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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S<sup>®</sup>

# Invasive Mediastinal Staging of Lung Cancer\*

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

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**Background:** The treatment of non-small cell lung cancer (NSCLC) is determined by accurate definition of the stage. If there are no distant metastases, the status of the mediastinal lymph nodes is critical. Although imaging studies can provide some guidance, in many situations invasive staging is necessary. Many different complementary techniques are available.

**Methods:** The current guidelines and medical literature that are applicable to this issue were identified by computerized search and were evaluated using standardized methods. Recommendations were framed using the approach described by the Health and Science Policy Committee of the American College of Chest Physicians.

**Results:** Performance characteristics of invasive staging interventions are defined. However, a direct comparison of these results is not warranted because the patients selected for these procedures have been different. It is crucial to define patient groups, and to define the need for an invasive test and selection of the best test based on this.

**Conclusions:** In patients with extensive mediastinal infiltration, invasive staging is not needed. In patients with discrete node enlargement, staging by CT or positron emission tomography (PET) scanning is not sufficiently accurate. The sensitivity of various techniques is similar in this setting, although the false-negative (FN) rate of needle techniques is higher than that for mediastinoscopy. In patients with a stage II or a central tumor, invasive staging of the mediastinal nodes is necessary. Mediastinoscopy is generally preferable because of the higher FN rates of needle techniques in the setting of normal-sized lymph nodes. Patients with a peripheral clinical stage I NSCLC do not usually need invasive confirmation of mediastinal nodes unless a PET scan finding is positive in the nodes. The staging of patients with left upper lobe tumors should include an assessment of the aortopulmonary window lymph nodes. (CHEST 2007; 132:202S–220S)

**Key words:** anterior mediastinotomy; bronchoscopy; Chamberlain procedure; clinical staging; endobronchial ultrasound; esophageal ultrasound; mediastinal lymph nodes; mediastinoscopy; N2; N3; pathologic staging; staging; transbronchial needle aspiration; transthoracic needle aspiration; video-assisted thoracic surgery

**Abbreviations:** APW = aortopulmonary window; EBUS = endobronchial ultrasound; EUS = endoscopic ultrasound; FN = false negative; FP = false positive; LUL = left upper lobe; NA = needle aspiration; NSCLC = non-small cell lung cancer; PET = positron emission tomography; SCLC = small cell lung cancer; TBNA = transbronchial needle aspiration; TTNA = transthoracic needle aspiration; VATS = video-assisted thoracic surgery

This chapter addresses invasive procedures for confirmatory staging of the mediastinum in patients with lung cancer. The focus is on patients in whom there is a strong suspicion of lung cancer. Such a presumptive clinical diagnosis is generally possible by an experienced clinician after an assessment of risk factors, and a review of the clinical presentation and the

radiographic appearance on a CT scan. If the presence of distant metastatic disease has been ruled out, the status of the mediastinum becomes the crucial factor in selecting the optimal treatment strategy. The initial clinical evaluation (*ie*, clinical presentation and CT scan findings) already yields a presumptive clinical stage with respect to the mediastinum, which may have been

**Table 1—Techniques of Invasive Mediastinal Staging**

Mediastinoscopy
EUS-NA
TBNA
EBUS-NA
TTNA
VATS staging
Chamberlain procedure
Extended cervical mediastinoscopy

supplemented by a positron emission tomography (PET) scan as well. However, noninvasive imaging tests can provide only a suspicion that involvement of the mediastinal nodes is present or absent, and in many clinical situations confirmation of the status of these nodes by an invasive test is necessary. The reliability of noninvasive tests is discussed in chapter 12 in this supplement. This chapter discusses the performance characteristics of the various invasive staging tests for the mediastinum, how to select a test, and how to interpret the results.

Several invasive tests are available to stage the mediastinum (Table 1). These include mediastinoscopy, the Chamberlain procedure (also known as an *anterior mediastinotomy*), transthoracic needle aspiration (TTNA) of the mediastinum, transbronchial needle aspiration (TBNA), endobronchial ultrasound (EBUS) with needle aspiration (NA), esophageal endoscopic ultrasound (EUS) with NA, and video-assisted thoracic surgery (VATS), which is also known as *thoracoscopy*. Invasive tests are also sometimes needed to confirm or exclude distant metastases, but these are not discussed in this chapter.

