), followed by transbronchial brushes (54%, 18 studies) and lavage/washings (43%, 14 studies).

Although TBNA showed a high sensitivity (65%, seven studies), the data deserve cautious interpretation because of the limited number of studies and large differences in sample size.<sup>19</sup> The overall sensitivity for all modalities in the diagnosis of peripheral disease was 78% (16 studies).

A few points must be made 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 increased the reported sensitivity of bronchoscopy.<sup>101</sup> Second, the number of transbronchial biopsy specimens taken was important, with a sensitivity of 45% for one sample

FIGURE 4. [Section 3.2.1] Sensitivity of flexible bronchoscopic diagnostic procedures for peripheral bronchogenic carcinoma.

First Author	Year	No. of Patients <sup>a</sup>	Sensitivity (%)				
			All Methods	TB Biopsy	Brush	BAL	TBNA
Kawaraya <sup>128</sup>	2003	1372	88	77	57	-	35
Rennard <sup>119</sup>	1990	730	-	-	-	47	-
Gasparini <sup>110</sup>	1999	480	76	50	-	-	70
Oswald <sup>77</sup>	1971	435	-	28	-	-	-
Buccheri <sup>96</sup>	1991	337	-	75	44	33	-
Hattori <sup>76</sup>	1971	208	-	-	83	-	-
Lam <sup>102</sup>	1983	155	86	61	52	52	-
Pirozynski <sup>118</sup>	1992	145	-	33	30	65	58
Wallace <sup>122</sup>	1982	143	-	19	-	-	-
Zavala <sup>109</sup>	1975	137	71	69	70	-	-
McDougall <sup>105</sup>	1981	130	62	48	36	36	-
Baaklini <sup>88</sup>	2000	129	61	-	-	-	-
Reichenberger <sup>111</sup>	1999	103	-	39	36	28	47
Bandoh <sup>130</sup>	2003	97	60	-	-	-	-
Bilaceroglu <sup>113</sup>	1998	92	64	-	-	-	-
Torrington <sup>117</sup>	1993	91	-	20	-	-	-
Baba <sup>131</sup>	2002	87	75	53	44	-	67
Popp <sup>97</sup>	1991	87	-	80	83	-	-
Mori <sup>120</sup>	1989	85	84	-	84	42	-
Pilotti <sup>73</sup>	1982	84	-	-	29	-	-
Radke <sup>106</sup>	1979	82	51	-	-	-	-
Naidich <sup>121</sup>	1988	65	48	-	-	-	-
Aristiazabal <sup>112</sup>	1998	64	-	34	-	-	-
Mak <sup>98</sup>	1990	63	56	37	29	38	-
de Gracia <sup>116</sup>	1993	55	-	-	-	33	-
Trkanjec <sup>129</sup>	2003	50	86	62	16	29	-
Castella <sup>95</sup>	1995	45	-	-	-	-	69
Debeljak <sup>115</sup>	1994	39	-	77	59	36	-
Wongsurakiat <sup>114</sup>	1998	30	50	17	-	47	-
Stringfield <sup>107</sup>	1977	29	-	48	-	-	-
Kvale <sup>108</sup>	1976	29	-	27	21	12	-
Sing <sup>70</sup>	1997	22	-	-	22	-	-
Cox <sup>101</sup>	1984	22	36	29	22	36	-
Gay <sup>99</sup>	1989	20	-	-	-	-	65
<b>Summary</b>		<b>5,742</b>	<b>78</b>	<b>57</b>	<b>54</b>	<b>43</b>	<b>65</b>

Inclusion criteria: studies of patients suspected of having lung cancer with peripheral lesions on CT scan undergoing bronchoscopy, up to December 2011. See Table 4 for expansion of abbreviations.

<sup>a</sup>Maximal number included in sensitivity calculations for any one method.



and 70% for six samples reported in one study.<sup>134,135</sup> And last, the sensitivity of bronchoscopy was reported to be higher if CT scanning showed a bronchus extending to the peripheral lesion (60% vs 25%)<sup>121,136</sup>

The sensitivity of bronchoscopy for peripheral lesions is most affected by the size of the lesion. Ten studies were identified that reported on the sensitivity of bronchoscopy (brush and/or biopsy) for peripheral lesions with a size < 2 or > 2 cm in diameter (Fig 5<sup>76,88,105-107,110,121,122,129,130</sup>). The sensitivity for peripheral lesions < 2 cm in diameter was 34%. Peripheral tumors with a diameter > 2 cm resulted in a sensitivity of 63%. The sensitivity of postbronchoscopy sputa as an adjunct to the above-mentioned bronchoscopic techniques is reported to be 35%.<sup>74,75,98,112,114,120</sup>

