Methods for Staging Non-small Cell 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: Correctly staging lung cancer is important because the treatment options and prognosis differ significantly by stage. Several noninvasive imaging studies and invasive tests are available. Understanding the accuracy, advantages, and disadvantages of the available methods for staging non-small cell lung cancer is critical to decision-making.

Methods: Test accuracies for the available staging studies were updated from the second iteration of the American College of Chest Physicians Lung Cancer Guidelines. Systematic searches of the MEDLINE database were performed up to June 2012 with the inclusion of selected meta-analyses, practice guidelines, and reviews. Study designs and results are summarized in evidence tables.

Results: The sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis were approximately 55% and 81%, respectively, confirming that CT scanning has limited ability either to rule in or exclude mediastinal metastasis. For PET scanning, estimates of sensitivity and specificity for identifying mediastinal metastasis were approximately 77% and 86%, respectively. These findings demonstrate that PET scanning is more accurate than CT scanning, but tissue biopsy is still required to confirm PET scan findings. The needle techniques endobronchial ultrasound-needle aspiration, endoscopic ultrasound-needle aspiration, and combined endobronchial ultrasound/endoscopic ultrasound-needle aspiration have sensitivities of approximately 89%, 89%, and 91%, respectively. In direct comparison with surgical staging, needle techniques have emerged as the best first diagnostic tools to obtain tissue. Based on randomized controlled trials, PET or PET-CT scanning is recommended for staging and to detect unsuspected metastatic disease and avoid noncurative resections.

Conclusions: Since the last iteration of the staging guidelines, PET scanning has assumed a more prominent role both in its use prior to surgery and when evaluating for metastatic disease. Minimally invasive needle techniques to stage the mediastinum have become increasingly accepted and are the tests of first choice to confirm mediastinal disease in accessible lymph node stations. If negative, these needle techniques should be followed by surgical biopsy. All abnormal scans should be confirmed by tissue biopsy (by whatever method is available) to ensure accurate staging. Evidence suggests that more complete staging improves patient outcomes.

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General Approach

2.1.1. For patients with either a known or suspected lung cancer who are eligible for treatment, a CT scan of the chest with contrast is recommended (Grade 1B)**.**

Remark: If PET scan is unavailable for staging, the CT of the chest should be extended to include the liver and adrenal glands to assess for metastatic disease.

2.1.2. For patients with either a known or suspected lung cancer, it is recommended that a thorough clinical evaluation be performed to provide an initial definition of tumor stage (Grade 1B)**.**

2.1.3. In patients with either a known or suspected lung cancer who have an abnormal clinical evaluation and no suspicious extrathoracic abnormalities on chest CT, additional imaging for metastases is recommended (Grade 1B)**.**

Remark: Site specific symptoms warrant directed evaluation of that site with the most appropriate study.

Extrathoracic Staging

3.1.1. In patients with a normal clinical evaluation and no suspicious extrathoracic abnormalities on chest CT being considered for curative-intent treatment, PET imaging (where available) is recommended to evaluate for metastases (except the brain) (Grade 1B)**.**

Remark: Ground glass opacities and an otherwise normal chest CT do not require a PET scan for staging.

Remark: In patients with peripheral stage cIA tumors a PET scan is not required.

Remark: If PET is unavailable, bone scan and abdominal CT are reasonable alternatives to evaluate for extrathoracic disease.

3.1.2. In patients with an imaging finding (eg, by PET) suggestive of a metastasis, further evaluation of the abnormality with tissue sampling to pathologically confirm the clinical stage is recommended prior to choosing treatment (Grade 1B)**.**

Remark: Tissue sampling of the abnormal site is imperative so that the patient is not excluded from potentially curative treatment.

Remark: Tissue sampling of a distant metastatic site is not necessary if there is overwhelming radiographic evidence of metastatic disease in multiple sites.

Remark: Tissue sampling of the mediastinal lymph nodes does not necessarily need to be performed if there is overwhelming radiographic evidence of metastatic disease in multiple distant sites.

3.4.1. In patients with clinical stage III or IV non-small cell lung cancer (NSCLC) it is suggested that routine imaging of the brain with head MRI (or CT if MRI is not available) should be performed, even if they have a negative clinical evaluation (Grade 2C)**.**

Mediastinal Staging

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

4.4.4.1. In patients with discrete mediastinal lymph node enlargement (and no distant metastases) with or without PET uptake in mediastinal nodes, invasive staging of the mediastinum

is recommended over staging by imaging alone (Grade 1C).

4.4.4.2. In patients with PET activity in a mediastinal lymph node and normal appearing nodes by CT (and no distant metastases), invasive staging of the mediastinum is recommended over staging by imaging alone (Grade 1C).

4.4.4.3. In patients with high suspicion of N2,3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no distant metastases), a needle technique (endobronchial ultrasound [EBUS]-needle aspiration [NA], EUS-NA or combined EBUS/EUS-NA) is recommended over surgical staging as a best first test (Grade 1B).

Remark: This recommendation is based on the availability of these technologies (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) and the appropriate experience and skill of the operator.

Remark: In cases where the clinical suspicion of mediastinal node involvement remains high after a negative result using a needle technique, surgical staging (eg, mediastinoscopy, video-assisted thoracic surgery [VATS], etc) should be performed.

Remark: The reliability of mediastinal staging may be more dependent on the thoroughness with which the procedure is performed than by which test is used.

4.4.6.1. In patients with an intermediate suspicion of N2,3 involvement, ie, a radiographically normal mediastinum (by CT and PET) and a central tumor or N1 lymph node enlargement (and no distant metastases), invasive staging of the mediastinum is recommended over staging by imaging alone (Grade 1C).

4.4.6.2. In patients with an intermediate suspicion of N2,3 involvement, ie, a radiographically normal mediastinum (by CT and PET) and a central tumor or N1 lymph node enlargement (and no distant metastases), a needle technique (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) is suggested over surgical staging as a best first test (Grade 2B).

Remark: This recommendation is based on the availability of these technologies (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) and the appropriate experience and skill of the operator.

Remark: In cases where the clinical suspicion of mediastinal node involvement remains high after a negative

result using a needle technique, surgical staging (eg, mediastinoscopy, VATS, etc) should be performed.

Remark: The reliability of mediastinal staging may be more dependent on the thoroughness with which the procedure is performed than by which test is used.

4.4.8.1. For patients with a peripheral clinical stage IA tumor (negative nodal involvement by CT and PET), it is suggested that invasive preoperative evaluation of the mediastinal nodes is not required (Grade 2B).

4.4.10.1. For the patients with a left upper lobe (LUL) cancer in whom invasive mediastinal staging is indicated as defined by the previous recommendations, it is suggested that invasive assessment of the Aortopulmonary Window (APW) nodes be performed (via Chamberlain, VATS, or extended cervical mediastinoscopy) if other mediastinal node stations are found to be uninvolved (Grade 2B).

In patients in whom non-small cell lung cancer (NSCLC) has been demonstrated or is strongly suspected, consideration must turn toward determining the extent of the disease, or its stage, because this will impact directly on the management and prognosis. The first step is to identify whether the patient has distant metastatic disease or tumor confined to the chest, to determine whether treatment should be aimed at palliation or at potential cure. If disease is localized to the chest, the status of the mediastinal nodes becomes crucial in determining the best curative treatment strategy. Patients with stage IA, IB, IIA, and IIB disease can benefit from surgical resection; patients with stage IIIA, IIIB, and IV disease rarely meet the criteria for surgery.

Staging with regard to a patient's potential for surgical resection is most applicable to NSCLC. Except in rare cases of surgically operable limited-stage small cell lung cancer (SCLC), staging in the management of SCLC amounts to chemotherapy and radiation for limited disease or chemotherapy alone for extensive disease. Stage evaluation of patients with SCLC is similar but is not addressed in this article; it is covered by Jett et al[2] "Treatment of Small Cell Lung Cancer," in the American College of Chest Physicians (ACCP) Lung Cancer Guidelines.

This article addresses the identification of distant or extrathoracic metastatic disease in patients with lung cancer and examines imaging studies and invasive procedures that accurately determine the status of the mediastinum. 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 physician after an assessment of risk factors and a review of the clinical presentation and the radiographic appearance on a CT scan. The next step is a clinical evaluation, consisting of a history and physical examination; the clinical evaluation and CT scan provide an initial presumptive definition of the clinical stage. In some cases, this is sufficiently reliable, but in most cases, the initial clinical stage must be confirmed with further tests. Many different tests are available, and selection of the right tests and their sequence has a major impact on how accurately and efficiently the patient's true clinical stage is determined. This iteration of the ACCP guidelines combines the articles that discussed noninvasive and invasive techniques in the previous iterations of the guidelines because it was recognized that from the clinical perspective, physicians use both methods together to accurately stage patients with lung cancer.[3,4]

When there is a strong suspicion of lung cancer, it is generally best to begin the process of stage evaluation before pursuing a diagnosis (see also Rivera et al,[5] "Establishing the Diagnosis of Lung Cancer," in the ACCP Lung Cancer Guidelines). In many situations, an invasive test can provide simultaneous confirmation of the diagnosis and its stage, leading to a more streamlined and efficient process. This requires a good understanding of which imaging findings need tissue confirmation and this is greatly aided by a multidisciplinary discussion of a patient's particular situation.

It seems intuitive that accurate staging of lung cancer is of paramount importance given the markedly different treatment options and prognosis for any given stage. Despite this, data have shown that the staging evaluation has often been carried out very poorly.[6-8] The impact of more thorough staging is marked. Farjah et al[6] assessed the use of multimodality staging for lung cancer among Medicare beneficiaries. They assessed the use of single (CT scan), bimodality (CT scan plus PET scan or CT scan plus invasive staging), or trimodality (CT, PET, and invasive staging) staging tests to assess for mediastinal metastases. At the end of the study period, only 30% had bimodality staging and 5% had trimodality staging, although the guidelines for many years have called for bimodality or trimodality staging in the majority of patients. After adjusting for differences in patient characteristics, those who underwent bimodality and trimodality staging had a significantly lower risk of death (hazard ratio, 0.58; 99% CI, 0.56-0.60; tri- vs single-modality: hazard ratio, 0.49; 99% CI, 0.45-0.54). These associations were maintained even after excluding various groups of poor-risk patients (eg, stage IV, anyone suffering early death within 1 month, patients not treated within 6 months, and so forth). These results may reflect unidentified sources of residual confounding, and it is likely that better staging serves as a marker for better care in general. Nevertheless, there can be little doubt that basing treatment decisions on poorly executed staging evaluations may well lead to suboptimal treatment and worse outcomes.

1.0 METHODS

The authors updated a systematic review of the diagnostic accuracy of different staging methods for patients with NSCLC. A more complete description of the methods can be found in the first edition of the ACCP guidelines.[3,4,9,10] Briefly, computerized searches of MEDLINE covering January 1991 to May 2006 for the previous guidelines and January 2006 to June 2012 for this iteration were performed. In addition, we searched the reference lists of included studies, practice guidelines, systematic reviews, and meta-analyses to ensure that all relevant studies were identified. Only articles published in English were considered. The search strategy and results are available on request. The searches were structured around the following population, intervention, comparator, outcomes (PICO) questions (detailed in Table 1S):

1. What is the role of PET scan in the staging of patients with NSCLC?
2. What is the impact of mediastinal staging by imaging and invasive staging procedures in patients with NSCLC?

1.1 Selection Criteria

Titles and abstracts, and the full text of all articles passing the title-and-abstract screen, were evaluated independently by three of the authors (G. S., A. G., M. J.) for inclusion or exclusion based on the following five criteria: (1) publication in a peer-reviewed journal; (2) a study size of ≥ 20 patients (except for studies involving CT scan evaluation of the mediastinum or mediastinoscopy, which required a study size of ≥ 50 patients); (3) patient group not included in a subsequent update of the study; (4) for noninvasive staging methods, histologic or cytologic confirmation of mediastinal nodes or extrathoracic sites in addition to the primary tumor; for invasive staging methods, confirmation of mediastinal nodal biopsy results by histology at the time of resection, or long-term clinical follow-up (≥ 1 year); and (5) availability of the raw data needed to calculate independently the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV), or the raw data needed to calculate the NPV of the clinical evaluation. Disagreements were resolved by consensus.

The data abstraction was performed for patients suspected of having lung cancer (eg, NSCLC, SCLC). Where possible, patients suspected of a diagnosis other than lung cancer were excluded. A definite diagnosis of any lung cancer in the mediastinal tissues was considered positive, whereas other diagnoses (benign disease, lymphoma, and so forth) were coded as negative for lung cancer. Equivocal test results were considered negative. Data were abstracted and results were tabulated on a per-patient basis, not per lymph node station. Calculation of subtotal or total summary performance characteristics was accomplished by calculating a median of the values (sensitivity, specificity, and other values) from each study; in other words, no weighting according to study size was performed. This method was chosen because of its simplicity. In this iteration of the guidelines, randomized controlled trials (RCTs) comparing the use of noninvasive staging tests with

control and those making comparisons among invasive staging techniques are reported separately.

Various parameters, including sensitivity, specificity, PPV, and NPV, can be used to assess the reliability of a test. Sensitivity is defined as the percentage of people with the disease who are detected by the test. (It is calculated as the number of true-positive (TP) results divided by the sum of TP and false-negative [FN] results). Specificity is defined as the percentage of people without the disease who were correctly labeled by the test as not having the disease. (It is calculated as the number of true-negative (TN) results divided by the sum of the TN and false-positive [FP] results). 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 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. The PPV is defined as the likelihood that a patient with a positive test result actually has the disease. It is calculated as the number of TP results divided by the sum of the TP and FP results. The NPV is defined as the likelihood that a patient with a negative test result really does not have the disease. It is calculated as the number of TN results divided by the sum of the TN and FN results. Thus, these measures provide information about the disease. Both the PPV and the NPV vary with the prevalence of disease, which is the frequency of disease in the population, and they are calculated as the number of patients with either a TP or an FN result divided by the total number of patients. However, the impact of the prevalence on the NPV and the PPV is minor unless the prevalence is very high or low, respectively; therefore, the NPV (or PPV) from studies with $>80\%$ (or $<20\%$) prevalence are excluded from summary calculations. All these parameters are reported where appropriate.