The invasive procedures listed in Table 1 are often needed to more accurately confirm the presumptive mediastinal stage, but they are also sometimes used simply to confirm the diagnosis of malignancy. This distinction is important because these are two en-

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tirely different situations, involving patients with very different tumor characteristics, with different test parameters that are of great importance, and therefore with differences in which test should be selected. For example, an invasive test in a patient with massive mediastinal infiltration by a malignancy is performed primarily for the purpose of diagnosis. In this case, the test to confirm the diagnosis is usually selected based on what can be accomplished more easily (both technically and for the patient), and the choice is driven primarily by patient-specific issues rather than the test-specific performance characteristics. On the other hand, in many patients invasive tests are needed to confirm the mediastinal stage. In this case, the choice of procedure is governed by how reliably the test will define the absence or presence of nodal involvement (*ie*, the test performance characteristics, and specifically the false-negative (FN) and false-positive (FP) rates for results of the test).

Obviously, in many situations an invasive test can provide both confirmation of the diagnosis and confirmation of the stage at the same time. This fact underlies the importance of not immediately pursuing a diagnostic test in patients but rather thinking through the presumptive diagnosis, the presumptive stage, and the need for further confirmatory staging tests first.

In general, patients with lung cancer can be separated into four groups (Table 2) with respect to intrathoracic radiographic characteristics (including both the primary tumor and the mediastinum), as was discussed in chapter 12 on noninvasive staging.

**Table 2—Definition of Radiographic Groups With Respect to Intrathoracic Radiographic Characteristics**

Group	Description	Definition
A	Mediastinal infiltration	Tumor mass within the mediastinum such that discrete lymph nodes cannot be distinguished or measured*
B	Enlarged discrete mediastinal nodes	Discrete mediastinal nodes $\geq 1$ cm in short-axis diameter on a transverse CT scan image
C	Clinical stage II or central stage I tumor	Normal mediastinal nodes ( $< 1$ cm) but enlarged N1 nodes ( $\geq 1$ cm) or a central tumor (within proximal one third of the hemithorax)
D	Peripheral clinical stage I tumor	Normal mediastinal and N1 nodes ( $< 1$ cm) and a peripheral tumor (within outer two thirds of hemithorax)

\*This does not include a tumor mass within the lung that is abutting the mediastinum and tangentially involving the mediastinal pleura or fat (this situation pertains to the T stage of the primary tumor and not the N stage of the mediastinum).

Briefly, the groups consist of patients with extensive mediastinal infiltration (radiographic group A), patients with enlargement of discrete mediastinal nodes the size of which can be measured (radiographic group B), patients with normal mediastinal nodes determined by CT scan but with a central tumor or suspected N1 disease (radiographic group C), and patients with normal mediastinal nodes and a peripheral clinical stage I tumor (radiographic group D).

The definition of the four radiographic groups is useful for several reasons. As described in chapter 12, it is helpful in determining the chance of finding distant metastases despite a negative clinical evaluation, as well as the FP and FN rates of the CT and PET scan predictions of mediastinal node involvement. In addition, the separation into radiographic groups helps to guide the choice of an invasive test and the performance characteristics of these tests. The radiographic groups are defined by the anatomic characteristics found on a CT scan for several reasons. First, a CT scan is relatively inexpensive and is essentially always performed as a preliminary step in order to define the nature of a pulmonary abnormality and to arrive at a clinical diagnosis of suspected lung cancer. Second, the technical reasons for choosing one invasive approach over another are governed primarily by anatomic factors (*ie*, the location and size of the nodes) rather than by metabolic factors (*ie*, PET scan uptake).