The FN rate of bronchoscopy has not yet been defined. In the case of a nondiagnostic bronchoscopy of a visible endobronchial abnormality, most physicians would pursue the diagnosis further. 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 plays an important role in the diagnosis of benign conditions, but the possibility of finding a benign condition in a patient who is clinically suspected of having lung cancer is only 1%.<sup>137</sup>

### 3.2.2 Recommendation

#### 3.2.2.1. 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 non-

#### diagnostic and suspicion of lung cancer remains (Grade 1B).

*Remark:* In recent years a number of complementary tools including radial endobronchial ultrasound and electromagnetic navigation have been added to flexible bronchoscopy to aid in the diagnosis of peripheral lung lesions.

### 3.3 Radial EBUS

*3.3.1 Key Question 4: What Are the Performance Characteristics of R-EBUS as a Diagnostic Modality for Peripheral Lung Cancer?* R-EBUS is a probe that houses an ultrasound transducer that provides a 360° radial image of the surrounding structures. The probe is inserted through the working channel of the bronchoscope and is advanced to different segments of the target lobe until a characteristic image of the lung nodule tissue is obtained confirming the exact location for sampling the target nodule. Most data on R-EBUS come from small retrospective or prospective studies and a handful of randomized controlled trials that suffer from either small size or selection bias.<sup>136,138-140</sup> A recently performed meta-analysis was of good quality and found R-EBUS to have a pooled sensitivity and specificity for the detection of lung cancer in peripheral lesions of 73% (95% CI, 70%-76%) and 100% (95% CI, 99%-100%), respectively.<sup>141</sup> Additionally, the diagnostic yield of R-EBUS was found to be lower in lesions ≤ 20 mm in size (56%) compared with lesions > 20 mm in size (78%) and appears to be positively influenced by the prevalence of malignancy in the studied patients. R-EBUS was noted to

FIGURE 5. [Section 3.2.1] Sensitivity of flexible bronchoscopy for the diagnosis of bronchogenic carcinoma by lesion size.

All Methods:		< 2 cm LESION				> 2 cm LESION			
First Author	Year	N	Pos	Neg	Sens	N	Pos	Neg	Sens
Gasparini <sup>110</sup>	1995	195	82	113	42	300	169	131	56
Hattori <sup>76</sup>	1971	17	13	4	76	182	150	32	82
Baaklini <sup>88</sup>	2000	16	4	12	25	135	93	42	69
Wallace <sup>122</sup>	1982	65	3	62	5	78	24	54	31
Bandoh <sup>130</sup>	2003	25	8	17	32	72	50	22	69
Radke <sup>106</sup>	1979	21	6	15	29	76	49	27	64
Naidich <sup>121</sup>	1988	15	4	11	27	46	26	20	57
Trkanjec <sup>129</sup>	2003	17	9	8	53	33	27	6	82
McDougall <sup>105</sup>	1981	9	1	8	11	36	21	15	58
Stringfield <sup>107</sup>	1977	3	1	2	33	26	13	13	50
<b>Summary</b>		383	131	252	34	984	622	362	63

Inclusion criteria: studies reporting sensitivity rates of bronchoscopy for peripheral lesions according to size in patients suspected of having lung cancer, up to December 2011.  
Sens = sensitivity (%)

be safe, with a pooled rate of pneumothorax of 1%. There remains a need for well-designed studies of sufficient size to quantify the diagnostic accuracy of EBUS in clinical practice and to characterize the patients likely to benefit from its use.

### 3.3.2 Recommendation

**3.3.2.1. In patients suspected of having lung cancer, who have a peripheral lung nodule, and a tissue diagnosis is required due to uncertainty of diagnosis or poor surgical candidacy, radial EBUS is recommended as an adjunct imaging modality (Grade 1C).**

*Remark:* Radial EBUS can confirm in real time the ideal location of bronchoscopic sampling and increase the diagnostic yield over conventional bronchoscopy for peripheral nodules.