1.2 Development and Grading of Recommendations

Recommendations were developed by the writing committee and were graded by a standardized method (described in detail by Lewis et al,[1] "Methodology for Development of Guidelines for Lung Cancer," in the ACCP Lung Cancer Guidelines). These were reviewed, revised, and eventually approved by all members of the lung cancer panel according to the standard process for these guidelines. After this, there were several additional levels of internal and external approval (the Thoracic Oncology NetWork, the Guidelines Oversight Committee, and the Board of Regents of the ACCP, as well as external reviewers and organizations), as described elsewhere.[1]

2.0 General Approach to Patients

The general approach to patients suspected of having lung cancer begins with a thorough history and physical examination. It is important to pay attention to both organ-specific (bone, brain) and nonspecific (fatigue, anorexia, weight loss) signs and symptoms of potential metastatic disease (Fig 1). The details of the clinical evaluation are discussed later, and were elucidated in detail in previous editions of the lung cancer guidelines.

Essentially, every patient suspected of having lung cancer should undergo a CT scan of the chest. This provides much information about the nature of the lesion seen on the chest radiograph or about the chest

Figure 1. [Section 2.0, 3.0] Clinical findings suggesting metastatic disease.

Component	Findings
Symptoms elicited in history	Constitutional: weight loss (>10 lb), anorexia, fatigue Musculoskeletal: focal skeletal pain Neurological: headaches, syncope, seizures, extremity weakness, recent changes in mental status
Signs found on physical examination	Supraclavicular lymphadenopathy (>1 cm) Hoarseness, superior vena cava syndrome Bone tenderness Hepatomegaly (>13-cm span) Focal neurologic signs, papilledema Soft-tissue mass
Routine laboratory tests	Hematocrit <40% in men, <35% in women Elevated alkaline phosphatase, GGT, AST, or calcium levels

AST = aspartate transaminase; GGT = γ-glutamyltransferase.

symptoms. The CT scan can either confirm the suspicion of lung cancer or raise suspicion of a different diagnosis. The radiographic appearance on a CT scan, together with appropriate risk factors, allows a clinical diagnosis of lung cancer to be made quite reliably by an experienced physician in the vast majority of patients (see Rivera et al,[5] "Establishing the Diagnosis of Lung Cancer," in the ACCP Lung Cancer Guidelines). This is an important step because it allows one to proceed with a thoughtful evaluation of the stage in most patients and to more efficiently establish both the diagnosis and the stage with one test, rather than pursue the diagnosis first, and then begin to consider the stage. Further details of chest imaging are covered in the section of this article on mediastinal staging.

Although a clinical evaluation may be reliable in some situations, further confirmation of the initial clinical stage is needed in many situations. In patients with a positive clinical evaluation and signs and symptoms of metastatic disease localized to a particular area, directed tests (plain bone films, needle aspiration [NA] of palpable lesions) may be sufficient to confirm the suspicion expediently. In patients with less localized or more subtle symptoms of possible distant metastases, imaging studies are needed. Finally, in most patients, further imaging is required even if the clinical evaluation is negative (Fig 2).[11-22] In particular, PET imaging has emerged as playing a prominent role, as discussed in the next section.

The chest CT scan is an important first step, not only to help define the clinical diagnosis, but to structure the subsequent staging and diagnostic evaluation. In general, patients with lung cancer can be separated into four categories with respect to intrathoracic radiographic characteristics (including both the primary tumor and the mediastinum), as shown in

FIGURE 2. [Section 2.0, 3.0] False-negative rate of a negative clinical evaluation, as compared with either further PET imaging or conventional imaging (brain MRI/CT scan, abdominal CT scan, or ultrasound and bone scan). Rates are percentages of patients with a negative clinical evaluation in whom actual distant metastases are found upon further evaluation, averaged from all available studies that published stage-specific data: stage cI-III conventional[13,16-18,20]; cIII PET scan[11,15,22]; cI, II conventional[13,14]; cI PET scan.[15,19,21,22,192]. The clinical stage is that suggested by the negative clinical evaluation (ie, M0) and by the chest CT scan.

False Negative Rate of Clinical Evaluation for Distant Metastases
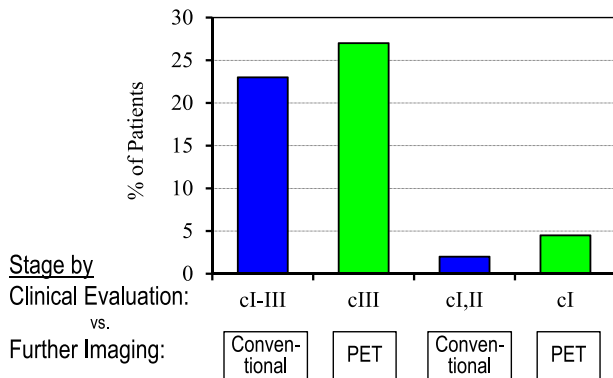
Figures 3 and 4. The first group (radiographic group A) involves patients with mediastinal infiltration that encircles the vessels and airways, so that the discrete lymph nodes can no longer be discerned or measured.

The second group (radiographic group B) involves patients with mediastinal node enlargement, in whom the size of the discrete nodes can be measured. 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%-25%) despite normal-sized nodes, and further confirmation is needed.[23-26] In the final group (ie, those with a peripheral clinical stage I tumor), the chance of either distant metastases or mediastinal involvement is quite low (radiographic group D).[24-26]

PET imaging has emerged as a particularly useful test in a large proportion of patients with lung cancer. It can be used for multiple purposes, including to help confirm or render less likely a diagnosis of lung cancer, to detect extrathoracic metastases in patients who are asymptomatic or have subtle symptoms, to provide further information regarding the status of the mediastinum, and to provide an indication of the tumor's metabolic activity (as a predictor of biologic aggressiveness); it also has other treatment-related uses. PET scanning is usually performed for a combination of reasons. The amount of data supporting a role for PET scanning in patients with lung cancer has increased significantly since the previous guidelines, and the most relevant studies are summarized in the next section.

FIGURE 3. [Section 2.0, 4.1, 4.3] American College of Chest Physicians intrathoracic radiographic (CT scan) categories of lung cancer. A, Mediastinal infiltration by tumor. B, Enlarged discrete N2,3 nodes. C, A central tumor or a tumor with enlarged N1 nodes, but a normal mediastinum. D, A peripheral small tumor (seen in lower left corner of image) with normal-sized lymph nodes.
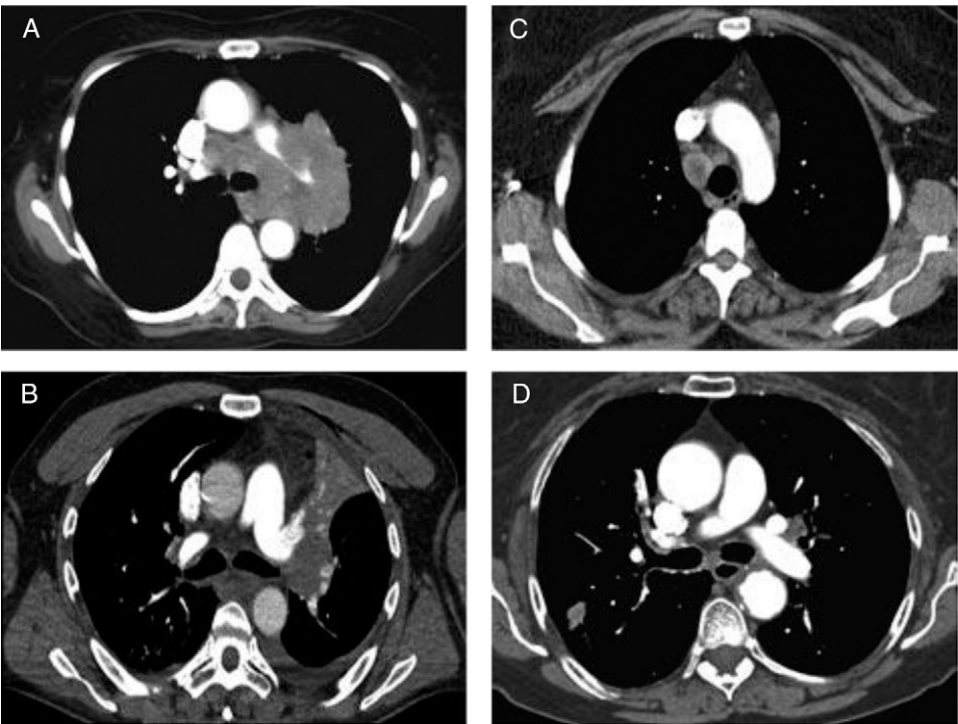
FIGURE 4. [Sections 2.0, 4.1] Definition of intrathoracic radiographic categories of lung cancer.

Group	Description	Definition (by chest CT scan)
A	Mediastinal infiltration	Tumor mass within the mediastinum such that discrete lymph nodes cannot be distinguished or measured[a]
B	Enlarged discrete mediastinal nodes	Discrete mediastinal nodes ≥ 1 cm in short-axis diameter on a transverse CT 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)

[a]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).

2.1 Recommendation

2.1.1. For patients with either a known or suspected lung cancer who are eligible for treatment, a CT scan of the chest with contrast is recommended (Grade 1B)**.**

Remark: If PET scan is unavailable for staging, the CT of the chest should be extended to include the liver and adrenal glands to assess for metastatic disease.

2.1.2. For patients with either a known or suspected lung cancer, it is recommended that a thorough clinical evaluation be performed to provide an initial definition of tumor stage (Grade 1B)**.**

2.1.3. In patients with either a known or suspected lung cancer who have an abnormal clinical evaluation and no suspicious extrathoracic abnormalities on chest CT, additional imaging for metastases is recommended (Grade 1B)**.**

Remark: Site specific symptoms warrant directed evaluation of that site with the most appropriate study.

2.2 Randomized Trials Involving PET Imaging

PET imaging plays a prominent role in the evaluation of patients with lung cancer, and the 2007 ACCP lung cancer guidelines recommended PET scans be performed in most patients. However, the situation is complex, because PET scans can provide information about the primary tumor, about the mediastinal lymph nodes, and about distant metastases. (PET scans can also provide information about the metabolic activity of the tumor, about the response to therapy, and for planning of radiotherapy treatment fields. However, these issues are not part of the stage evaluation and are not discussed in this article.) Furthermore, the contribution of PET scanning to the stage evaluation of patients is influenced by many factors, such as the likelihood that the patient has

cancer, the likelihood that metastases are present, and to what extent the searching for metastases is accomplished by means other than PET scanning. Finally, PET scanning is not a definitive test, and tissue confirmation is often needed; how aggressively this is done also affects the impact PET scanning can have.

Five RCTs that evaluated the role of PET scanning in the evaluation of patients with lung cancer have been reported (Fig 5)[21,27-30] with somewhat different results. Given the fact that the impact of PET scanning involves a complex interplay of many factors, this should come as no surprise. This section summarizes these studies and discusses nuances to provide a better understanding of the factors involved, so that a thoughtful integration of PET scanning into patient management in particular settings can be accomplished.

Two RCTs of PET scanning found a marked benefit in terms of a reduction, from approximately 40% to 20%, in the number of noncurative resections performed (defined as the presence of benign disease, unsuspected N2 involvement, unresectable disease or recurrence, or death from any cause within 1 year).[27,30] One study found no difference in the rate of thoracotomy or incidence of distant metastatic disease.[21] Another study reported no difference in survival or the rate of thoracotomy, but found that PET scanning, as compared with conventional imaging, led to a higher rate of correctly identifying M1b disease (14% vs 7%), albeit at the minor expense of a higher rate of incorrect upstaging (5% vs 1%). In addition, the final pretreatment stage was less often understaged in the PET scan vs the conventional staging arm (15% vs 30%) when compared with subsequent events (ie, unsuspected pN2.3 or recurrence within 1 year). PET scanning, as compared with conventional imaging, also resulted in a lower rate of incorrectly understaging, albeit at the minor expense of a higher rate of incorrectly upstaging.[29] A final study focused on the number of tests needed to stage a patient with lung cancer and did not find a difference between

FIGURE 5. [Section 2.2] Randomized trials of PET scanning for staging lung cancer.

First Author	No.	Extent of Preenrollment Workup	Risk of Advanced Stage[a]	Thoroughness of Preoperative Staging[b]		% Having Surgery		% Noncurative Resection		% N2,3, M1 Identified Preoperatively		% M1 or Recurrence Within 1 y[c]	
				M1	% N2,3	Conv	PET	Conv	PET	Conv	PET	Conv	PET
Herder[28]	465	Minimal	++++	...	17	38	41	...	...	36	34	2[d]	4[d]
van Tinteren[30]	188	Minimal	+++	Low	69	81	65	41	21	12	29	14	4
Fischer[27]	189	Moderate	+++	Low	94	80	60	42	21	20	37	19	5
Maziak[29]	337	Moderate	++	High	51	78	81	...	...	14	19	4	8
Viney[21]	183	Good	+	High	5	98	96	...	...	1	(5)[e]	...	...

Inclusion criteria: randomized controlled trials of PET imaging in the pretreatment evaluation of patients with lung cancer.
Conv = conventional imaging (brain CT scan/MRI, abdominal CT scan/ultrasound, bone scan).
[a]Risk based on presence of clinical markers of advanced disease (>5% weight loss, performance status ≥2).
[b]Extent of imaging for possible distant metastases and % of patients undergoing invasive mediastinal staging.
[c]Figures do not include noncancer deaths within 1 y.
[d]Within 6 mo.
[e]Reported rate of 5% reflects a policy of primary surgery despite the presence of N2 involvement; the rate would be approximately 15% if a policy of preoperative identification of N2,3 nodes were followed.

upfront PET scanning and conventional staging (average of 7.9 tests per patient in both arms).[28]

A closer look at the details of these studies reveals significant differences in the patients involved, the extent of preenrollment workup, the risk of advanced disease, and the extent of investigation for mediastinal and distant disease. For example, one study included patients referred by general practitioners on the basis of an abnormal chest radiograph only and the suspicion of lung cancer, with nearly one-third of patients having had >5% weight loss,[28] whereas another involved primarily patients with stage cI tumors (92%), as assessed by a thoracic surgeon, with histologic verification of lung cancer and brain and abdominal imaging in all.[21] In the first study,[28] which involved relatively limited investigation for distant and mediastinal metastases despite clinical findings indicating a high risk of metastases, PET scanning was clearly beneficial in identifying potential metastatic disease. The second study,[21] involving primarily patients with stage I disease and extensive imaging prior to randomization, found few distant metastases in either the PET scan or the conventional arm. Although in this study PET scanning correctly raised suspicion of N2 involvement, the surgical practice in this region was to nevertheless proceed with thoracotomy, without preoperative mediastinal staging, and thus, the rate of thoracotomy was not affected by PET imaging.