The interpretation and application of the results of invasive staging procedures are difficult because the published data are defined by patients who have undergone a particular test, rather than by radiographic or clinical criteria that could be used prospectively to select patients for a particular approach. The patients who have undergone a particular procedure are a mix of the different radiographic groups just discussed, and often include patients in whom the primary issue was confirmation of the diagnosis, those in whom it was confirmation of nodal involvement, and those in whom it was confirmation of the lack of nodal involvement. Furthermore, the location of suspected nodal involvement influences which test is performed because some nodal stations are easily accessible by one test and not by another. Therefore, the patient cohorts included in series of particular invasive procedures are likely not the same. This makes a comparison of the sensitivity and specificity of the different tests inappropriate. However, we have attempted to make a loose comparison for patients in particular radiographic subgroups, with recognition that this assessment must be taken with a large grain of salt. In addition, the amount of experience is very likely to affect the performance characteristics of a procedure and must also be taken into

account in choosing an invasive staging procedure in a specific practice setting. At any rate, it is best to view the different invasive staging tests as complementary and not competitive.

The approach taken in this chapter is to summarize the performance characteristics of each invasive test first, with the recognition that the patients included in studies of a particular test are generally poorly defined, and that direct comparisons between tests are inappropriate. This is followed by a somewhat speculative discussion about which types of patients were included and an analysis of the test results for particular subgroups, whenever this is possible. Finally, the last section uses the available data and the nuances of patient subgroups to attempt to define an integrated approach for use in invasive staging tests of the mediastinum.

It must be emphasized that all of the tests discussed in this chapter are used to refine the clinical stage as defined by the American Joint Committee on Cancer. The clinical stage is the stage that is determined using all information available prior to any treatment, and thus is the most useful staging classification in actual practice. The information available may be limited (*ie*, involving only a chest CT scan) or extensive (*ie*, involving invasive procedures). An invasive staging procedure is still considered to be part of clinical staging, even though it may involve a surgical procedure (*ie*, mediastinoscopy) and evaluation by a pathologist. The pathologic stage is applicable only to patients who have undergone surgical resection, including an accurate assessment of potential areas of spread (such as lymph nodes) by the surgeon and the pathologist. In general, the pathologic stage is viewed as the closest approximation to the true stage, but is useful only for postoperative prognostication, and is not applicable during patient evaluation and selection of a treatment strategy.

## MATERIALS AND METHODS

The data presented here are based on a systematic search and evaluation of the published literature from January 1980 through June 2006. Articles published prior to July 2001 were identified according to the criteria laid out in the previous version of the American College of Chest Physicians lung cancer guidelines.<sup>1</sup> Subsequent literature was identified by the authors using the same search strategy and selection criteria (briefly, studies published in the English language, peer-reviewed, nonoverlapping, having at least 20 patients, containing an adequate assessment of the true nodal status, and with the ability to calculate performance characteristics).<sup>1</sup>

The data abstraction was performed for patients suspected of having lung cancer (*eg*, non-small cell lung cancer [NSCLC] and small cell lung cancer [SCLC]). Patients suspected of a diagnosis other than lung cancer were excluded from the study, where possible. A definite diagnosis of any lung cancer in the medias-

tinal tissues was considered to be positive, while other diagnoses (eg, benign disease or lymphoma) were coded as negative for lung cancer. Equivocal test results were considered to be negative. Biopsies that were aborted or yielded insufficient tissue are included as negative findings and are counted as such in the statistics. The reported feasibility of the test is also reported (ie, the proportion of patients undergoing the test in whom an adequate biopsy was able to be obtained) in order to have an assessment of the technical success rate. The calculation of the subtotal or total summary performance characteristics was accomplished by the calculation of an average of the values (eg, of sensitivity and specificity) from each study; in other words, no weighting according to study size was performed. This was chosen for simplicity, and because a comparison of the results using both methods revealed minimal differences (ie, 1 to 2 percentage points).