## 3.4 Electromagnetic Navigation

**3.4.1 Key Question 5: What Are the Performance Characteristics of EMN in the Diagnosis of a PLL?** EMN is an image-guided localization device that assists in placing endobronchial accessories in the peripheral target areas of the lung<sup>142-159</sup> (Fig 6). A prospective, single-center pilot study involving 60 individuals with PLLs showed that EMN had a diagnostic yield for PLL of 74%. The overall yield was 80%, irrespective of the size and location of the lesion.<sup>146</sup> Prospective studies by Makris et al<sup>147</sup> and Eberhardt et al<sup>148</sup> confirmed a diagnostic yield of EMN of 67% and 63%, respectively, independent of the size of the PLL and without using fluoroscopic guidance. Thus, EMN can be used as a stand-alone procedure without compromising diagnostic yield or increasing the risk of pneumothorax. A prospective, randomized trial established that the combination of EBUS and EMN improves the diagnostic yield of FB for PLL without compromising safety.<sup>136</sup> In this study, 72% of all 118 patients recruited had a positive diagnostic yield via FB. Combined EBUS/EMN had a significantly higher diagnostic yield of 88% compared with that of EBUS (69%) and EMN (59%) alone. In another study of 42 patients, combining EBUS and EMN resulted in a diagnostic rate of 90%. The use of EMN/EBUS averted 32 surgical biopsies at the expense of only one pneumothorax. Emerging data also suggest that the combination of EMN, PET-CT scanning, and rapid on-site cytologic evaluation can further augment the diagnostic yield of FB for PLL.<sup>153</sup> In a study involving 51 patients with PLLs, a positive CT scan bronchus sign was also shown to improve the overall yield of EMN from 67% (34 of 51) to 79% (30 of 38) by both univariate and multivariate analysis.<sup>154</sup> A prospective study involving 53 patients reported that the sam-

pling method of “catheter aspiration” was superior to the traditional forceps biopsy of PLL while using EMN ( $P = .035$ ).<sup>155</sup> When EBUS verified the lesion location after EMN, the diagnostic yield was 93%, compared with 48% when EBUS was not used.<sup>155</sup>

### 3.4.2 Recommendation

**3.4.2.1. In patients with peripheral lung lesions difficult to reach with conventional bronchoscopy, electromagnetic navigation guidance is recommended if the equipment and the expertise are available (Grade 1C).**

*Remark:* The procedure can be performed with or without fluoroscopic guidance and it has been found complementary to radial probe ultrasound

*Remark:* If electromagnetic navigation is not available, TTNA is recommended.

## 3.5 Transthoracic Needle Aspiration

**3.5.1 Key Question 6: What Are the Performance Characteristics of TTNA as a Diagnostic Modality, with Particular Emphasis on the Size and Location of the Suspected Cancer?** In the first edition of the published lung cancer guidelines, Schreiber and McCrory<sup>19</sup> analyzed data from a meta-analysis<sup>159</sup> of 46 studies and an additional 19 studies<sup>160-178</sup> that focused on the performance characteristics of TBNA or biopsy for the diagnosis of localized pulmonary lesions. The meta-analysis by Lacasse et al<sup>159</sup> encompassed a comprehensive search (up to 1995) of English-language reports on the use of needle aspiration or biopsy for the evaluation of solitary or multiple pulmonary lesions. At least 90% of the study populations had to have 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. At least 90% of the patients in each study had a histologic reference standard diagnosis. Cytology alone, even when confirmed by another site, was not accepted as a reference standard. In the reanalysis of the data, Schreiber and McCrory used 41<sup>178-219</sup> of the 46 studies in the Lacasse meta-analysis; five studies with < 50 patients were excluded.<sup>19</sup> They considered only one cut-point: definite malignancy or suspicious for malignancy as test positive, and all other test results (including non-diagnostic, benign, nonspecific, and specific benign diagnoses) as test negative (this corresponded to cut-point “b” in the published meta-analysis).<sup>19</sup> In 2007, five additional studies<sup>219-223</sup> published from 2001 to 2004 were identified and incorporated into a reanalysis of the data and results were reported previously<sup>20</sup>

FIGURE 6. [Section 3.4] Diagnostic yield of electromagnetic navigation for peripheral pulmonary nodules.