Those studies involving patients with a relatively high risk of advanced disease (frequent weight loss, poor performance status, and high rate of mediastinal node enlargement) have generally found that PET scanning increased the rate of preoperative detection of metastases and decreased the appearance of metastases during the following year. Furthermore, the studies with more thorough investigation of the mediastinum revealed a trend toward a higher rate of suspected N2.3 involvement through PET scanning. As the risk of advanced disease diminishes, and the extent of baseline staging evaluation increases, the impact of PET scanning appears to diminish.

Other population-based studies suggest that PET scanning has had a major positive impact on the stage classification of patients at a higher risk of having distant metastases. In the US national cancer database, as well as in the Surveillance, Epidemiology and End Results (SEER) registry, stage migration of a significant proportion of patients classified as stage III into stage IV has occurred, tracking with an increased use of PET scanning.[31,32] However, PET scanning appears to have little impact in patients with stage cI tumors.[31,33] A subset analysis of the patients with stage cI tumors in the American College of Surgeons Oncology Group PET scanning study found that PET scanning detected N2,3 or M1 involvement in 7% of patients

with stage cI tumors, but at a price of falsely suggesting N2,3/M1 disease in 14%.[34] Furthermore, although PET scanning had the potential to reduce the rate of biopsy for benign lesions from 21% to 11%, this would have come at the price of avoiding (or delaying) resection in 13% of cancers. The role of PET scanning is likely also limited in patients with ground-glass opacities with or without a solid component (but > 50% ground-glass opacities), although this is based on indirect arguments. These patients have a low rate of nodal involvement or distant metastases, making it unlikely that PET scanning would be of benefit (see the article on stage I, II NSCLC in the ACCP lung cancer guidelines).[35]

Overall, with PET scanning, about 20% more patients are correctly suggested as harboring distant or N2,3 metastases compared with conventional staging in the RCTs.[21,27,30] However, confirmation of PET scan findings is essential, because PET scanning also carries a significant rate of incorrect upstaging.[17] A potential harm of PET scanning is that if suspected PET scan findings are not confirmed, patients may be erroneously directed away from a potentially curative resection. In the RCTs involving PET scans, this would have occurred in 5% to 42% of patients; however, in these studies, the requirement of a definite confirmation of suspicious PET scan findings prevented this.[21,27,29,30] Although PET scanning clearly has the potential to be of benefit, in a less structured setting it also has the potential to be of harm if confirmation of the findings is not pursued.

Another potential issue is the type of PET scan and the setting in which it is performed, although there are few data to define the impact of this factor. Some of the RCTs of PET scanning for lung cancer evaluation involved an integral PET-CT scan, but in some others it was only PET scanning without CT scan correlation. These RCTs were conducted in organized health-care facilities, and generally relied on only one central PET scanner and interpretation despite involving many referral centers. The Canadian study is different in that it involved five PET scanners and eight centers.[29] However, the Canadian health-care system is still regionally well organized. This contrasts with the United States, in which care may be very decentralized, involving many smaller institutions and even mobile PET scanners. The ability to communicate clinical history, discuss interpretation, and provide feedback to radiologists in such a setting is much more challenging and likely affects the reliability of the interpretation. This underscores the need for confirmation of findings and for adaption of guidelines, such as those for PET scanning, to particular clinical settings. Nevertheless, the preponderance of data (including RCTs, prospective studies, and population studies) suggests that the PET scanning is much more of a benefit than a harm, and that this may be particularly true for physicians who have less clinical experience in treating lung cancer.

3.0 EXTRATHORACIC STAGING

The work-up of patients with newly diagnosed lung cancer should begin with a thorough clinical evaluation focusing on history, physical examination, and laboratory testing germane to patients with cancer. The current preferred "expanded" clinical evaluation includes organ-specific and constitutional signs and symptoms, along with simple laboratory tests, as shown in Figure 1.[36] It is well established that abnormal symptoms, physical findings, and routine blood tests in the initial clinical evaluation of patients with NSCLC are associated with a high likelihood of metastasis.[36] In addition, the NPV of the clinical evaluation (Fig 2)[11-22] is high enough in most circumstances to not warrant extrathoracic conventional scanning (bone scan, brain scan, and abdominal CT scan) if the clinical evaluation is negative (this recommendation does not apply to patients with clinical stage III and IV lung cancer, in which unsuspected metastases occur even with a negative clinical evaluation). Similarly, PET or PET-CT scanning has been found to be useful irrespective of the findings on the clinical evaluation.

The purpose of extrathoracic scanning in 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.[4,36] However, scans can only detect macroscopic metastatic deposits that have reached a size within the resolution capability of a given imaging modality, and this can be considered a major shortcoming of all conventional tests currently used to detect distant metastases in NSCLC. The search for metastatic disease continues to evolve, with increased recognition of rapid dissemination in some patients with NSCLC. Mohammed et al[37] found that distant metastases may become evident on serial CT scans or PET scans in 3% of untreated patients at 4 weeks, in 13% at 8 weeks, and in 13% at 16 weeks, leading the authors to propose complete restaging after 4 to 8 weeks of delay. Most advances in the area of metastatic disease are the result of exploding interest in PET and PET-CT scans for staging and a host of additional possible clinical applications.

Current literature continues to demonstrate that PET and PET-CT scans are superior to conventional staging tests (bone scan and abdominal CT scan) in terms of performance characteristics. Specifically, PET scanning discloses previously unsuspected metastases in 6% to 37% of cases,[38-43] which results in more accurate TNM designation,[41] stage migration,[31,45] and

important changes in management,[46,47] including the indication for surgery.[41]

Recent data confirm the superiority of the performance characteristics of PET and PET-CT scans compared with conventional scans in the evaluation of metastatic disease in key specific distant sites. This concept is underscored by studies focusing on possible metastases to the adrenal glands,[48,49] liver,[50] and bone.[51] In addition, numerous reports document PET or PET-CT scan detection of unsuspected metastases to unusual distant sites such as the small bowel and skeletal muscle, thereby importantly changing the clinical stage and management of individual patients.[52-54]

The brain remains problematic because of the small size of most brain metastases, background brain F-fluoro-2-deoxy-D-glucose (FDG) uptake, and the variable biologic characteristics of brain metastases, which can be either hypermetabolic or hypometabolic.[55] However, in one series, the accuracy of integrated PET-CT scanning for brain metastases rivaled that of diagnostic brain CT scanning, and the need for a separate brain CT scan was obviated.[56] But, importantly, others have found that MRI improves detection when added to PET-CT scanning.[57] Biannual follow-up MRI may detect early brain metastases, thereby providing opportunities for radiosurgery.[58] Overall, it appears that the detection of brain metastases remains critical, and the detection of early metastases while still asymptomatic is increasingly important; treatment of such lesions is associated with better control of neurologic manifestations and longer survival.[59]

Since the publication of the last ACCP lung cancer guidelines, several studies have evaluated additional key outcomes related to PET and PET-CT scanning as staging modalities and have compared them with conventional staging (bone scan, abdominal CT scan). In general, these analyses suggest that PET scanning is cost effective compared with CT scanning[60] and correlates better with long-term outcomes.[61] Søgaard et al[62] found that PET-CT scanning increased cost by 3,927 Euros and that 4.92 PET-CT scans are needed to prevent one noncurative resection. Others also found decreases in unnecessary surgery when using PET or PET-CT scanning in the staging algorithm.[46,47,63,64]

Many other uses for PET scanning are emerging. The PET scan standard uptake value in the primary tumor may correlate with distant metastases[65] and help predict treatment response[66] and recurrences.[57] Dual-time PET scanning may be even more accurate in identifying malignant lesions.[67,68] PET scanning helps plan radiotherapy[69] and may reflect inhibition of glucose metabolism in chemotherapy-treated patients with NSCLC.[70-72]

Additional experience has underscored a few limitations of PET scanning. A PET scan-positive focus requires careful clinical correlation and biopsy confirmation if there is only one site of disease and if it changes the clinical stage. Verification bias can easily affect the sensitivity and specificity of PET scan-based tests when scan findings are not validated with tissue confirmation of the presence or absence of metastatic disease.[73] Lardinois et al[74] found that nearly one-half of the patients with NSCLC undergoing PET-CT scans with solitary extrapulmonary FDG accumulations had unrelated malignancies or benign disease at the solitary site in question. Overdiagnosis of nodal metastases can result in missed opportunities for surgical cure.[75] Incorrect upstaging was found in 4.8% of patients in Maziak's[29] series (compared with 0.6% in conventionally staged patients). Incorrect upstaging was equally likely in the mediastinum and in distant sites. Lung metastases (stage T4) were overlooked in 5% of subjects in one study using PET-CT scanning,[76] and understaging (30%) and overstaging (21%) were substantial concerns.

Finally, limited data are available comparing PET-CT scanning with PET scanning alone. In one retrospective study of 217 patients, PET-CT scanning was found to be significantly more accurate than PET or CT scanning alone.[77] A second retrospective study of 50 patients suggested that integrated PET-CT scanning is superior to PET scans, CT scans, and visually correlated separate PET and CT scans that are not coregistered.[44]

Several important caveats pertain to scanning for distant metastases in general. First is the issue of FP scans. Clinical entities that frequently give rise to FP scans include adrenal adenomas (present in 2%-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 the complications and costs resulting from such subsequent investigations have received insufficient attention.[78,79]

3.1 Recommendations

3.1.1. In patients with a normal clinical evaluation and no suspicious extrathoracic abnormalities on chest CT being considered for curative-intent treatment, PET imaging (where available) is recommended to evaluate for metastases (except the brain) (Grade 1B).

Remark: Ground glass opacities and an otherwise normal chest CT do not require a PET scan for staging.

Remark: In patients with peripheral stage cIA tumors a PET scan is not required.

Remark: If PET is unavailable, bone scan and abdominal CT are reasonable alternatives to evaluate for extrathoracic disease.

3.1.2. In patients with an imaging finding (eg, by PET) suggestive of a metastasis, further evaluation of the abnormality with tissue sampling to pathologically confirm the clinical stage is recommended prior to choosing treatment (Grade 1B).

Remark: Tissue sampling of the abnormal site is imperative so that the patient is not excluded from potentially curative treatment.

Remark: Tissue sampling of a distant metastatic site is not necessary if there is overwhelming radiographic evidence of metastatic disease in multiple sites.

Remark: Tissue sampling of the mediastinal lymph nodes does not necessarily need to be performed if there is overwhelming radiographic evidence of metastatic disease in multiple distant sites.

3.2 Detection of Abdominal Metastases

In the past iteration of the guideline, 13 studies evaluated the usefulness of clinical evaluation in detecting abdominal metastases in 1,291 patients using CT scanning as the reference standard.[4] Most of the studies limited enrollment to patients with a negative clinical evaluation. The median predictive value of a negative clinical evaluation was 97% (82%-100%). 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,[36,80] but not other, studies.[81,82] In the presence of clinical T1N0, NSCLC adenomas predominate,[83,84] whereas adrenal metastases are frequently associated with large intrathoracic tumors or other extrathoracic metastases.[36,85] Many studies suggest that the size of a unilateral adrenal abnormality on a CT scan is an important predictor of metastatic spread, but this is not a universal finding.[86]

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.[87,88] However, small lesions (<15 mm) were underrepresented in these series,

and others have noted rare FPs in this site.[89-91] Four possible approaches to distinguishing between malignant and benign adrenal masses have been proposed: evaluation by specific CT scanning or MRI criteria, evaluation with additional or serial imaging, percutaneous biopsy, and adrenalectomy. Well-defined, low-attenuation (fatty) lesions with a smooth rim on an unenhanced CT scan are more likely to be benign adenomas,[92-94] but the CT scanning appearance of many lesions is insufficiently distinctive.[92] Follow-up scanning with repeat CT scans, serial ultrasounds, MRI (especially with chemical shift and dynamic gadolinium-enhanced techniques),[95] 131-6-betaiodomethylnorcholesterol scanning,[96] or PET scanning can often help distinguish metastatic disease from adenoma, which is critical. 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.[97,98] However, this procedure may be nondiagnostic or unfeasible because of anatomic constraints. When insufficient material results from a biopsy, repeat aspiration or even adrenalectomy should be considered.[86,92]

Most liver lesions are benign cysts or hemangiomas, but contrast CT scanning (or ultrasound) is often required to establish a likely diagnosis.[99] Percutaneous biopsy can be performed when diagnostic certainty is required. One meta-analysis that specifically reviewed hepatic studies derived a pooled yield of 3% for liver metastases in asymptomatic patients with NSCLC.[79] PET scanning can detect liver metastases with an accuracy of 92% to 100% and there are only rare FPs, although data in NSCLC are very limited at present.[88,100]

3.3 Detection of Brain Metastases

In most studies, the yield of CT/MRI scanning of the brain in patients with NSCLC and negative clinical examinations is 0% to 10%.[101-107] In the last iteration of this guideline, 18 studies evaluated the ability of clinical evaluation to detect brain metastases in comparison with CT scanning in 1,830 patients.[4] These data were not updated in this iteration of the guideline. Nine studies limited enrollment to patients with a negative clinical evaluation. In these studies, the median prevalence of brain metastasis was 3% (range, 0%-21%), and the median predictive value of a negative clinical evaluation was 97% (range, 79%-100%). Nine other studies enrolled patients with both positive and negative clinical evaluations. In these studies, the median prevalence of brain metastasis was higher, at 14% (range, 6%-32%). Pooled sensitivity and specificity were 73% (95% CI, 60%-83%) and 85% (95% CI, 72%-92%), respectively.