Various parameters can be used to assess the reliability of a test, including sensitivity, specificity, and FN and FP rates (typically expressed as a percentage). The latter two measures are sometimes expressed in a less intuitive manner as the converse, known as the negative predictive value ( $1 - \text{FN rate}$ ) or the positive predictive value ( $1 - \text{FP rate}$ ). Sensitivity and specificity are derived from patient populations in whom the true disease status is already known, who either all have or do not have the condition in question. These parameters provide data about how often the test results will be positive or negative for these respective populations. Thus, these measures provide information about the test, because the disease status has already been determined in the patients. In theory, these measures can be used to compare different tests, provided the patient populations in which the tests are used are the same. Unfortunately, particularly with regard to invasive staging tests, the patients selected for different tests are not the same, limiting the value of the measures of sensitivity and specificity. Furthermore, the FN and FP rates are of much greater practical use to the clinician, who must interpret the reliability of a test result (positive or negative) in an individual patient. The clinician does not know the true disease status of the patient, only that the patient falls within the group of those with a negative or positive test result. It is important to point out that the FN rate or FP rate of the test cannot be estimated from the sensitivity or specificity, because these are each derived from different formulas. This is a common misconception that frequently creates confusion and inappropriate interpretation of the test results. The only exception to this fact is in the case of "perfect" test performance (ie, a sensitivity of 100% does, in fact, imply an FN rate of 0%, and a specificity of 100% implies an FP rate of 0%).

This chapter focuses on the clinician's viewpoint and therefore places an emphasis on the FN and FP rates. The clinician is caring for individual patients. From this perspective, a test is useful if one is comfortable basing treatment decisions on the result, because it is sufficiently predictive of the true disease status in that patient.

## TECHNIQUES OF INVASIVE MEDIASTINAL STAGING

### *Mediastinoscopy*

Mediastinoscopy is performed in the operating room, usually under general anesthesia, and in most United States centers patients are discharged from the hospital the same day.<sup>2-4</sup> The procedure involves an incision just above the suprasternal notch, insertion of a mediastinoscope alongside the trachea, and

biopsy of the mediastinal nodes. Rates of morbidity and mortality as a result of this procedure are low (2% and 0.08%, respectively).<sup>5</sup> Right and left high and low paratracheal nodes (stations 2R, 2L, 4R, and 4L), pretracheal nodes (stations 1 and 3), and anterior subcarinal nodes (station 7) are accessible via this approach. Node groups that cannot be biopsied with this technique include posterior subcarinal nodes (station 7), inferior mediastinal nodes (stations 8 and 9), aortopulmonary window (APW) nodes (station 5), and anterior mediastinal nodes (station 6). The availability of a videomediastinoscope allows better visualization, more extensive sampling (including posterior station 7), and even performance of a complete lymph node dissection through this approach.<sup>6,7</sup>

The average sensitivity of mediastinoscopy to detect mediastinal node involvement from cancer is approximately 80%, and the average FN rate is approximately 10% (Table 3).<sup>6,8,12,13,15,16,77-88</sup> Several authors<sup>8-13</sup> have shown that approximately half (range, 42 to 57%) of the FN cases were due to nodes that were not accessible by the mediastinoscope. The FN rate at mediastinoscopy is probably also affected by the diligence with which nodes are dissected and sampled at mediastinoscopy. Ideally, five nodal stations (stations 2R, 4R, 7, 4L, and 2L) should routinely be examined, with at least one node sampled from each station unless none are present after actual dissection in the region of a particular node station. Videomediastinoscopy appears to yield some improvement in sensitivity (90%) and FN rates (7%).<sup>6,13,14</sup> The specificity and the FP rates of mediastinoscopy are reported to be 100% and 0%, respectively. Strictly speaking, these values cannot really be assessed because patients with a positive biopsy finding were not subjected to any further procedures (such as thoracotomy) to confirm the results. Nevertheless, it seems reasonable to assume that the FP rate is low. Few studies have reported feasibility, but in general it appears to be quite high.

The patients included in these series have had potentially operable, nonmetastatic lung cancer with very few exceptions. The majority of these patients were in the radiographic groups B, C, and D. Only a few studies have reported on specific subgroups of patients. In patients with peripheral clinical stage I tumors, the sensitivity was found to be approximately 45%, the FN rate 8%, and the prevalence 15%.<sup>15,16</sup> Thus, mediastinoscopy appears to be very good in ruling out mediastinal node involvement in patients with normal-sized nodes (because of the low FN rate). An explanation for the lower sensitivity in this population is not readily apparent, but underscores