First Author	Year	No.	ROSE used?	Size mm <sup>a</sup>	Diagnostic Yield (%)	Pneumo-thorax rate (%)
<b>Prospective</b>						
Eberhardt <sup>148</sup>	2007	120	no	26	<b>59<sup>b</sup></b>	6
Eberhardt <sup>137</sup>	2007	89	no	24	<b>67</b>	2
Gildea <sup>146</sup>	2006	60	no	24	<b>74</b>	3
Bertoletti <sup>157</sup>	2009	54	no	28	<b>71</b>	4
Eberhardt <sup>154</sup>	2009	54	no	23	<b>76</b>	2
Seijo <sup>153</sup>	2010	51	yes	25	<b>67<sup>c</sup></b>	-
Makris <sup>147</sup>	2007	40	no	24	<b>63</b>	8
Schwarz <sup>144</sup>	2006	13	no	34	<b>69</b>	0
<b>Subtotal</b>					<b>68</b>	4
<b>Retrospective</b>						
Wilson <sup>151</sup>	2007	248	yes	21	<b>70</b>	3
Pearlstein <sup>158</sup>	2012	104	yes	28	<b>85</b>	6
Mahajan <sup>155</sup>	2011	48	no	20	<b>77</b>	10
Becker <sup>142</sup>	2005	29	no	40	<b>69</b>	3
Lamprecht <sup>152</sup>	2009	13	yes	30	<b>77</b>	0
Weiser <sup>156</sup>	2008	9	yes	-	<b>67</b>	-
<b>Subtotal</b>					<b>74</b>	
<b>Total</b>		<b>932</b>			<b>71</b>	<b>4</b>

Inclusion criteria: studies reporting the yield of electromagnetic navigation bronchoscopy in patients with peripheral lung lesions, up to December 2011. ROSE = rapid on-site cytologic evaluation.

<sup>a</sup>Mean or median.

<sup>b</sup>88% yield when combined with endobronchial ultrasound.

<sup>c</sup>Higher yield with positive bronchus sign.

(Fig 7). Since then, no new studies have been identified by our current search. The pooled sensitivity of TTNA for the diagnosis of peripheral bronchogenic carcinoma was 90% (95% CI, 88%-91%). Individual study estimates ranged from 62% to 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 the location of the lesion; thus, there were limited data with which to address the question of differences in test performance based on lesion location.<sup>19</sup> TTNA of a PLL can be performed under either fluoroscopic or CT scan guidance. Lacasse et al<sup>159</sup> did not find any differences in test operating characteristics between CT scanning and fluoroscopic guidance of TTNA in their original meta-analysis. However, using substantially more data from CT scan-guided TTNA studies, the analysis by Schreiber and McCrory<sup>19</sup> found that studies using CT scan guidance showed greater sensitivity than did those using fluoroscopy

guidance. Using a random-effects model, pooled sensitivities were 92% (95% CI, 90% to 94%) and 88% (95% CI, 85% to 90%) for studies of CT scan-guided and fluoroscopy-guided TTNA, respectively. Two studies<sup>161,178</sup> reported direct comparisons between aspiration cytology and cutting needle biopsy histologic diagnosis. Both studies found that transthoracic needle core biopsy compared with FNA showed similar sensitivity for malignancy (86% vs 92%<sup>161</sup> and 98% vs 98%<sup>178</sup>) but a better ability to determine a specific diagnosis for non-malignant lesions (100% vs 44%<sup>161</sup> and 100% vs 50%)<sup>178</sup> and that transthoracic needle core biopsies are more likely to yield enough tissue for mutation analysis.

In summary, for PLLs, the sensitivity of TTNA is greater than that of bronchoscopy. In patients who have lung cancer, TTNA has an approximately 90% chance of providing confirmation of the diagnosis. Furthermore, given the false-positive rate of 1% to 2%, a positive TTNA for cancer is reliable. On the other hand, the FN rate of TTNA is high (in the range of 20%-30%)<sup>224</sup>; thus, TTNA is generally not useful



FIGURE 7. [Section 3.5.1] Test performance characteristics of transthoracic needle aspiration and/or biopsy for diagnosis of peripheral bronchogenic carcinoma.