An association among brain metastases, N2 disease in the chest, and adenocarcinoma histology has been described.[104,106,108] The FN rate of CT scanning (ie, where patients return with brain metastases within 12 months of the original scan) is reported to be 3%.[106] FP scans can be a problem in up to 11% of cases because of brain abscesses, gliomas, and other lesions[109]; therefore, biopsy may be essential in cases in which 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,[110] but in some studies, this has not translated into a clinically meaningful difference in terms of survival.[111] Although studies show that MRI can identify additional lesions in patients with metastases, the direct comparisons have not shown that MRI is able to identify more patients with metastases from lung cancer, compared with CT scanning. Therefore, CT scanning is an acceptable modality for evaluating patients for metastatic disease. In one study of 29 patients with NSCLC and a primary lesion > 3 cm in size (ie, stage more advanced than T1N0M0), MRI with contrast identified asymptomatic, verifiable metastases to the brain in 22%.[112] However, to date, the use of routine MRI in staging patients with NSCLC and negative clinical evaluations has not been studied adequately; a role in patients with large cell carcinoma or stage III adenocarcinoma has been suggested.[113]

3.4 Recommendation

3.4.1. In patients with clinical stage III or IV NSCLC it is suggested that routine imaging of the brain with head MRI (or CT if MRI is not available) should be performed, even if they have a negative clinical evaluation (Grade 2C).

3.5 Detection of Bone Metastases

The problem of FP 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. FP bone imaging also occurs with MRI, which may be no more accurate than nuclear bone imaging.[112] Eight studies examined the ability of clinical evaluation to detect bone metastases in 723 patients, using bone scanning as the reference standard.[4] Two studies limited enrollment to patients with negative clinical evaluations.[114,115] Using radionuclide bone scanning as the reference standard, the pooled negative predicted value of the clinical assessment was 90% (95% CI, 86%-93%). PET scanning appears to have excellent performance characteristics in assessing bone metastases, with specificity, sensitivity, NPV, PPV, and accuracy all exceeding 90%,[88,116] although FP and FN findings are seen occasionally.[19,88,91] The accuracy of PET scanning surpassed that of radionuclide bone scanning in two direct comparative studies.[117,118]

3.6 Pleural Effusions/Lung Metastases

Limited data suggest that PET scanning can be useful in identifying lung metastases[88,119] and malignant pleural effusions in NSCLC,[120,121] although much of the data pertains to nonpulmonary malignancies. FPs and FNs are noted occasionally.[90,120,122]

4.0 STAGING OF THE MEDIASTINUM

4.1 General Concepts

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, because in many cases, the status of these nodes determines whether there is surgically resectable disease. Clinical staging of lung cancer is usually directed by noninvasive imaging modalities. On the basis of such tests, physicians 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 Figures 3 and 4. Distinguishing these groups is particularly useful in defining the need 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) is generally accepted based on imaging alone, and the major issue is to obtain tissue by whatever approach is easiest, to distinguish between SCLC and NSCLC. However, in such patients, sampling the mediastinum can often confirm both the stage of disease and the diagnosis with minimal, if any, additional risk, compared with sampling the primary tumor alone. 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 mediastinal nodes that are not enlarged. 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%-25%) despite normal-sized nodes, and further confirmation is needed.[24-26,123] In the final group (ie, those 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).[24-26]

A widely accepted definition of normal-sized mediastinal lymph nodes is a short-axis diameter of ≤ 1 cm on a transverse CT scan image. Discrete nodal enlargement implies that discrete nodes are seen on the CT scan and are defined well enough that their size can be measured (and are > 1 cm). 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 the nodes. This occurs when multiple nodes are matted together to the point at which the boundary between them is obscured and it can be assumed that extensive extranodal spread of the tumor is involved. It may progress to the point where mediastinal vessels and other structures are partially or completely encircled. Finally, the distinction between a central and 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 generally requires that the physician look at the images himself or herself because there is no standard format defining 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 on a CT scan (ie, size, location, extent), and not by metabolic characteristics (ie, PET scan) for many reasons. First, a CT scan is relatively inexpensive and essentially is always done as a preliminary step to define the nature of a pulmonary abnormality and arrive at a clinical diagnosis of suspected lung cancer. Second, the information gained from the clinical history, physical examination, and chest CT can determine 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 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 or not the node in question is metabolically active on PET scan.

4.2 Imaging Studies

4.2.1 Chest Radiographs: The majority of lung cancers are detected initially by plain chest radiograph, although this has likely changed in recent years with the increasing use of chest CT scanning for a myriad of indications. In some situations, the plain film may be sufficient to detect spread 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 further imaging evaluation of the chest. This may be particularly true if the patient is too ill or 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, and thus, further noninvasive and/or invasive assessment is usually necessary.

4.2.2 CT Scanning of the Chest: CT scanning of the chest is the most widely available and most commonly used noninvasive modality for evaluation of the mediastinum in lung cancer. The vast majority of reports evaluating the 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 scans for this indication but it may be useful in helping distinguish vascular structures from lymph nodes, as well as in delineating mediastinal invasion by centrally located tumors. Experienced chest radiologists can usually make this distinction with respect to mediastinal nodes, provided the scan was performed with appropriately thin sections (≤ 5 mm), but identification of N1 nodes and the relationship to central pulmonary vessels remains an issue. 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 he/she is unwilling to undergo further evaluation.

Various CT scanning criteria have been used to define 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 ≥ 1 cm on a transverse CT scan. However, numerous other criteria have also been used, including (1) long-axis diameter ≥ 1 cm, (2) short-axis diameter ≥ 1.5 cm; (3) short-axis diameter ≥ 1 cm plus evidence of central necrosis or disruption of the capsule; and (4) short-axis diameter ≥ 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.[124,125] The majority of studies evaluating CT scan accuracy have used short-axis ≥ 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 FP evaluations without producing an unacceptable number of FN evaluations.

For the purposes of these guidelines, three authors of this section (G. S., A. G., M. J. G.) conducted a systematic review of the medical literature relating to the accuracy of CT scanning for noninvasive staging of the mediastinum in lung cancer and updated the data using the methods from previous guidelines.[4,10] When combined with the previous iterations of these guidelines, the combined studies yielded 7,368 evaluable patients (Fig 6).[19,24,44,47,88,90,126-162] The median prevalence of mediastinal metastasis was 30%. Almost all studies specified that CT scanning was performed following administration of IV contrast, and that a positive test result was defined as the presence of one or more lymph nodes that measured > 1 cm in short scanning axis diameter. The median sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis were 55% and 81%, respectively. CT scanning has limited ability to either rule in or exclude mediastinal metastasis. The combined estimates should be interpreted with caution because the studies were statistically heterogeneous. Still, these findings mirror those of other analyses addressing the accuracy of CT scanning for staging of the mediastinum in NSCLC[163,164] and are similar to the last iteration of this guideline.[4]

CT scanning is clearly an imperfect means of staging of the mediastinum, but it remains the best overall anatomic study available for the thorax. CT scanning usually guides the choice of nodes for selective node biopsy by invasive techniques, and thus continues to be an important diagnostic tool in 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 NA; mediastinoscopy; or more extensive surgery), are typically 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 IA) tumors are found to have positive lymph node involvement by surgical lymph-node sampling.[99]

Based on the currently available data relating to the performance characteristics of CT scanning for the evaluation of the mediastinum in NSCLC, two important messages emerge. First, an unacceptably high percentage of lymph nodes deemed malignant by CT scan criteria are actually benign. Second, a significant number of lymph nodes deemed benign by CT scan criteria are actually malignant. Chest CT scans can both overstage and understage the

FIGURE 6. [Section 4.2.2] Accuracy of CT scanning for staging of the mediastinum in patients with lung cancer.

First Author	Year	No.	Tech	Prev	Sens	Spec	PPV	NPV
Eggeling[137]	2002	73	CE	70	82	50	79	55
Wallace[143]	2001	121	CE	69	87	35	75	54
Marom[88]	1999	79	CE	56	59	86	84	63
Vansteenkiste[150]	1998	56	CE	50	86	79	80	85
Aaby[156]	1995	57	…	44	72	91	86	81
Schillaci[136]	2003	83	CE	42	69	75	67	77
Vansteenkiste[151]	1998	68	CE	41	75	63	58	78
Primack[157]	1994	159	CE	38	63	86	73	79
Turkmen[130]	2007	59	CE	36	43	66	41	68
Laudanski[141]	2001	92	CE	33	60	73	51	79
Yokoi[58]	1994	113	CE	33	62	80	61	81
Gdeedo[153]	1997	100	CE	32	63	57	41	76
Bury[155]	1996	53	CE	32	71	81	63	85
McLoud[159]	1992	143	CE	31	64	62	44	79
Pieterman[90]	2000	102	CE	31	75	66	50	85
Yen[127]	2008	96	CE	31	47	80	52	77
Osada[146]	2001	335	CE	30	56	93	77	83
Jolly[160]	1991	336	CE	30	71	86	69	87
Subedi[47]	2009	91	CE	29	50	86	59	81
Buccheri[154]	1996	80	CE	28	64	74	48	84
Pozo-Rodriguez[24]	2004	132	CE	27	86	67	49	93
Kiernan[138]	2002	92	CE	27	64	94	80	88
Reed[19]	2003	302	CE	25	37	91	58	81
Nosotti[139]	2002	87	CE	25	64	88	64	88
Dunagan[144]	2001	72	CE	25	50	87	56	84
Kimura[135]	2003	203	CE	24	63	97	88	89
Yi[29]	2007	143	CE	24	65	89	65	89
Suzuki[149]	1999	440	CE	23	33	92	56	82
Bury[152]	1997	64	CE	22	79	84	58	93
De Wever[44]	2007	50	CE	22	91	72	48	97
Webb[162]	1991	154	CE	21	52	69	31	84
Cole[161]	1993	150	…	21	26	81	26	81
Takamochi[132]	2005	71	CE	21	20	89	33	81
Kamiyoshihara[145]	2001	546	CE	20	33	90	46	84
Takamochi[147]	2000	401	CE	20	30	82	30	83
Lee[126]	2009	182	CE	20	36	79	30	83
Yang[128]	2008	122	CE	20	52	73	33	86
Kelly[134]	2004	69	CE	19	46	86	(43)[a]	87
Saunders[148]	1999	84	…	18	20	90	(30)[a]	84
Nomori[133]	2004	80	…	18	50	95	(70)[a]	90
Ebihara[131]	2006	205	CE	15	32	83	(26)[a]	87
Poncelet[142]	2001	62	CE	15	56	68	(23)[a]	90
Von Haag[140]	2002	52	CE	12	50	65	(16)[a]	91
Median: prevalence > 30					67	74	62	79
Median: prevalence 21-30					63	87	58	84
Median: prevalence ≤ 20					41	83	30	87
Summary: Median		7,368		30	55	81	58	83

Inclusion criteria: studies reporting test characteristics of chest CT scanning to identify benign or malignant mediastinal nodes in patients with lung cancer, involving ≥ 50 patients from 1980 to 2011. CE = contrast enhanced; NPV = negative predictive value; Prev = prevalence; PPV = positive predictive value; Sens = sensitivity; Spec = specificity; Tech = technical details of imaging.
[a]Because PPV is increasingly affected by prevalence as prevalence is < 20% these values are excluded from summary calculations.

mediastinal nodes. In sum, there is no node size that can reliably determine stage and operability. In cases in which the CT scan criteria for identification of a metastatic node are met, the physician must still prove by biopsy 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 NSCLC. Nonetheless, CT scanning continues to play an important and necessary role in the evaluation of these patients. In the mediastinum, CT scanning can provide a road map that guides the physician to the location and modality for subsequent biopsy procedures.

4.2.3 PET Scanning: PET scanning is an imaging modality based on the biologic activity of neoplastic cells. Lung cancer cells demonstrate increased cellular uptake of glucose and a higher rate of glycolysis when compared with normal cells.[165] The radio-labeled glucose analog[157] F-fluoro-2-deoxy-d-glucose (FDG) undergoes the same cellular uptake as glucose, and is phosphorylated by hexokinase, generating FDG-6-phosphate. The combination of increased uptake of FDG and a decreased rate of dephosphorylation by glucose-6-phosphatase in malignant cells results in an accumulation of FDG-6-phosphate in these cells.[166,167] The accumulated isotope can then be identified using a PET scan camera. FDG-PET scanning (subsequently referred to as PET scanning) is thus a metabolic imaging technique based on the function of a tissue rather than its anatomy. Standardized quantitative criteria for an abnormal PET scan in the mediastinum are unfortunately lacking. A qualitative assessment is usually based on a comparison of uptake in the lesion or structure in question and the background activity of the lung or liver. A standard uptake value of > 2.5 is sometimes used as a threshold level for malignancy, but this value is based on the uptake of peripheral masses >2 cm; the applicability to mediastinal nodes is questionable at best. 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 because 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 current generation PET scanners being approximately 7 to 10 mm. Nevertheless, smaller lesions may be detected, depending on the intensity of uptake of the isotope in abnormal cells.[90,168] Additionally, certain well-differentiated low-grade malignancies, particularly adenocarcinoma in situ, well-differentiated invasive adenocarcinomas, and typical carcinoid tumors, are known to have a higher risk of FN results.[169-173]

A burgeoning number of studies in the past several years have reported on the use of PET scanning in the assessment of the mediastinum in patients with lung cancer. Increasing availability of the technology now allows PET scanning to be used widely as a diagnostic tool. It has already been noted that PET scanning is primarily a metabolic examination and has limited anatomic resolution. It is usually possible to identify lymph node stations, but not individual lymph nodes, by PET scanning. CT scanning provides much more anatomic detail, but lacks the functional information provided by PET scanning.

As was done for CT scanning, the authors of this article updated the 2003 and 2007 guidelines by performing a systematic review of the medical literature relating to the accuracy of PET scanning for noninvasive staging of the mediastinum in lung cancer, using the methods described previously.[4,10] All studies were either combined PET-CT scans or were interpreted in conjunction with patients' CT scans so that the findings on PET scanning were correlated with the anatomic location of the lesion on CT scanning. In all studies, FDG was the radiopharmaceutical used for imaging. A total of 4,105 patients were included in this evaluation (Fig 7).* The median prevalence of mediastinal metastasis was 28%. The median sensitivity and specificity for identifying mediastinal metastasis were 80% and 88%, respectively. These findings demonstrate that PET scanning is more accurate than CT scanning for staging of the mediastinum in lung cancer, although it is not perfect.