**Table 3—Cervical Mediastinoscopy in Lung Cancer Patients\***

Study/Year	Patients, No.	Patient Type	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Hammoud et al <sup>12</sup> /1999	1,369	cI–III	100	85	100	0	8	36	?% SCLC
Coughlin et al <sup>8</sup> /1985	1,259	cI–III		92	100	0	3	29	4% SCLC
Luke et al <sup>77</sup> /1986	1,000	cI–III		85	100	0	9	39	12% SCLC
De Leyn et al <sup>78</sup> /1996	500	cI–III		76	100	0	13	39	NSCLC only
Lardinois <sup>13</sup> /2003	181	cI–III		87	100	0	8	34	VMS
Brion et al <sup>79</sup> /1985	153	cI–III		67	100	0	15	35	5% SCLC
Jolly et al <sup>80</sup> /1991	136	cI–III		92	100	0	9	54	7% SCLC
Ratto et al <sup>81</sup> /1990	123	cI–III		88	100	0	6	33	NSCLC only
Ebner et al <sup>82</sup> /1999	116	cI–III	96	81	100	0	18	50	11% SCLC
Gdeedo et al <sup>83</sup> /1997	100	cI–III		78	100	0	9	32	NSCLC only
Deneffe et al <sup>84</sup> /1983	124	cI–III	100	68	100	0	12	31	NSCLC only
Aaby et al <sup>85</sup> /1995	57	cI–III		84	100	0	11	44	NSCLC only
Subtotal	5,118	cI–III		82	100	0	10	38	
Pagé et al <sup>86</sup> /1987	345	cII–III†		73	100	0	20	48	18% SCLC
Dillemans et al <sup>87</sup> /1994	331	cII,III†		72	100	0	16	41	NSCLC only
Kimura <sup>14</sup> /2003	125	cII–III		85	100	0	8	36	VMS
Ríordáin et al <sup>88</sup> /1991	74	cII–III†		81	100	0	16	50	3% SCLC
Vennisac <sup>6</sup> /2003	154	cIII	100	97	100	0	6	71	VMS
Subtotal	1,029	cII–III		82	100	0	13	49	
Choi et al <sup>15</sup> /2003	291	cI		44	100	0	9	15	NSCLC
Gürses <sup>16</sup> /2002	67	cN0		40	100	0	7	15	
Subtotal	358	cI		42	100	0	8	15	
Total	6,505			78	100	0	11	39	

\*VMS = videomediastinoscopy; ? = not defined.

†Excluded peripheral cI; included central, cII, and cIII.

the need for caution in extrapolating the performance characteristics of a test derived from one patient population to another population.

### EUS-NA

EUS-NA of mediastinal lymph nodes through the wall of the esophagus has been performed with a negligible risk of infection or bleeding. Only one complication (transient fever) has been reported among 6 studies involving 369 patients.<sup>17–22</sup> No mortality has been reported. This technique is particularly useful for inferior pulmonary ligament, esophageal, subcarinal, and APW nodes (stations 9, 8, 7, and 5). Nodes that are anterolateral to the trachea (stations 2R, 2L, 4R, and 4L) are difficult to sample reliably (but are more commonly involved with lung cancer). This procedure requires a skilled endoscopist with specific experience and the necessary equipment, which is becoming more commonly available at many tertiary referral centers.

Sixteen studies<sup>17–24,26–29,31,34,89,90</sup> met the inclusion criteria and assessed the use of EUS-NA in the mediastinal staging of 973 evaluable lung cancer patients (Table 4). There are no data regarding the feasibility of EUS-NA, but it is assumed to be high

for well-selected patients at experienced centers. For the detection of malignant mediastinal (*ie*, N2 or N3) lymph nodes, the overall sensitivity was 84%, and the overall FN rate was 19% (range, 0 to 61%). The overall specificity was 99.5%, and the overall FP rate was 0.4%, but only one study<sup>23</sup> truly allowed the evaluation of these performance characteristics because it is the only study in which a positive result was investigated further. In this study, a surgical excision of lymph nodes that were positive, as determined by EUS-NA, was performed; a specificity of 97% and an FP rate of 7% were found.<sup>23</sup> Interestingly, this is the same as the average FP rate for TBNA in those studies that have assessed this.