Study	Year	No.	Type of Needle	Prevalence	Sensitivity	Specificity	FP Rate <sup>a</sup>	FN Rate <sup>a</sup>
<b>Type of Imaging: CT</b>								
Geraghty et al <sup>119</sup>	2003	846	C	74	91	99	0	19
Böcking <sup>178</sup>	1995	371	A, C	79	99	94	2	4
Santambrogio <sup>176</sup>	1997	220	A	64	93	99	1	11
Laurent <sup>168</sup>	2000	202	C	80	94	1	0	18
Charig <sup>170</sup>	2000	185	C	93	93	1	0	(48) <sup>b</sup>
Larscheid <sup>173</sup>	1998	130	A, C	80	91	1	0	26
Klein <sup>161</sup>	1996	129	A, C	64	95	1	0	8
Arslan et al <sup>221</sup>	2002	121	A	78	89	1	0	27
Cattelan <sup>177</sup>	1997	119	A	67	93	1	0	13
Yankelevitz <sup>174</sup>	1997	114	A	76	94	1	0	16
Yamagami et al <sup>220</sup>	2003	110	C	78	95	1	0	15
Li <sup>160</sup>	1996	97	A	88	89	1	0	(43) <sup>b</sup>
Lucidarme <sup>172</sup>	1998	89	C	84	93	1	0	(26) <sup>b</sup>
Garcia Rio <sup>181</sup>	1994	84	A	80	84	1	0	39
Lopez Hanninen <sup>167</sup>	2001	79	C	63	96	1	0	6
Burbank <sup>182</sup>	1994	60	C	72	95	1	0	11
Wallace <sup>223</sup>	2002	57	A, C	68	82	1	0	28
Hirose <sup>169</sup>	2000	50	C	58	83	1	0	19
<b>Type of Imaging: Fluoro, CT</b>								
Swischuk <sup>171</sup>	1998	612	C	76	96	99	0	13
Gasparini <sup>110</sup>	1995	589	A, C	72	93	99	0	15
Stanley <sup>192</sup>	1987	440	A	73	97	97	1	9
Cristallini <sup>165</sup>	1992	390	A, B	77	94	99	0	16
Johnson <sup>161</sup>	1983	200	A, B	68	95	98	1	9
Zakowski <sup>163</sup>	1992	176	A	84	84	1	0	(47) <sup>b</sup>
Collins <sup>185</sup>	1992	129	B, C	91	94	1	0	(39) <sup>b</sup>
Tan <sup>222</sup>	2002	100	A	76	93	96	1	18
Westcott <sup>175</sup>	1997	62	A, C	67	93	1	0	12
<b>Type of Imaging: Fluoro, CT, US</b>								
Crosby <sup>199</sup>	1985	180	A	93	82	1	0	(69) <sup>b</sup>
Lees <sup>195</sup>	1985	86	A, B	83	85	1	0	(42) <sup>b</sup>
<b>Type of Imaging: US</b>								
Knudsen <sup>101</sup>	1996	128	A	68	95	95	2	9
Yang <sup>164</sup>	1992	120	A	82	62	1	0	(63) <sup>b</sup>
Targhetta <sup>183</sup>	1993	64	B	83	91	1	0	(31)
<b>Type of Imaging: Fluoro</b>								
Lalli <sup>212</sup>	1978	1204	B	78	85	99	0	36
Sagell <sup>211</sup>	1978	1153	B	78	96	99	0	13
Westcott <sup>206</sup>	1980	400	B	73	98	94	2	5
Samuelsson <sup>179</sup>	1982	367	A	67	97	96	2	6
Stevens <sup>198</sup>	1984	348	A, B, C	64	92	99	0	13
Balslov <sup>190</sup>	1988	284	C	73	78	1	0	37
Flower <sup>210</sup>	1979	282	B	72	87	96	2	25
Francis <sup>214</sup>	1977	244	B	68	82	95	3	29
Simpson <sup>187</sup>	1988	227	B	93	82	1	0	(73) <sup>b</sup>
Grode <sup>184</sup>	1993	219	A, B, C	80	89	1	0	31
Calhoun <sup>166</sup>	1986	197	A	81	87	1	0	35
Winning <sup>193</sup>	1986	165	A	76	77	1	0	43
Greene <sup>196</sup>	1985	150	B	81	97	1	0	(13) <sup>b</sup>
Allison <sup>205</sup>	1981	147	B	62	89	1	0	15
Nasiel <sup>217</sup>	1967	144	B	60	72	1	0	29
Weisbrod <sup>191</sup>	1987	133	C	71	78	1	0	36
Pilotti <sup>203</sup>	1982	130	A	88	92	93	1	(39) <sup>b</sup>
Nahman <sup>194</sup>	1985	120	B	86	98	94	1	(11) <sup>b</sup>
Milman <sup>162</sup>	1995	103	A	76	69	1	0	49
Veale <sup>186</sup>	1988	100	A	87	84	1	0	(52) <sup>b</sup>
Taff <sup>207</sup>	1980	100	B	80	83	95	1	42
Stevens <sup>216</sup>	1968	100	B	62	90	95	3	14
Poe <sup>208</sup>	1980	95	B	81	90	94	1	(32) <sup>b</sup>
Lovett <sup>188</sup>	1988	92	A	86	90	1	0	(38) <sup>b</sup>
<b>Study</b>	<b>Year</b>	<b>No.</b>	<b>Type of Needle</b>	<b>Prevalence</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>FP Rate<sup>a</sup></b>	<b>FN Rate<sup>a</sup></b>
Vine <sup>202</sup>	1982	91	C	69	87	1	0	22
Harrison <sup>199</sup>	1984	89	C	78	96	1	0	14
House <sup>213</sup>	1977	88	B	65	96	97	2	6
Jamieson <sup>204</sup>	1981	82	A, B	80	94	1	0	19
McEvoy <sup>200</sup>	1983	81	C	86	87	1	0	(45) <sup>b</sup>
Pavy <sup>215</sup>	1974	59	B	89	86	1	0	(54) <sup>b</sup>
King <sup>218</sup>	1967	59	A	81	88	1	0	(35) <sup>b</sup>
Levine <sup>189</sup>	1988	58	-	60	71	1	0	30
Pak <sup>209</sup>	1981	52	A, B	83	98	1	18	(100) <sup>b</sup>
<b>Average<sup>c</sup></b>				<b>90</b>	<b>97</b>	<b>1</b>	<b>22</b>	
Confidence Interval					88-91	96-98		