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 to use PET scans 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 scanning are correlated visually. This limitation has been addressed by the development of "dual-modality" or "integrated" PET-CT scanning systems, in which a CT scanner and PET scanner are combined in a single gantry. Since the last iteration of these guidelines, more studies evaluating the accuracy of integrated PET-CT scanners for lung cancer staging have been performed. For this iteration of the guidelines, we have separated studies that used PET scanning alone from those that used PET-CT scanning.[150,151,196-198] From 2000 to 2111, a total of 19 studies were identified that included 2,014 patients who met the inclusion criteria and underwent PET-CT scanning; the results of these 19 studies are displayed in Figure 8.[29,40,44,47,76,126,128,129,199-209] Although the specificity of this technique was slightly higher than with PET scanning alone, the sensitivity was significantly lower. The reason for this is unclear.

PET scanning is less sensitive for lymph nodes with diameters < 7 to 10 mm, and most of the invasive technologies (mediastinoscopy, endobronchial ultrasound [EBUS], and endoscopic ultrasound [EUS]) have discovered unsuspected mediastinal metastases in patients with normal-sized lymph nodes without PET scanning activity.[210,211] The clinical presentation in which controversy can arise is the patient with a peripheral clinical T1a lesion (small pulmonary nodule) who has normal-sized lymph nodes without PET scanning avidity, particularly if the density of

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*References 12,19,24,26,40,64,88,90,127,130-134,138,140,142,144, 148,150-152,155,174-195.

FIGURE 7. [Section 4.2.3] Accuracy of PET scanning for staging of the mediastinum in patients with lung cancer.

FIGURE 8. [Section 4.2.3] Accuracy of integrated PET-CT scanning for staging of the mediastinum in patients with lung cancer.

First Author	Year	No.	Prev	Sens	Spec	PPV	NPV
Changlai[185]	2001	127	64	88	83	90	79
Marom[88]	1999	79	56	73	94	85	88
Bury[155]	1996	30	53	88	86	88	86
Vansteenkiste[150]	1998	56	50	86	43	60	75
Sazon[192]	1996	32	50	100	100	100	100
Nosotti[64]	2008	413	48	97	97	97	97
Fritscher-Ravens[179]	2003	33	48	75	88	86	79
Wahl[195]	1994	23	48	82	75	75	82
Tatsumi[186]	2000	21	48	80	82	80	82
Guhlmann[190]	1997	32	47	87	100	100	89
Verhagen[26]	2004	56	46	58	90	83	71
Vansteenkiste[151]	1998	68	41	93	95	93	95
Vesselle[184]	2002	118	36	81	96	92	90
Turkmen[130]	2007	59	36	76	79	67	86
Zimny[182]	2003	33	36	83	81	71	89
Liewold[187]	2000	78	35	93	78	69	95
Scott[193]	1996	27	33	100	100	100	100
Magnani[189]	1999	28	32	67	84	67	84
Pieterman[90]	2000	102	31	91	86	74	95
Yen[127]	2008	96	31	73	92	81	88
Chin[194]	1995	30	30	78	81	64	89
Demura[178]	2003	50	30	87	63	50	92
Steinert[191]	1997	47	28	92	97	92	97
Melek[175]	2008	170	28	75	68	48	87
Kiernan[138]	2002	88	28	88	86	71	95
Halpern[177]	2005	36	28	50	77	45	80
Pozo-Rodriguez[24]	2005	132	27	81	76	56	91
Dunagan[144]	2001	81	26	52	88	61	84
Reed[19]	2003	302	25	61	84	56	87
Bernasconi[176]	2006	51	25	54	76	44	83
Roberts[188]	2000	100	24	88	91	75	96
Gonzalez-Stawinski[180]	2003	202	23	66	78	48	88
Bury[152]	1997	64	22	86	100	100	96
Takamochi[132]	2005	71	21	40	88	46	84
Saunders[148]	1999	84	20	71	97	86	93
Kernstine[183]	2002	237	19	82	82	51	95
Kelly[134]	2004	69	19	62	98	(89)a	92
Nomori[133]	2004	80	18	86	97	(86)a	97
Lee[40]	2007	210	17	61	94	(69)a	92
Ebihara[131]	2006	205	15	74	90	(58)a	95
Poncelet[142]	2001	61	15	67	85	(43)a	94
Von Haag[140]	2002	52	12	67	91	(50)a	95
Yamamoto[174]	2008	34	9	33	84	(17)a	93
Konishi[181]	2003	54	9	80	92	(50)a	98
Farrell[12]	2000	84	5	100	93	(40)a	100
Median: prevalence > 30				85	87	84	88
Median: prevalence 21-30				77	83	56	89
Median: prevalence ≤ 20				71	92	51	95
Summary: median		4,105	28	80	88	75	91

First Author	Year	No.	Prev	Sens	Spec	PPV	NPV
Cerfolio[200]	2004	40	100	75	…	…	…
Plathow[204]	2008	52	73	100	100	100	100
Fischer[361]	2011	79	33	85	100	100	93
Lee[202]	2009	41	32	38	89	63	76
Yi[209]	2008	150	30	62	94	82	85
Maziak[29]	2009	167	29	48	93	74	82
Subedi[47]	2009	91	26	92	85	69	97
Yi[129]	2007	143	24	56	100	100	88
Carnochan[76]	2009	194	23	42	87	50	83
Lee[40]	2007	126	22	86	81	56	95
De Wever[44]	2007	50	22	73	82	53	91
Lee[126]	2009	182	20	81	73	42	94
Yang[128]	2008	122	20	52	73	33	86
Perigaud[203]	2009	51	20	40	85	40	85
Billé[199]	2009	159	19	48	93	(63)a	88
Toba[207]	2010	42	19	100	88	(67)a	100
Usuda[208]	2011	63	17	36	92	(50)a	87
Sanli[205]	2009	78	14	82	90	(56)a	97
Shin[206]	2008	184	13	48	95	(58)a	93
Summary: median		2,014	22	62	90	63	90

Inclusion criteria: studies reporting test characteristics of PET scanning to identify benign or malignant mediastinal nodes in patients with lung cancer, involving ≥ 20 patients from 1980 to 2011. See Figure 4 legend for expansion of abbreviations.
aBecause PPV is increasingly affected by prevalence as prevalence is < 20% these values are excluded from summary calculations.

Inclusion criteria: studies reporting test characteristics of integrated PET-CT scanning to identify benign or malignant mediastinal nodes in patients with lung cancer, involving ≥ 20 patients from 2000 to 2011. See Figure 6 for expansion of abbreviations.
aBecause PPV is increasingly affected by prevalence as prevalence is < 20% these values are excluded from summary calculations.

the nodule is ground glass (ie, not solid). On the one hand, confirmation of the negative PET scan findings by any of the invasive staging methods may not be necessary because the incidence of this clinical situation of mediastinal nodal metastases is so low (although not zero) as to not warrant the test.[34] Conversely, approximately 4% of patients with stage I disease have unsuspected mediastinal disease, discovered in those patients with a radiographically and PET scan-normal mediastinum.[210,211] Ultimately, the decision as to whether a negative PET scan can be used to obviate invasive staging preoperatively requires clinical judgment that incorporates multiple factors, including the clinical pretest probability of mediastinal metastasis, patient preferences, and local availability and expertise in both invasive procedures and PET imaging.

A recent phenomenon with regard to PET scanning is that published studies often assess the usefulness of PET scanning as it relates to a single aspect of the patient's presentation (eg, solitary pulmonary nodule, mediastinal disease, or distant metastatic disease) and they often find flaws in the technology as it relates to the specific indication for which the study was undertaken. However, the physician does not view a PET or PET-CT scan in a vacuum; these studies often provide information about the primary site of the tumor in the chest as well as intrathoracic and extrathoracic metastases. The resultant information can lead the physician to undertake a biopsy of a different area than the one initially anticipated by CT scan, which often provides more accurate staging, especially when unsuspected metastatic disease is discovered by PET scanning.

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, although this technology is not infallible. FP PET scan findings may result in missed opportunities for cure by surgical resection. Conversely, FN PET scan findings may lead to noncurative resection. The potential consequences of both FP and FN 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. One should not preclude a potential curative surgery based on a positive PET scan alone without tissue confirmation. However, PET scanning is the most accurate noninvasive imaging modality available to evaluate the mediastinum in patients with lung cancer. PET scanning is also a whole-body study (excluding the brain), offers additional information relating to extrathoracic sites of possible disease involvement, and can reduce noncurative resections. PET scanning has now assumed a central role in the staging of lung cancer.

4.2.4 MRI: Like CT scanning, MRI is an anatomic study. Data relating to the accuracy of the evaluation of the mediastinum in patients with NSCLC with MRI are limited, but available reports suggest that the accuracy of MRI is as good as that of CT scanning.[162,212] Two reports also suggest that the use of contrast enhancement may improve the accuracy of MRI in this situation.[212,213] MRI may be superior to CT scanning in 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.[162,214-217] 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 the potential mediastinal spread of lung cancer. In summary, an MRI of the chest should not be performed routinely for staging of the mediastinum. MRI is useful in patients with NSCLC when there is concern about involvement of the superior sulcus or the brachial plexus.

4.3 Invasive Techniques to Stage the Mediastinum

After performing the initial imaging studies, the physician selects his or her next test based on the radiographic presentation (see radiographic groups mentioned previously and Fig 3) and local availability and expertise of the physicians performing these procedures. The separation into radiographic groups helps guide the choice of invasive test and the performance characteristics of these tests. The radiographic groups are defined by anatomic characteristics on a CT scan for several reasons. First, a CT scan is relatively inexpensive and is always done as a preliminary step to define the nature of a pulmonary abnormality and 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).

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 a lack of nodal involvement. Furthermore, the location of the 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 the series of particular invasive procedures are likely not the same. This makes comparison of sensitivity and specificity of the different tests inappropriate. In addition, operator 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 imaging and invasive staging tests as complementary and not competitive.

4.3.1 Surgical Staging:

4.3.1.1 Mediastinoscopy—Mediastinoscopy is performed in the operating room, usually under general anesthesia, and in most US centers, patients are discharged the same day.[218-220] The procedure involves an incision just above the suprasternal notch, insertion of a mediastinoscope alongside the trachea, and biopsy of mediastinal nodes. Rates of morbidity and mortality as a result of this procedure are low (2% and 0.08%).[221] Right and left high and low paratracheal nodes (stations 2R, 2L, 4R, 4L), pretracheal nodes (stations 1, 3), and anterior subcarinal nodes (station 7) are accessible via this approach. Node groups that cannot undergo a biopsy with this technique include the posterior subcarinal (station 7) nodes, the inferior mediastinal (stations 8, 9) nodes, the aortopulmonary window (APW) (station 5) nodes, and the anterior mediastinal (station 6) nodes. A videomediastinoscope allows better visualization, more extensive sampling (including posterior station 7), and even the performance of a lymph node dissection.[222,223]

As was done for the noninvasive tests, the authors, using previously described methodology, updated the 2003 and 2007 guidelines by performing a systematic

review of the medical literature relating to the accuracy of mediastinoscopy for staging of the mediastinum in lung cancer.[3,10] The median sensitivity of standard cervical mediastinoscopy to detect mediastinal node involvement from cancer was 78% in 9,267 patients (Fig 9).[125,156,160,222,224-245] The median NPV was 91%. Several authors have shown that approximately one-half (42%-57%) of the FN cases were due to nodes that were not accessible by the (traditional) mediastinoscope.[153,235,243,246-248] 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 be examined routinely,

FIGURE 9. [Sections 4.3.1.1] Accuracy of mediastinoscopy in patients with lung cancer.

First Author	Year	No.	Stage	Thoro	Prev	Sens	Spec[a]	PPV[a]	NPV
TM									
Hammoud[235]	1999	1,369	cN0-3	Sel	36	85	(100)[a]	(100)[a]	92
Lemaire[230]	2006	1,362	cN0-3	Sys	29	86	(100)[a]	(100)[a]	95
Coughlin[243]	1985	1,259	cN0-3	Sel	29	92	(100)[a]	(100)[a]	97
Luke[242, b]	1986	1,000	cN0-2	Sel	39	85	(100)[a]	(100)[a]	91
De Leyn[238]	1996	500	cN0-2	Sys	39	76	(100)[a]	(100)[a]	87
Anraku[227]	2010	352	cN0-3	Sys	37	92	(100)[a]	(100)[a]	96
Page[241, b]	1987	345	cN0-2	Sel	48	73	(100)[a]	(100)[a]	80
Dillemans[239]	1994	331	cN0-3	Sys	41	72	(100)[a]	(100)[a]	84
Brion[244]	1985	153	cN0-2	Sel	35	67	(100)[a]	(100)[a]	85
Fibla[231]	2006	142	cN0-3	Sel	42	67	(100)[a]	(100)[a]	80
Jolly[160]	1991	136	cN0-2	Sel	54	92	(100)[a]	(100)[a]	91
Ratto[125]	1990	123	cN0-2	Sel	33	88	(100)[a]	(100)[a]	94
Ebner[236, b]	1999	116	cN0-2	Sys	50	81	(100)[a]	(100)[a]	82
Annema[228]	2010	110	cN0-3	Sel	46	80	(100)[a]	(100)[a]	86
Gdeedo[153]	1997	100	cN0-3	Sys	32	78	(100)[a]	(100)[a]	91
Riordain[240]	1991	74	cN0-2	Sel	50	81	(100)[a]	(100)[a]	84
Aaby[156]	1995	57	cN0-3	Sys	44	84	(100)[a]	(100)[a]	89
Block[226]	2010	54	cN0-3	Sel	44	88	(100)[a]	(100)[a]	91
Kim[224]	2011	750	cN0	Sys	15	44	(100)[a]	(100)[a]	91
Choi[233]	2003	291	cN0	Sys	15	44	(100)[a]	(100)[a]	91
Meyers[229]	2006	169	cN0	Sel	8	38	(100)[a]	(100)[a]	95
Cerfolio[232]	2006	153	cN0-1	Sys	14	32	(100)[a]	(100)[a]	90
Deneffe[245]	1983	124	cN0	Sel	31	68	(100)[a]	(100)[a]	88
Park[225]	2010	78	cN0	Sys	8	50	(100)[a]	(100)[a]	96
Gurses[234]	2002	67	cN0	Sys	15	40	(100)[a]	(100)[a]	93
Leschber[222]	2008	52	cN0	Sys	19	…	(100)[a]	…	81
Median: cN0-3			*cN0-3*	*39% sys*	**40**	**83**			**90**
Median: cN0			*cN0*	*75% sys*	**16**	**47**			**91**
Median: sys			*46% cN0*	*sys*	**27**	**74**			**91**
Median: sel			*17% cN0*	*sel*	**39**	**81**			**91**
Summary TM: median		**9267**			**33**	**78**	**(100)[a]**	**(100)[a]**	**91**
VAM									
Venissac[223]	2003	154	cN2-3	Sys	71	97	(100)[a]	(100)[a]	94
Kimura[250]	2007	209	cN0-3	Sel	31	78	(100)[a]	(100)[a]	91
Lardinois[246]	2003	195	cN0-3	Sys	34	87	(100)[a]	(100)[a]	92
Kimura[135]	2003	125	cN0-3	Sys	36	85	(100)[a]	(100)[a]	92
Sayar[249]	2011	104	cN0-2	Sel	29	90	(100)[a]	(100)[a]	96
Anraku[227]	2010	89	cN0-3	Sys	22	95	(100)[a]	(100)[a]	99
Leschber[222]	2008	119	cN0	Sys	17	…	(100)[a]	…	83
Summary VAM: median		**995**			**31**	**89**	**(100)[a]**	**(100)[a]**	**92**
LA									
Zielinski[364]	2007	256	cN0-2	Compl	31	94	(100)[a]	(100)[a]	97
Witte[365]	2006	130	cN0-2	Compl	…	94	(100)[a]	(100)[a]	99
Summary LA: median		**386**		**compl**	**31**	**94**	**(100)[a]**	**(100)[a]**	**98**
Summary ALL: median		**10,648**			**34**	**81**	**(100)[a]**	**(100)[a]**	**91**