The patients included in these studies had NSCLC without evidence of distant metastases. Most of the patients had enlarged lymph nodes, which is further corroborated by an overall prevalence of disease of 61% (exactly what is predicted by a CT scan FP rate of 40%). Furthermore, it must be remembered that patients undergoing EUS were generally selected because they had suspected nodal involvement in locations amenable to EUS-NA. Thus, the population undergoing EUS has been

**Table 4—EUS-NA of the Mediastinum in Lung Cancer Patients\***

Study/Year	Patients, No.	Patient Type	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Annema et al <sup>34</sup> /2005	193	cN0–3†	100	90	100	0	27	79	
Annema et al <sup>29</sup> /2004	36	?		93	100	0	20	78	All PET+
Caddy et al <sup>89</sup> /2005	33	?	100	91	100	0	15	67	
Fritscher-Ravens et al <sup>90</sup> /2003	33	cN0–3†	100	88	100	0	11	48	Excluding bulky nodes
Larsen et al <sup>27</sup> /2005	55	cN0–3†		92	100	0	6	47	
Subtotal	350	cN0–3	100	91	100	0	16	64	
Wallace et al <sup>22</sup> /2001	107	cN2,3‡	100	87	100	0	32	79	7% SCLC
Annema et al <sup>23</sup> /2005	93	cN2,3	100	71	97	7	15	38	
Kramer et al <sup>21</sup> /2004	81	cN2,3‡	100	72	100	0	61	85	
Wiersema et al <sup>20</sup> /2001	33	cN2,3	100	100	88	4	0	76	9% SCLC
Larsen et al <sup>25</sup> /2002	29	cN2,3		90	100	0	18	69	
Silvestri et al <sup>19</sup> /1996	26	cN2,3‡		88	100	0	18	65	19% SCLC
Fritscher-Ravens et al <sup>18</sup> /2000	25	cN2,3		96	§	§	§	§	42% SCLC
Gress et al <sup>17</sup> /1997	24	cN2,3	100	93	100	0	10	63	
Subtotal	418	cN2,3	100	87	98	2	22	68	
Eloubeidi et al <sup>26</sup> /2005	104	cN0,1	100	93	100	0	4	38	Prior negative mediastinoscopy findings
Wallace et al <sup>24</sup> /2004	64	cN0,1	100	61	100	0	18	36	
LeBlanc et al <sup>31</sup> /2005	67	cN0,1	100	45	100	0	21	33	
Subtotal	235	cN0,1	100	66	100	0	14	36	
Total	1,003			84	99.5	0.7	19	61	

\*See Table 3 for abbreviations not used in the text.

†Approximately 60% cN,3.

‡80% cN2,3.

§Not defined because all subjects had mediastinal disease.

||Some patients had enlarged nodes but negative mediastinoscopy findings.

primarily in radiographic group B, only some in group C, and probably fewer in group A. However, it is clear that nodes that are < 1 cm can be sampled using this technique.<sup>18,22</sup>

Some studies<sup>17,19–22,24–30</sup> have reported on more specific groups of patients. Among patients with enlarged lymph nodes seen on CT scan, the sensitivity is 87% and the FN rate is 22% (specificity, 98%; FP rate, 2%). In these studies, the prevalence of N2,3 involvement was 68%. Among patients with normal-sized lymph nodes seen on CT scans, the sensitivity is 66% and the FN rate is 14% (specificity, 100%; FP rate, 0%).<sup>24,31</sup> In these studies, the prevalence of N2 or N3 disease was 36%, which is higher than the expected rate (20 to 25%) based on the CT scan data for normal-sized mediastinal nodes, even for patients with central tumors or cN1 involvement.<sup>32</sup> Thus, it can be surmised that many of these patients were selected based on PET scan positivity. Nevertheless, it is reasonable to assume that the performance characteristics of EUS-NA apply broadly to patients with cN0,1 tumors, because the technical issues are probably governed by the size of the nodes and should be relatively unaffected by PET scan results.

Emerging data suggest that the combination of EUS-NA and EBUS-NA may allow complementary and nearly complete access to all mediastinal lymph node stations. One study found a sensitivity of 97% and an FN rate of 2% for combined EUS and EBUS in a population with a prevalence of mediastinal metastases of 42%.<sup>33</sup> The ability to perform both procedures in a single session is appealing, although there are many unresolved issues regarding the training and availability of personnel with combined endoscopic and bronchoscopic expertise.