Inclusion criteria: studies reporting performance characteristics of transthoracic needle biopsy in >50 patients with suspected lung cancer, up to December 2011. Studies not having a true gold standard (ie, histologic confirmation or follow-up of ≥ 1 y) are excluded. A = aspiration needle; B = aspiration biopsy needle; C = cutting biopsy needle; Fluoro = fluoroscopy; FN = false-negative; FP = false-positive; US = ultrasound.

<sup>a</sup>FP rate is 1 minus the positive predictive value of the test; FN rate is 1 minus the negative predictive value of the test. These parameters are affected by the prevalence of disease, especially at high of low prevalence.

in ruling out cancer. In patients with lesions that are even moderately suspicious for lung cancer, 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, and therefore, further testing to establish a definitive diagnosis is necessary.

Establishing a specific benign diagnosis such as tuberculosis, fungal infection, or hamartoma on TTNA 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 on TTNA further decreases the risk of missing a cancer.

Data on complications after transthoracic needle lung biopsy are limited to case series from selected institutions. A cross-sectional analysis of 15,865 adults who had undergone TTNA was performed to determine the risks of complication after TTNA of a pulmonary nodule.<sup>225</sup> Hemorrhage complicated only 1% (95% CI, 0.9%-1.2%) of biopsies, but of these, 18% (95% CI, 12%-24%) required a blood transfusion. In contrast, the risk of any pneumothorax was 15% (95% CI, 14%-16%), and 7% (95% CI, 6%-7.2%) of all biopsies resulted in pneumothorax requiring a chest tube. Compared with patients without complications, those who experienced hemorrhage or pneumothorax requiring a chest tube had longer lengths of stay ( $P < .001$ ) and were more likely to develop respiratory failure requiring mechanical ventilation ( $P = .020$ ). Patients aged 60 to 69 years (as opposed to younger or older patients), smokers, and those with COPD had a higher risk of complications. The results of this population-based study should help patients and physicians make more informed choices about whether to perform a biopsy of a pulmonary nodule.<sup>225</sup>

### 3.5.2 Recommendation

**3.5.2.1. In patients suspected of having lung cancer who have a peripheral lesion, and who require tissue diagnosis before further management can be planned, TTNA is diagnostic option. However, it is recommended that further testing be performed if TTNA results are non-diagnostic and suspicion of lung cancer remains (Grade 1B).**

### 3.6 Cell Type Accuracy

*3.6.1 Key Question 7: What Is the Diagnostic Error When Differentiating Between NSCLC and SCLC Generated by Various Diagnostic Techniques*

<sup>b</sup>FN rate excluded from calculations if Prevalence is >80% and FP rate excluded if Prev is <20% because these results become increasingly affected by the prevalence.

<sup>c</sup>Excluding values in parentheses.

(*Bronchoscopy, TTNA, and Sputum Cytology*)? In a patient with lung cancer, distinguishing between SCLC and NSCLC is of paramount importance because each of these cancers is treated in a radically different manner. The distinction between SCLC and NSCLC on sputum cytology, TTNA cytology, and bronchoscopic washings, brushings, and BAL cytology is quite reliable. Multiple studies<sup>52,71,73,77,87,189,197,201,210,216,219,224</sup> have shown that the overall accuracy of distinguishing between SCLC and NSCLC is 98%, with individual studies showing results ranging from 94% to 100%. Indeed, the chance that a preoperative diagnosis of NSCLC is in error (the tumor is actually SCLC) is 2% (range, 1%-7%). On the other hand, the error rate of a diagnosis of SCLC (the tumor is actually NSCLC) is, on average, 9%, with individual study results ranging from 0% to 33%.