Inclusion criteria: studies of mediastinoscopy for lung cancer staging, involving ≥50 patients from 1980 to 2011 reporting test characteristics. Compl = complete; LA = mediastinal lymphadenectomy (via cervical mediastinoscopy approach); Sel, selective assessment; Sys = systematic assessment; Thoro = level of thoroughness of the procedure (complete, systematic, selective, limited or visual assessment of mediastinal node stations[354]; TM = traditional mediastinoscopy; VAM = video-assisted mediastinoscopy.
[a]Technically, the specificity and PPV cannot be assessed in those studies reporting 100% values because a positive result was not followed up with an additional gold standard test.

with at least one node sampled from each station unless none are present after dissection in the region of a particular node station. It has been suggested that videomediastinoscopy provides a higher yield than conventional mediastinoscopy. In pooling the data from 995 cases for this iteration of the guidelines, the sensitivity of videomediastinoscopy was higher at 89% than that of traditional mediastinoscopy (Fig 9).[135,222,223,227,246,249,250] 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 result were not subjected to any further procedures (such as thoracotomy) to confirm the results. Nevertheless, it seems reasonable to assume that FP results are rare. The patients included in these series had had potentially operable, nonmetastatic lung cancer with very few exceptions. The majority of these patients were in the radiographic groups B, C, and D.

Further assessment of the results of mediastinoscopy demonstrated that the newer techniques (mediastinal lymphadenectomy and videomediastinoscopy) have better results than traditional mediastinoscopy (median sensitivity of 94%, 89%, and 78% and median FN rates of 2%, 8,% and 9%, respectively). The performance of traditional mediastinoscopy is affected by the type of patients (sensitivity of 47% vs 83% for cN0 vs cN0-3), although there is little difference in the FN rates. Whether a systematic or selective level of thoroughness (level B or C) was used via traditional mediastinoscopy had little impact (as well as can be judged from the available reports). However, this may be reflective of the type of patients: systematic sampling was more common for patients with cN0 disease and selective sampling for patients with stage cN0-3 disease. It may be that using a more thorough technique is particularly important in patients without clinical suspicion of node involvement. The impact of the level of thoroughness of the procedure or the clinical node status when using the newer techniques cannot be assessed. Thus, it appears that the better visualization afforded by videomediastinoscopy should be considered to be an important feature associated with better results, whereas the importance of the thoroughness of sampling (levels A-C) is less clear. However, limited or no sampling (level D) cannot be considered acceptable.

4.3.1.2 Assessment of APW 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 not accessible by standard cervical mediastinoscopy. It has been suggested that nodes in this region not be viewed as mediastinal nodes and that resection

of patients be performed regardless of APW node involvement, making assessment of these nodes superfluous.[257] 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, analysis of all the data in this regard show that the survival of patients with only APW node involvement is not different from that of patients with involvement of only a single N2 node station in another location.[252] 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 method to invasively assess 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. This procedure traditionally required an overnight hospital stay, but in many institutions this is no longer necessary, especially because surgeons have used visualization between the ribs more frequently as opposed to removal of a costal cartilage. The accuracy of this procedure has not been documented extensively, despite its common use. The median sensitivity of a Chamberlain procedure for the detection of the involvement of station 5,6 nodes in patients with LUL tumors was approximately 71% among 238 patients (Fig 10).[241,245,253,254] The median NPV was 91%.

Extended cervical mediastinoscopy offers an alternative method to invasively assess APW nodes but is used in only a few institutions (Fig 10).[255-258] With this procedure, a mediastinoscope is inserted through the suprasternal notch and directed lateral to the aortic arch.[256] In 456 patients with LUL cancers, standard mediastinoscopy accompanied by extended mediastinoscopy was found to have a median sensitivity of 71% for identifying station 5,6 node involvement.[255-258] The median NPV was 91%.

Video-assisted thoracic surgery (VATS) has been used to assess APW lymph nodes. The general results of this technique are reported in Figure 11. 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.

The patients included in these series of Chamberlain procedures, extended cervical mediastinoscopy, and VATS had potentially operable lung cancer with very few exceptions. These patients were 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 as compared with thoracotomy in patients with lung cancer.

[S...s 4.3.1.2] Test para...
(...d 6).

	Year
...otomy	200...

that preclude resection. Radiographically suspected T4 involvement was shown to be absent by VATS in 38% (29%-50%) of patients in three studies.[137,261,262] Furthermore, in 40% of patients with cytologically negative pleural effusions, the effusions were shown not to be due to malignant involvement by VATS.[262] On the other hand, routine VATS found unsuspected pleural studding in 4% (0%-5%) of patients in several studies.[137,260,261,264-267] An unsuspected malignant pleural effusion was also found in 6% in one study.[265] Most of the patients in these studies of pleural involvement had CT scan evidence of discrete node enlargement.

4.3.2 Needle Techniques:

4.3.2.1 Transthoracic NA—Transthoracic NA (TTNA) or biopsy for diagnosis of the mediastinum is distinct from TTNA of parenchymal masses to achieve a diagnosis. The ability to carry out TTNA for diagnosis and staging of the mediastinum has generally been reported to be high (about 90%), although approximately 10% of patients require placement of a catheter for evacuation of a pneumothorax.[252] The sensitivity has usually been reported to be 94%, and no studies have been added since the previous iteration of this guideline (Fig 12).[3,266-272] Patients selected for this procedure have most often had quite extensive mediastinal involvement (radiographic group A, with some group B). The mediastinal lymph nodes have generally been at least 1.5 cm, which is also likely related to the fact that the prevalence of cancer in the mediastinal nodes was very high (>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. Extra-

polation 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 biopsy of multiple mediastinal nodes such as would be needed in patients in radiographic groups C, D, and even B. The thoroughness of assessment in the reported studies has been limited to obtaining a biopsy specimen from one site only.

4.3.2.2 Transbronchial NA—Transbronchial NA (TBNA), also known as a Wang NA, can be performed safely with no significant morbidity and on an outpatient basis, as with most bronchoscopic procedures. "Blind" or unguided TBNA is used most frequently to assess subcarinal nodes. Biopsies may also be performed with TBNA on paratracheal lymph nodes, but these are sometimes more difficult to access because of the difficulty of sufficiently angulating the bronchoscope and the needle. It is reported that it is feasible to get adequate specimens via TBNA in approximately 80% to 90% of cases.[273-276]

For this iteration of the guideline, 2,408 patients were included in an updated systematic review (Fig 13).[176,273-298] The overall median sensitivity was 78%, with values ranging from 14% to 100%. The reported specificity and FP rates were 100% and 0%, respectively, although a few studies confirmed positive TBNA results with further invasive procedures. Occasional FP results have been reported in series in which this has been specifically examined with a confirmatory test (average, 7%).[285,289,299] The median NPV, excluding studies with a prevalence >80%, was 77%.

Patients included in studies of TBNA have generally had a very high prevalence of N2,3 involvement (average, 81%), and the general implication is that the mediastinal nodes have been markedly enlarged, although specifics about node size are generally

FIGURE 12. [Section 4.3.2.1] Transthoracic needle aspiration (percutaneous) of the mediastinum in patients with lung cancer.

First Author	Year	No.	Stage	Guidance	Prev	Sens	Spec[a]	PPV[a]	NPV
Moinuddin[271]	1984	40	cN2,3[b]	CT scan	78	100	(100)[a]	(100)[a]	100
Protopapas[268]	1996	32	cN2,3	CT scan	91	100	(100)[a]	(100)[a]	(100)[c]
Böcking[269]	1995	23	cN2,3	CT scan	65	80	(100)[a]	(100)[a]	100
de Gregorio[270]	1991	48	cN2,3[b]	Fluoro	90	72	(100)[a]	(100)[a]	(42)[c]
Westcott[272]	1981	72	cN2,3[b]	Tomo	…	94	…[d]	…[d]	…[d]
Summary: median		**215**			**84**	**94**	**(100)[a]**	**(100)[a]**	…

Inclusion criteria: studies reporting test characteristics of TTNA of mediastinal nodes/tissue in patients with lung cancer, involving >20 patients from 1980 to 2011. Fluoro = fluoroscopy; Tomo = tomography; TTNA = transthoracic needle aspiration. See Figure 6 for expansion of other abbreviations.
[a]Technically, the specificity PPV cannot be assessed in these studies because a positive result was not followed up with an additional gold standard test.
[b]Bulky masses, corresponding to radiographic group A.
[c]Because NPV is increasingly affected by prevalence as prevalence is >80% these values are excluded from summary calculations.
[d]Not defined because all subjects had mediastinal disease.

FIGURE 13. [Section 4.3.2.2] Transbronchial needle aspiration of the mediastinum in patients with lung cancer.

Study	Year	No.	Stage	Prev	Sens	Spec[a]	PPV[a]	NPV
Fernandez-Villar[277]	2010	280	cN1-3	…	68	(100)[a]	(100)[a]	10
Utz[294]	1993	61	cN0/N2	100	56	(100)[a]	(100)[a]	…
Selcuk[291]	2003	26	cN2-3	100	100	(100)[a]	(100)[a]	…
Wilsher[298]	1996	24	cN2-3	96	90	(100)[a]	(100)[a]	…
Katis[279]	1998	76	cN2-3	95	74	(100)[a]	(100)[a]	(20)[b]
Bilaceroglu[273]	1998	134	cN1-3	88	75	(100)[a]	(100)[a]	(36)[b]
Melloni[282]	2009	51	cN2-3	88	76	(100)[a]	(100)[a]	(33)[b]
Shannon[293]	1996	24	cN2-3	88	90	(100)[a]	(100)[a]	(60)[b]
Stratakos[294]	2008	77	cN1-3	86	88	(100)[a]	(100)[a]	(58)[b]
Schenk[288]	1993	64	cN2-3	86	56	(100)[a]	(100)[a]	(82)[b]
Wang[297]	1983	39	cN2-3	86	76	(100)[a]	(100)[a]	(71)[b]
Schenk[290]	1989	29	cN2-3	86	80	(100)[a]	(100)[a]	(44)[b]
Medford[281]	2010	79	cN2-3	84	79	(100)[a]	(100)[a]	(58)[b]
Mak[280]	2004	24	cN1-3	83	60	(100)[a]	(100)[a]	(33)[b]
Vansteenkiste[276]	1994	80	cN2	79	79	(100)[a]	(100)[a]	55
Rodriguez de castro[286]	1997	80	cN2-3	78	66	(100)[a]	(100)[a]	45
Harrow[278]	2000	264	cN1-3	72	93	99	99	80
Shah[292]	2006	129	cN1-3	71	68	(100)[a]	(100)[a]	56
Rodriguez de castro[275]	1995	56	cN2-3	70	77	(100)[a]	(100)[a]	70
Patelli[283]	2002	182	cN2	67	98	(100)[a]	(100)[a]	83
Rong[287]	1998	49	cN1-3	66	100	(100)[a]	(100)[a]	100
Rakha[284]	2010	182	cN1-3	57	84	(100)[a]	(100)[a]	70
Garpestad[274]	2001	32	cN1-3	57	83	(100)[a]	(100)[a]	67
Schenk[289]	1986	88	cN2-3	39	50	96	89	75
Bernasconi[176]	2006	113	cN2-3	31	54	(100)[a]	(100)[a]	91
Wallace[296]	2008	138	cN2-3	30	36	(100)[a]	(100)[a]	78
Ratto[285]	1988	47	cN2	30	14	(100)[a]	(100)[a]	73
Summary: median		**2,408**		**81**	**78**	**(100)[a]**	**(100)[a]**	**77**

Inclusion criteria: studies reporting test characteristics of TBNA of mediastinal nodes/tissue in patients with lung cancer, involving ≥ 20 patients from 1980 to 2011. TBNA = transbronchial needle aspiration. See Figure 6 for expansion of other abbreviations.

[a]Technically, the specificity and PPV cannot be assessed in the studies reporting 100% values because a positive result was not followed up with an additional gold standard test.

[b]Because NPV is increasingly affected by prevalence and prevalence was > 80% these values are excluded from summary calculations.

vague. The results should not be applied to patients without extensive mediastinal involvement.[300] Furthermore, the high FN rate makes this test less useful for staging of the mediastinum in patients with normal-sized nodes. Positive TBNA results demonstrate mediastinal node involvement fairly reliably. Negative TBNA results, however, cannot sufficiently exclude mediastinal nodal involvement, and additional staging procedures should be performed. When compared directly with other needle technologies, TBNA has a much lower sensitivity than the ultrasound-guided technologies, either alone or in combination (see later discussion).[296] Where available, ultrasound-guided needle techniques such as EBUS-NA or EUS-NA have largely replaced TBNA for staging of the mediastinum in patients with lung cancer.