EUS-FNA is also capable of detecting metastatic disease to subdiaphragmatic sites such as the left adrenal gland, celiac lymph nodes, and the liver. The overall yield is 4% (37 of 834 patients) for such M1 disease detected by EUS-NA.<sup>18,20,23,24,26,27,31,34</sup> The 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). Eight studies<sup>18,23,24,26,27,31,34,35</sup> have evaluated the prevalence of T4 disease, but only one study<sup>35</sup> has

specifically evaluated the reliability of EUS for T staging. This study found a sensitivity of 88%, a specificity of 98%, an FN rate of 1%, and an FP rate of 30%. Overstaging appeared to occur when a tumor was seen only to invade the mediastinal soft tissues. The FP rate was 0% if a tumor was seen within a blood vessel or the esophagus. Thus, although EUS can be helpful in determining the T stage, the high FP rate, in general, limits the basing of treatment decisions on this test.

The cost of EUS is less than surgical staging procedures, probably due to the ability to perform EUS without general anesthesia in an ambulatory setting. Two studies<sup>36,37</sup> have suggested that EUS may be more cost-effective compared to mediastinoscopy, although these studies assumed that mediastinoscopy frequently required inpatient hospital admission.

### TBNA

TBNA, also known as a Wang NA, can be performed safely with no significant morbidity. It can be

performed on an outpatient basis, as is the case with most bronchoscopic procedures. TBNA is used most frequently to assess subcarinal nodes. Paratracheal lymph nodes may also be biopsied with TBNA, but these are sometimes more difficult to access, due to the difficulty in sufficiently angulating the bronchoscope and the needle. It has been reported<sup>38–41</sup> that it is feasible to obtain adequate specimens via TBNA in approximately 80 to 90% of cases.

Seventeen studies<sup>38–42,44,91–101</sup> met the inclusion criteria for mediastinal staging with TBNA (Table 5). The overall sensitivity was 78% with values ranging from 14 to 100%. The average FN rate was approximately 28% (range, 0 to 66%). The reported specificity and FP rates were 100% and 0%, respectively, although few studies confirmed positive TBNA results with further invasive procedures. Occasional FP results have been reported in series<sup>42–44</sup> in which this has been specifically examined with a confirmatory test (average, 7%).

The patients included in studies of TBNA have

**Table 5—TBNA of the Mediastinum in Lung Cancer Patients\***

Study/Year	Patients, No.	Patient Type	Technique	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Harrow et al <sup>91</sup> /2000	264	cN1–3	Flex TBNA (various ga)	100	93	100	0	16	72	22% SCLC
Bilaceroglu et al <sup>35</sup> /1998	134	cN1–3	Rigid/flex TBNA (18 and 21 ga)	100	75	100	0	64	88	18% SCLC
Hermens et al <sup>92</sup> /2003	106	cN1–3	Flex TBNA (19 ga)	100	98	100	0	7	60	26% SCLC
Rong and Cui <sup>93</sup> /1998	44	cN1–3	CT-guided flex TBNA (? ga)	100	100	100	0	0	66	10% SCLC
Patelli et al <sup>94</sup> /2002†	183	cN2,3	Flex TBNA (19 and 22 ga)	100	98	100	0	17	67	0% SCLC
Schenk et al <sup>44</sup> /1986	88	cN2,3	Flex TBNA (22 ga)	100	50	96	11	25	39	17% SCLC
Vansteenkiste et al <sup>39</sup> /1994	80	cN2	Transcarin rigid TBNA (17 ga)	100	79	100	0	45	79	18% SCLC
Katis et al <sup>95</sup> /1998	76	cN2,3	Flex TBNA (20 and 21 ga)	100	74	100	0	(90)‡	95	50% SCLC
Schenk et al <sup>111</sup> /1993	64	cN2,3	Flex TBNA (19 vs 22 ga)	100	91	100	0	18	86	27% SCLC
Utz et al <sup>96</sup> /1993§	61	cN2	Transcarin flex TBNA (cyto vs histo needle)	100	56	100	0	(100)‡	100	33% SCLC
Rodríguez de Castro et al <sup>40</sup> /1995	56	cN2,3	Flex TBNA (22 ga)	100	77	100	0	19	70	23% SCLC
Ratto et al <sup>42</sup> /1988	47	cN2	Transcarin flex TBNA (21 ga)	100	14	100	0	27	30	8% SCLC
Wang et al <sup>97</sup> /1983	39	cN2,3	Flex TBNA	100	76	100	0	29	86	21% SCLC
Schenk et al <sup>96</sup> /1989	29	cN2,3	Flexible TBNA (18 ga)	100	80	100	0	66	86	28% SCLC
Selcuk and Firat <sup>99</sup> /2003	27	cN2,3	Flex TBNA (22 ga)	100	100	100	0	(0)‡	100	56% SCLC
Garpestad et al <sup>41</sup> /2001	21	cN2,3	CT scan fluoro-guided flex TBNA (22 and 19 ga)	86	83	100	0	33	57	17% SCLC
Wilsher and Gurley <sup>100</sup> /1996	20	cN2,3	Rigid TBNA (? ga)	100	90	100	0	(100)‡	100	15% SCLC
Summary	1,339				78	99	1	28	75	