Although it is reassuring that the accuracy of differentiating between SCLC and NSCLC by various diagnostic techniques is excellent, reporting a diagnosis of NSCLC is simply not enough. NSCLCs are clinically, pathologically, and molecularly heterogeneous tumors (see “Molecular Biology of Lung Cancer” by Nana-Sinkam and Powell<sup>226</sup> and “Diagnostic Surgical Pathology in Lung Cancer” by Schwartz and Rezzaei<sup>227</sup> in the ACCP Lung Cancer Guidelines for a more comprehensive review). In the past decade, paradigm shifts in the treatment of NSCLCs have emerged as the result of clinical trials that have shown us that NSCLCs respond to different therapeutic agents based on histologic phenotypes and molecular characteristics<sup>228-230</sup> (see “Treatment of Stage IV Non-small Cell Lung Cancer” by Socinski et al<sup>231</sup> in the ACCP Lung Cancer Guidelines for a more comprehensive review). Histology is recognized as a potential predictive factor in advanced NSCLC treated with chemotherapy,<sup>232</sup> with significant positive interactions reported between histology and survival in nonsquamous NSCLC treated with select chemotherapy and targeted agents,<sup>228,229</sup> as well as increased toxicity with select agents (bevacizumab) in patients with squamous cell histology.<sup>233</sup> The ability to detect driver mutations, such as the epidermal growth factor receptor (EGFR) and EML4 and anaplastic lymphoma kinase inhibition (EML4-ALK), in patients with lung cancer and to administer agents targeting those molecular lesions has revolutionized the treatment of adenocarcinoma of the lung.<sup>230,234,235</sup> On the basis of the results of five phase 3 trials, the American Society of Clinical Oncology provisional clinical opinion on EGFR mutation testing states that “patients with advanced NSCLC who are being considered for first-line therapy with an EGFR TKI should have their tumor tested for EGFR mutations to determine whether an EGFR TKI or chemotherapy is the appropriate first-line therapy.”<sup>236</sup>

The physician evaluating the patient with suspected lung cancer must understand that obtaining adequate amounts of tissue at the time of diagnosis is essential if accurate histologic differentiation (squamous cell vs adenocarcinoma) is to be achieved and, when applicable, the tissue can then be evaluated for driver mutations (*K-ras*, EGFR, EML4-ALK, and *c-ros* oncogene 1 [ROS1] translocations). Ideally, one would like to obtain core or surgical biopsy specimens in patients with lung cancer to accurately define histology and obtain molecular analysis; however, the majority of patients with NSCLC present with unresectable advanced disease, which means that small biopsy specimens or cytologic specimens are the primary means of diagnosis.

Obtaining adequate amounts of tissue can be challenging, especially in clinical practice when minimally invasive procedures such as EBUS-NA are commonly used. Several studies<sup>235-245</sup> have reported high feasibility (range, 67%-100%) of performing immunohistochemical and molecular analysis on specimens obtained via EBUS-NA. One study reported that immunohistochemical analysis was feasible in all studied specimens obtained by EBUS-NA from mediastinal lymph nodes.<sup>237</sup> Schuurbiens et al<sup>239</sup> found that molecular testing of EGFR and *K-ras* on cytologic material obtained by EBUS-NA could be performed on 77% of their specimens. Smouse et al<sup>240</sup> showed that 67% of cytology specimens were adequate for molecular testing. Arcila et al<sup>241</sup> noted that 79% of cytology specimens and 89% of small biopsy specimens submitted for molecular testing were sufficiently cellular. The rate of EGFR and *K-ras* mutations detected in cytologic specimens in the study was comparable to the rate detected on surgical specimens. In a recently published trial, EGFR gene analysis of EBUS-NA samples was technically feasible in 72% of patients (26 of 36) with lymph node metastasis.<sup>243</sup> Specimen insufficiency rates for DNA sequencing for EGFR and *K-ras* mutations were low (6%) in a study involving 203 cytologic specimens (99 EBUS, 67 TTNA, 27 body fluid, and 10 image-guided FNA specimens) from patients with lung cancer.<sup>244</sup> EBUS and bodily fluid specimens showed lower insufficiency rates (4% for each) than in other cases.<sup>244</sup> EGFR mutations were detected in 19% of specimens of NSCLC (34 of 175), with a significantly higher frequency in adenocarcinoma (29%). The results support the clinical use of routinely prepared cytology specimens.<sup>227</sup> ALK fusion genes were detected in 6% (a rate similar to that found in other studies) of 109 samples of lymph node metastases obtained by EBUS-NA, with consistency between immunohistochemical, fluorescence in-situ hybridization, and polymerase chain reaction analyses.<sup>245</sup>