4.3.2.3 Endoscopic Ultrasound With NA—EUS-NA of mediastinal lymph nodes through the wall of the esophagus has been performed with a negligible risk of infection or bleeding. Complications are rare[143,301-305] and no mortality has been reported. This technique is particularly useful for the inferior pulmonary ligament and the esophageal, subcarinal, and APW nodes (stations 9, 8, 7, 4L, 5). Nodes that are anterolateral to the trachea (stations 2R, 2L, 4R) are difficult to sample reliably (but are commonly involved in lung cancer). This procedure requires a skilled endoscopist with specific experience and the necessary equipment.

Overall, 2,433 patients with evaluable lung cancer were included in this analysis (Fig 14).[143,179,296,301,305-325] For the detection of malignant mediastinal (N2 or N3) lymph nodes, the median sensitivity and specificity were 89% and 100%, respectively. The median NPV was 86%.

The patients included in these studies were patients with NSCLC without evidence of distant metastases. Most of the patients had enlarged lymph nodes, which is further corroborated by an overall prevalence of

Figure 14. [Section 4.3.2.3] Endoscopic ultrasound-guided needle aspiration of the mediastinum in patients with lung cancer.

First Author	Year	No.	Stage	Thoro	Prev	Sens	Spec	PPV	NPV
Nadarajan[310]	2010	34	cN2-3	Sel	88	100	(100)[a]	(100)[a]	(100)[b]
Tournoy[312]	2008	100	cN0-3	Sys	83	95	(100)[a]	(100)[a]	(81)[b]
Wallace[143]	2001	121	cN2-3	Sel	79	87	(100)[a]	(100)[a]	68
Annema[323]	2004	36	cN2-3	Sys	78	93	(100)[a]	(100)[a]	80
Wiersema[305]	2001	29	cN2-3	Sel	76	100	(100)[a]	(100)[a]	100
Fritscher-Ravens[301]	2000	35	cN2-3	Lim	74	96	(100)[a]	(100)[a]	90
Annema[316]	2005	215	cN0-3	Sys	71	91	(100)[a]	(100)[a]	74
Larsen[324]	2002	29	cN2-3	Lim	69	90	(100)[a]	(100)[a]	82
Annema[306]	2010	551	cN2-3	Sys	66	83	(100)[a]	(100)[a]	75
Caddy[320]	2005	36	cN0-3	Sel	65	92	(100)[a]	(100)[a]	83
Kalade[311]	2008	33	cN1-3	Sel	64	95	(100)[a]	(100)[a]	92
Silvestri[304]	1996	26	cN0-3	Sys	62	89	(100)[a]	(100)[a]	82
Gress[302]	1998	24	cN2-3	Sel	58	93	(100)[a]	(100)[a]	90
Herth[307]	2010	139	cN1-3	Sel	52	89	(100)[a]	(100)[a]	82
Talebian[309]	2010	152	cN2-3	Sys	49	74	(100)[a]	(100)[a]	73
Sawhney[313]	2006	65	cN2-3	Sys	48	87	(100)[a]	(100)[a]	90
Fritscher-Ravens[179]	2003	33	cN0-3	Sys	48	88	(100)[a]	(100)[a]	89
Larsen[324]	2005	58	cN0-3	Sys	47	87	(100)[a]	(100)[a]	87
Eloubeidi[315]	2005	104	cN2-3	Sys	41	93	(100)[a]	(100)[a]	96
Eloubeidi[318]	2005	35	cN2-3	Sys	37	91	(100)[a]	(100)[a]	97
Annema[317]	2005	100	cN2-3	Sys	36	71	90	86	85
Wallace[322]	2004	69	cN0	Sys	36	61	(100)[a]	(100)[a]	82
LeBlanc[321]	2005	67	cN0	Sel	33	45	(100)[a]	(100)[a]	79
Wallace[296]	2008	138	cN2-3	Sys	30	69	(100)[a]	(100)[a]	88
Szlubowski[308]	2010	120	cN0	Sel	22	50	99	93	87
Fernandez-Esparrach[314]	2006	47	cN0	Sys	21	50	(100)[a]	(100)[a]	88
Median: prevalence > 80		% sys	50%			**96**			**90**
Median: prevalence 60-79		% sys	40%			**92**			**82**
Median: prevalence 40-59		% sys	71%			**88**			**88**
Median: prevalence 20-39		% sys	71%			**61**			**87**
Median: cN1-3		% sys	47%			**92**			**89**
Median: cN0-1		% sys	50%			**50**			**85**
Summary: median		**2,443**			**58**	**89**	**(100)[a]**	**(100)[a]**	**86**

Inclusion criteria: studies reporting test characteristics of EUS-NA for staging of lung cancer, involving ≥ 20 patients from 1980 to 2011. EUS-NA = endoscopic ultrasound and needle aspiration; Lim = limited. See Figures 6 and 9 for expansion of other abbreviations.

[a]Technically, the specificity and PPV cannot be assessed in those studies reporting 100% values because a positive result was not followed up with an additional gold standard test.

[b]Because NPV is increasingly affected by prevalence and prevalence was > 80% these values are excluded from summary calculations.

disease of about 60%. 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 primarily in radiographic group B, with only some in C and probably fewer in A. However, it is clear that nodes that are < 1 cm can be sampled using this technique.[301,325]

EUS-NA 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 was 4% (37 of 834 patients) for such M1 disease detected by EUS-NA.[301,305,315-317,319,321,322] Actual performance characteristics for the detection of M1 disease by EUS-NA cannot be calculated because patients generally do not undergo exploration of the abdomen.

EUS is also capable of evaluating the presence of direct tumor invasion into the mediastinum (T4). Several groups[301,315-317,319,321,325,326] have evaluated the prevalence of T4 disease, but only one[326] has specifically evaluated the reliability of EUS for T staging. The FP rate in that study was 30%, making this technique unreliable for assessing mediastinal invasion.

The cost of EUS is lower than that of surgical staging procedures, probably because of the ability to perform EUS without general anesthesia in an ambulatory setting. Two studies have suggested that EUS may be more cost effective than mediastinoscopy, although these studies assumed that mediastinoscopy frequently required inpatient admission.[326,327]

4.3.2.4 Endobronchial Ultrasound With NA—Since the last iteration of this guideline, endobronchial ultrasound with NA has been used increasingly to stage lung cancer, as evidenced by the marked

increase in publications on the subject. This has been accompanied by a better understanding of the indications and performance characteristics of this procedure. Overall, 2,756 patients met the inclusion criteria for mediastinal staging with EBUS-NA (Fig 15).[210,296,307,308,329-350] The overall median sensitivity was 89%, with values ranging from 46% to 97%. The median NPV was 91%.

For the most part, studies using EBUS have involved patients with discrete lymph node enlargement (radiographic group B and some group A and C), consistent with a disease prevalence of approximately 58%. Initial studies focused on patients with fairly sizable lymph nodes who were clinically likely nonoperable. However, some studies reporting the performance characteristics of EBUS in patients who were potentially operable have been published. Two studies focused on patients with a radiographically normal mediastinum by either CT scan or CT and PET scans and discovered unsuspected mediastinal metastases.[210,351]

Most of the studies evaluating EBUS have used a systematic approach, evaluating representative nodes from each node station. Comparing results from studies using a systematic approach with those using a more selective approach shows only small differences. However, most of the patients evaluated had suspected N2,3 disease, and the level of thoroughness (systematic vs selective) may be less important in this group. The impact of a complete assessment or a limited assessment cannot be assessed at this point because sufficient data are not available.

FIGURE 15. [Section 4.3.2.4] Real-time endobronchial ultrasound-guided transbronchial needle aspiration of the mediastinum in patients with lung cancer.

Study	Year	No.	Stage	Thoro	Prev	Sens	Spec[a]	PPV[a]	NPV
Fielding[341]	2009	68	cN1-3	Sel	87	95	(100)[a]	(100)[a]	(67)[b]
Steinfort[334]	2011	117	cN1-3	Sys	80	97	(100)[a]	(100)[a]	87
Cetinkaya[332]	2011	52	cN2-3	Sys	80	95	(100)[a]	(100)[a]	83
Rintoul[344]	2009	109	cN1-3	Sys	77	91	(100)[a]	(100)[a]	60
Gilbert[339]	2009	67	cN1-3	Sel	70	93	(100)[a]	(100)[a]	83
Yasufuku[349]	2005	108	cN1-3	Sys	69	95	(100)[a]	(100)[a]	90
Yasafuku[350]	2004	70	cN1-3	Sys	67	96	(100)[a]	(100)[a]	92
Szlubowski[343]	2009	226	cN0-3	Sys	64	89	(100)[a]	(100)[a]	84
Ye[333]	2011	101	cN1-3	Sel	63	95	(100)[a]	(100)[a]	93
Cerfolio[336]	2010	92	cN2	Sys	63	57	(100)[a]	(100)[a]	79
Lee BE[329]	2012	73	cN0-3	Sys	62	95	(100)[a]	(100)[a]	94
Bauwens[345]	2008	106	cN1-3	Sys	58	95	(100)[a]	(100)[a]	91
Sun[337]	2010	49	cN1-3	Sys	53	85	96	96	85
Herth[307]	2010	139	cN1-3	Sel	52	91	(100)[a]	(100)[a]	92
Memoli[331]	2011	100	cN1-3	Sys	47	87	(100)[a]	(100)[a]	89
Omark Petersen[340]	2009	151	cN2-3	Lim	43	85	(100)[a]	(100)[a]	89
Yasufuku[330]	2011	153	cN0-3	Sys	35	81	(100)[a]	(100)[a]	91
Hwangbo[335]	2010	150	cN2-3	Sys	31	84	(100)[a]	(100)[a]	93
Wallace[296]	2008	138	cN2-3	Sys	30	69	(100)[a]	(100)[a]	88
Lee HS[346]	2008	102	cN2-3	Sys	30	94	(100)[a]	(100)[a]	97
Hwangbo[342]	2009	117	cN2-3	Sys	26	90	(100)[a]	(100)[a]	97
Yasufuku[348]	2006	102	cN1-3	Sys	25	92	(100)[a]	(100)[a]	97
Szlubowski[343]	2010	120	cN0	Sel	22	46	99	93	86
Herth[211]	2006	100	cN0	Sys	21	92	(100)[a]	(100)[a]	96
Nakajima[338]	2010	49	cN1-3	Sys	18	67	(100)[a]	(100)[a,c]	93
Herth[210]	2008	97	cN0	Sys	10	89	(100)[a]	(100)[a,c]	99
Median: Prevalence ≥ 80						96			83
Median: Prevalence 60-79						91			83
Median: Prevalence 40-59						87			89
Median: Prevalence 20-39						87			95
Median: Prevalence < 20						78			96
Median: cN1-3						91			89
Median: cN0						89			96
Summary: median		2,756			58	89	(100)[a]	(100)[a]	91

Inclusion criteria: studies reporting test characteristics of EBUS-TBNA for staging of lung cancer, involving ≥ 20 patients from 1980 to 2011. EBUS-TBNA = endobronchial ultrasound and transbronchial needle aspiration. See Figures 6 and 9 for expansion of other abbreviations.
[a]Technically, the specificity and PPV cannot be assessed in those studies reporting 100% values because a positive result was not followed up with an additional gold standard test.
[b]Because NPV is increasingly affected by prevalence and prevalence was > 80% these values are excluded from summary calculations.
[c]Because PPV is increasingly affected by prevalence as prevalence is < 20% these values are excluded from summary calculations.

4.3.2.5 Combined EUS/EBUS—Emerging data suggest that the combination of EUS-NA and EBUS-NA may allow complementary and near-complete access to all mediastinal lymph node stations. Seven studies with 811 patients used this combined approach and met the inclusion criteria for this analysis. The pooled median sensitivity and specificity were 91% and 100%, respectively, with a prevalence of cancer of 33% in this population (Fig 16).[228,296,307,308,335,352,353] The median NPV was 96%. The ability to perform both procedures in a single session is appealing, although there are many unresolved issues regarding training and the availability of combined endoscopic and bronchoscopic expertise.

4.3.2.6 Comparative Effectiveness Trials—Most of the published literature for staging of the mediastinum in patients with lung cancer has been single-institution studies that compare one technology for staging lung cancer (eg, EBUS) with the historic gold standard (ie, surgical lymphadenectomy) to assess the performance characteristics of the technology in question. What has been lacking is a direct comparison of staging technologies in similar patients to help inform physicians about which technology may be most useful in a given clinical situation. Two studies provide insight into how these techniques compare with one another. Wallace et al[296] compared TBNA, EBUS-NA, EUS-NA, and combined EBUS/EUS NA in the same patient. The procedures were performed consecutively, and pathologists were blinded to the source of the specimen. The sensitivities were 93%, 69%, 69%, and 35% for the combined procedure (EBUS/EUS), EBUS alone, EUS alone, and TBNA, respectively. Even among bronchoscopy-favorable locations such as the subcarinal nodes, TBNA performed poorly (sensitivity, 47%) in comparison with the ultrasound-guided approaches.

A multicenter RCT of 241 patients compared surgical staging alone with combined EBUS/EUS (endosonography) followed by surgical staging if the needle approach was negative.[228] The sensitivities of surgery, endosonography, and endosonography followed by surgery if the needle technique was negative were 79%, 85% and 94%, respectively. Parenthetically, the sensitivities of each technique individually are nearly identical to the pooled estimates published in this guideline. This study involved a systematic level of thoroughness for both the endosonography and mediastinoscopy and complete dissection (level A) for intraoperative staging. The rate of noncurative resection was 18% in the mediastinoscopy arm compared with 7% in the endosonography arm ($P < .02$). The complication rate was similar in both groups (6% vs 7%); however, 12 of the 13 complications were in patients who underwent surgical staging. The conclusion of this study was that patients should start with endosonography and if it is negative, move to surgical staging of the mediastinum. Nearly two-thirds of the patients in this study had discrete N2,3 node enlargement, with most of the rest having central (hilar) tumors of c N1 involvement.

4.4 Approach to the Patient

In patients with lung cancer and no distant metastases, accurate assessment of the status of mediastinal nodes is critical in choosing the best treatment strategy. Many different tests and procedures are available as discussed in the previous sections, making it seem difficult to choose which approach is best.

In choosing an invasive staging test, several issues must be considered. First of all is the availability of different procedures. All invasive tests require some specialized experience and skill, and physicians who

FIGURE 16. [Section 4.3.2.5] Real-time EBUS-TBNA and EUS-NA of the mediastinum in patients with lung cancer.

First Author	Year	No.	Stage	Thoro	Prev	Sens	Spec[a]	PPV[a]	NPV
Vilmann[353]	2005	31	cN0-3	sys	65	100	(100)[a]	(100)[a]	100
Annema[228]	2010	123	cN1-3	sys	54	82	(100)[a]	(100)[a]	80
Herth[307]	2010	139	cN1-3	sel	52	96	(100)[a]	(100)[a]	96
Ohnishi[352]	2011	110	cN0-3	sys	35	72	(100)[a]	(100)[a]	87
Hwangbo[335]	2010	150	cN2-3	sys	31	91	(100)[a]	(100)[a]	96
Wallace[296]	2008	138	cN2-3	sys	30	93	(100)[a]	(100)[a]	97
Szlubowski[308]	2010	120	cN0	sel	22	68	98	91	91
Median: prevalence 40-65						**96**			**96**
Median: prevalence 20-39						**82**			**94**
Summary: median		**811**			**33**	**91**	**(100)[a]**	**(100)[a]**	**96**

Inclusion criteria: studies reporting test characteristics of combined EBUS-TBNA/EUS-NA for staging of lung cancer, involving ≥ 20 patients from 1980 to 2011. See Figures 6 and 9 for expansion of abbreviations.
[a]Technically, the specificity and PPV cannot be assessed in those studies reporting 100% values because a positive result was not followed up with an additional gold standard test.

perform these procedures infrequently may not be able to achieve the diagnostic accuracy reported by high-volume institutions. This is equally true of both the surgical staging techniques and the needle techniques. Second, the location of the suspicious nodes is important, because nodes in one location may be accessible only by a particular approach (eg, stations 5 and 6 cannot be accessed by the needle techniques, and either a VATS approach or a left anterior mediastinotomy are required to reach those areas) There may be factors related to patient comorbidity that argue against certain approaches, such as mediastinoscopy, which usually requires general anesthesia. The morbidity and mortality of invasive procedures may be a consideration, although complications appear to be infrequent. Finally, cost may be a consideration.

A key factor in applying the data and recommendations presented here is how a procedure to evaluate stage is performed. A classification of levels of thoroughness has been developed and provides a guide.[354] Level A involves complete sampling of each node in each major mediastinal node station (2R, 4R, 2L, 4L, 7, and possibly 5 or 6), level B involves a systematic sampling of each node station, level C involves a selective sampling of suspicious nodes only, and level D involves very limited or no sampling, with only visual assessment. Which level of thoroughness is necessary for different situations has not been well established, but it is important to recognize that much of the literature involves a level B assessment; centers performing a level C or D assessment may not experience the same results.

The sensitivity of various invasive mediastinal staging tests in patients with cN2,3 disease appears to be similar. A strict comparison is not justified, because the patients undergoing these procedures are not comparable because of differences in how they are selected for a particular procedure (eg, the location of the nodes). Furthermore, the sensitivity and the NPV may depend on the experience of those performing the procedure and on the level of thoroughness with which it is performed.

4.4.1 Mediastinal Infiltration: In patients with extensive mediastinal infiltration, the radiographic evidence of mediastinal involvement is almost universally considered adequate (Fig 17).[225,229,252,355,356] There are no data to prove this, because invasive confirmation is not carried out. However, even though staging is not an issue, tissue is needed to confirm the diagnosis and to define the histologic and molecular genetic characteristics of the tumor. In this case, it does not matter whether the tissue is obtained from the primary tumor or from a mediastinal site.

In patients in whom diagnosis is the primary issue, tissue should be obtained by whichever method is

FIGURE 17. [Section 4.4.1, 4.4.3, 4.4.5, 4.4.7] False-positive and false-negative rates for CT scan and PET scan assessment of mediastinal nodes by the American College of Chest Physicians intrathoracic radiographic (CT scan) classification categories. References by radiographic category: A, Estimated. B, CT scan[252] and PET scan.[25,123,164,355] C, CT scan[252] and PET scan.[24-26,123] D, CT scan[252] and PET scan.[24-26,225,229,356] % FN = % of negative test results that are false negative (100 − negative predictive value %); % FP = % of positive test results that are false positive (100 − positive predictive value %); NA = not applicable; ?* = estimated; no actual data available for A.

Confirmation of Intrathoracic Stage
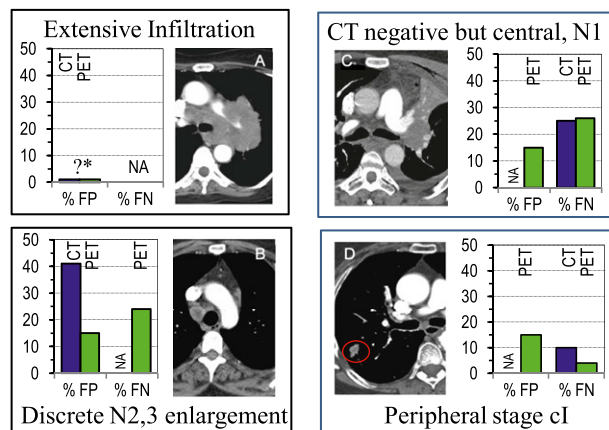
easiest. In other words, the choice of procedure will be governed primarily by patient-specific (anatomic, convenience, and comorbidity) factors, instead of the performance characteristics of a test. Although sputum cytology was adequate in the past, in an era in which molecular diagnostics are being performed more routinely to help guide treatment decisions, it is likely that more specimens will be needed to adequately perform diagnostic analysis.

4.4.2 Recommendation

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

4.4.3 Discrete Mediastinal Node Enlargement: Many patients present with a CT scan demonstrating enlargement of discrete mediastinal (N2,3) lymph nodes. In such patients, the risks of FP test results from either CT scanning and/or PET scanning are too high to rely on imaging alone to determine the mediastinal stage of the patient, and tissue confirmation is necessary (Fig 17).

The sensitivity of various invasive mediastinal staging tests in patients with cN2,3 disease appears to be similar. A strict comparison is not justified, because the patients undergoing these procedures are not comparable because of differences in how they are

selected for a particular procedure (eg, the location of the nodes). Needle-based mediastinal staging is the best approach; the invasive staging procedure has a high chance of being positive and the needle-based techniques have lower morbidity than surgical staging. Furthermore, the RCT of mediastinoscopy alone vs combined EBUS/EUS with surgical staging if the needle approach was negative demonstrated advantages to the needle-first approach.[228]

An option for the treatment of patients with stage IIIA NSCLC and discrete mediastinal node involvement is induction therapy followed by surgery (see Ramnath et al,[362] "Treatment of Stage III Non-small Cell Lung Cancer," in the ACCP Lung Cancer Guidelines). If this approach is chosen, the role of mediastinal restaging after induction therapy is unclear. However, some people argue 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 that CT scan evidence of tumor shrinkage is notoriously misleading.[169,170] PET scanning for mediastinal restaging has also been shown to have high FP and FN rates.[169,1703] A repeat mediastinoscopy is generally safe and feasible (82% to 100% of the time), but sensitivity is limited to about 70% to 82%,[249,358-360] 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 the induction therapy. All of this applies only 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).

4.4.4 Recommendations

4.4.4.1. In patients with discrete mediastinal lymph node enlargement (and no distant metastases) with or without PET uptake in mediastinal nodes, invasive staging of the mediastinum is recommended over staging by imaging alone (Grade 1C)**.**

4.4.4.2. In patients with PET activity in a mediastinal lymph node and normal appearing nodes by CT (and no distant metastases), invasive staging of the mediastinum is recommended over staging by imaging alone (Grade 1C)**.**

4.4.4.3. In patients with high suspicion of N2,3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no distant metastases), a needle technique (EBUS-NA,

EUS-NA or combined EBUS/EUS-NA) is recommended over surgical staging as a best first test (Grade 1B)**.**

Remark: This recommendation is based on the availability of these technologies (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) and the appropriate experience and skill of the operator.

Remark: In cases where the clinical suspicion of mediastinal node involvement remains high after a negative result using a needle technique, surgical staging (eg, mediastinoscopy, VATS, etc) should be performed.

Remark: The reliability of mediastinal staging may be more dependent on the thoroughness with which the procedure is performed than by which test is used.

4.4.5 Central and Clinical N1 Nodes: 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 CT scanning with respect to the mediastinal nodes in these individuals is 20% to 25%.[255] More limited data demonstrate that the FN rate for PET scanning in the mediastinal nodes in this situation is similarly high (about 25%) (Fig 17).[24-26,123] Thus, invasive staging is required in these patients despite the negative CT scan and even a negative PET scan.

In general, a needle technique, with mediastinoscopy reserved for patients with a negative needle results, appears to be a good first choice, if performance of such an approach with a thorough technique is available. This is based on the results of a multicenter RCT,[231] although patients with central or cN1 involvement were not analyzed separately. How thoroughly a needle technique is performed (as well as the availability and thoroughness of mediastinoscopy) also likely has a bearing on the importance of following up on a negative needle result with mediastinoscopy.

4.4.6 Recommendations

4.4.6.1. In patients with an intermediate suspicion of N2,3 involvement, ie, a radiographically normal mediastinum (by CT and PET) and a central tumor or N1 lymph node enlargement (and no distant metastases), invasive staging of the mediastinum is recommended over staging by imaging alone (Grade 1C)**.**

4.4.6.2. In patients with an intermediate suspicion of N2,3 involvement, ie, a radiographically normal mediastinum (by CT and PET) and a central tumor or N1 lymph node enlargement (and no distant metastases), a needle technique (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) is suggested over surgical staging as a best first test (Grade 2B)**.**

Remark: This recommendation is based on the availability of these technologies (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) and the appropriate experience and skill of the operator.

Remark: In cases where the clinical suspicion of mediastinal node involvement remains high after a negative result using a needle technique, surgical staging (eg, mediastinoscopy, VATS, etc) should be performed.

Remark: The reliability of mediastinal staging may be more dependent on the thoroughness with which the procedure is performed than by which test is used.

4.4.7 Peripheral Stage I Tumors: For patients with peripheral tumors in whom there is no enlargement of N1-N3 nodes by CT scan, the FN rate of this radiographic assessment in the mediastinum is approximately 10%.[255] The incidence is lower in patients with T1 tumors (9%) than in those with T2 tumors (13%).[255] Whether this is viewed as high enough to justify invasive staging is a matter of judgment. A negative PET scan in the mediastinum carries an FN rate of approximately 4% (3%-6%) in this group of patients (Fig 3).[24-26,232] Thus, invasive staging is probably not needed in this patient group, especially if a PET scan is negative in the mediastinum.

4.4.8 Recommendation

4.4.8.1. For patients with a peripheral clinical stage IA tumor (negative nodal involvement by CT and PET), it is suggested that invasive preoperative evaluation of the mediastinal nodes is not required (Grade 2B)**.**

4.4.9 Patients With LUL Tumors: Patients with tumors in the LUL deserve special mention because the aortic arch raises the technical issue 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 a 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 (stations 4L, 4R, 2L and 2R) areas. 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 raise questions about whether a separate invasive test for assessment of these nodes is really necessary (see section on involvement of APW nodes).

The definition of radiographic 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 those for patients with a tumor in a different lobe (patients with either 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 (2R, 4R, 7, 2L, and 4L) are found to be negative, whether a separate procedure to assess the station 5 area is needed is controversial. 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 to assess the APW area, the guidelines committee favors pursuing an invasive assessment of the APW nodes (using VATS, Chamberlain, or extended cervical mediastinoscopy). A finding of involvement in one mediastinal area may preclude the necessity of biopsy of other areas, especially if an additional procedure should be necessary.

Modification of these suggestions may be necessary because of the availability of expertise with the invasive procedures. However, it is suggested that referral to a center with the appropriate volume and expertise be considered if there is not expertise with at least one invasive APW staging procedure at the referring institution.

4.4.10 Recommendation

4.4.10.1. For the patients with a LUL cancer in whom invasive mediastinal staging is indicated as defined by the previous recommendations, it is suggested that invasive assessment of the APW nodes be performed (via Chamberlain, VATS, or extended cervical mediastinoscopy) if other mediastinal node stations are found to be uninvolved (Grade 2B)**.**

5.0 Summary

CT scanning of the chest is useful in providing anatomic detail that better identifies the location of

the tumor and its proximity to local structures and determines whether lymph nodes in the mediastinum are enlarged. Unfortunately, the accuracy of chest CT scans in differentiating benign from malignant lymph nodes in the mediastinum is unacceptably low. PET scanning provides functional information of 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 scans, and noncurative resections can be averted. Still, positive findings on PET scans can occur from nonmalignant causes (eg, infections), so tissue sampling to confirm suspected metastasis is almost always required to ensure that potential surgical candidates are not misclassified as having advanced disease. Confirmation of mediastinal nodal status can be performed using a myriad of invasive tools. Although this guideline recommends the use of minimally invasive guided needle techniques as the test of first choice, the location of the lymph node, patient comorbidities, and local availability of and expertise with the different invasive staging tools will continue to drive which tool is used in which patient. It is far more important to obtain a tissue sample of the mediastinal node or nodes in question than to quibble over which invasive staging tool was used to get there.

The clinical evaluation tool (ie, a thorough history and physical examination) remains the best predictor of distant metastatic disease. PET or PET-CT scanning is used increasingly to stage lung cancer because these tests provide important information about the tumor, the mediastinum, and distant metastatic disease, excluding in the brain. There is evidence that the use of PET scanning decreases the number of noncurative resections and may be cost effective in patients with NSCLC.

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, when it will make a difference in treatment, all abnormal scans require tissue confirmation of malignancy so that patients are not denied the opportunity to have potentially curative treatment.

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