The amount of tissue needed to accurately diagnose the lung cancer histologic type and assess molecular

markers has not been studied formally. Lee et al<sup>246</sup> found that to establish a cancer diagnosis, three aspirations per lymph node station during EBUS-TBNA without rapid on-site cytologic evaluation was best; sample adequacy was 90% for one aspiration, compared with 100% for three aspirations in 163 node stations in 102 potentially operable patients with NSCLC. Therefore, we suggest that physicians obtain at least three TBNA samples to establish the diagnosis of NSCLC; once the diagnosis has been made, additional samples should be collected and sent for cell block. In the case of TTNA, it is recommended that core needle biopsies be performed when feasible. Furthermore, it is likely that the ability to fully characterize lung cancers from limited specimens depends not only on the amount of tissue but also on the systems in place to handle and prepare the specimen. The reported results in the preceding paragraph likely come from institutions with a focused interest and efficient systems in place. Currently, to care adequately for patients with lung cancer, institutions should assess their own ability to obtain adequate specimens and refine their process as needed.

The physician evaluating the patient with suspected lung cancer must remember that limited tissue acquisition contributes to the difficulty of accurate molecular and histologic subtyping. For this reason, multidisciplinary thoracic oncology teams, which include pulmonologists, thoracic surgeons, chest radiologists, medical and radiation oncologists, and pathologists, must decide collectively how best to obtain tissue and then use the available tissue optimally by performing the minimal immunohistochemical stains needed to diagnose the likely NSCLC subtype (squamous cell vs adenocarcinoma) so that more tissue is available for molecular diagnosis.<sup>247</sup>

### 3.6.2 Recommendations

**3.6.2.1. In patients suspected of having lung cancer, the diagnosis of non-small cell lung cancer made on cytology (sputum, TTNA, bronchoscopic specimens, or pleural fluid) is reliable. However, it is recommended that adequate tissue be obtained to accurately define the histologic type and to perform molecular analysis when applicable (Grade 1B).**

*Remark:* It is critical to obtain adequate tissue to characterize a lung cancer. Within an institution, effective communication between those obtaining the biopsies, those interpreting them, and those delivering the treatment must be in place so that collectively, the members of varying subspecialties involved in the care of the lung cancer patient can decide how best to obtain and optimally use the tissue. If specimens are not adequate for histologic and molec-

ular characterization then obtaining a second biopsy is acceptable given the importance of accurate tumor characterization.

**3.6.2.2. 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 be performed to establish a definitive cell type (Grade 1B).**

## 4.0 CONCLUSION

A variety of techniques are available to assist the physician 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, a chest radiologist, a thoracic surgeon, and a pathologist. 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 (large pleural effusion or metastatic disease). Sputum cytology is a reasonable first step in patients with central lesions, but its 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 navigational bronchoscopy, R-EBUS, and TTNA is greater than that of conventional bronchoscopy.

We have at our hands an array of diagnostic tools, and we must make every effort to work in a multidisciplinary way to ensure that the right test and the right studies are performed on the patient suspected of having lung cancer. We have newer, less invasive procedures such as EBUS-TBNA, which means that FNAs for cytologic specimens are usually the primary means of diagnosis. There is ample evidence, however, that even with needle aspirates of lung lesions or lymph nodes, accurate molecular and histologic subtyping can be achieved.

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*Dr Rivera:* contributed to the writing of all sections and recommendations except for the navigation bronchoscopy and R-EBUS sections and recommendations; the evidence review for PICO questions 2, 3, 6, and 7 to update these sections; and the review and editing of the manuscript.

*Dr Mehta:* contributed to the writing of the section and recommendation on electromagnetic navigation, and provided feedback on the final manuscript.



Dr Wahidi: contributed to the writing of the section and recommendation on R-EBUS, and provided feedback on the final manuscript.

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**Additional information:** The supplement table can be found in the "Supplemental Materials" area of the online article.

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