\*cyto = cytology; flex = flexible; fluoro = fluoroscopy; ga = gauge; histo = histology; transcarin = transcarinal; transtrach = transtracheal. See Table 3 for abbreviation not used in the text.

†Analyzed by the number of TBNA biopsies performed rather than the number of patients.

‡Excluded from calculations because NPV is relatively less reliable with a prevalence of > 90%.

§Patients with negative TBNA findings and lack of surgical confirmation were excluded from analysis.



generally had a very high prevalence of N2,3 involvement, and the general implication is that the mediastinal nodes have been markedly enlarged, although the specifics about node size are generally vague. The results should not be applied to patients without extensive mediastinal involvement. Furthermore, the high FN rate makes this test less useful for staging of the mediastinum in patients with normal-sized nodes. Positive TBNA results fairly reliably demonstrate mediastinal node involvement. Negative TBNA results, however, cannot sufficiently exclude mediastinal nodal involvement, and additional staging procedures should be performed.

### EBUS-NA

EBUS-NA is a relatively new technique for mediastinal staging. Initially, EBUS was accomplished by introducing a catheter with an ultrasound transducer at the tip of the catheter through the working channel of the bronchoscope. The lymph node was localized with the probe, and the catheter was then withdrawn. The lymph node would then be sampled with TBNA without real-time guidance. More recently, a bronchoscope with a convex ultrasound probe has been developed that allows for real-time ultrasound-guided TBNA.<sup>45</sup> EBUS-NA can be used to sample the highest mediastinal, upper and lower paratracheal, and subcarinal lymph nodes, as well as hilar lymph nodes.

Eight studies<sup>46,47,101–105,112</sup> met the inclusion criteria for mediastinal staging with EBUS-NA (see Table 6). The overall sensitivity was 90%, with values ranging from 79 to 95%. The average FN rate in general was 24% (range, 1 to 37%). One study<sup>46</sup> with an extremely high FN rate (89%) was excluded from this calculation. This FN rate is explained by an extremely high disease prevalence

(98%), because extremely high (or low) prevalence makes the FN rate (or FP rate) unreliable purely on mathematical grounds.<sup>32</sup> The specificity and FP rates were 100% and 0%, respectively, but these values are artificial because positive EBUS-NA results were not confirmed.

The studies using EBUS have for the most part involved patients with discrete lymph node enlargement (patients in radiographic group B and some in groups A and C), which is consistent with a disease prevalence of approximately 70%. Although including many patients with lymph nodes < 2 cm, studies to date have not published performance characteristics of EBUS-NA in lymph nodes 1 to 2 cm in size vs lymph nodes > 2 cm in size. One multiinstitutional study<sup>47</sup> has specifically focused on patients with lymph nodes between 0.5 and 1 cm. This study demonstrated an extremely low FN rate of 1%. This supports a general sense that real-time imaging of nodes with EBUS and the immediate proximity of nodes to the airway holds a great deal of promise for this staging method, even in small nodes. However, at this point the experience with this technique is limited to only a few centers, and whether such excellent results in normal-sized nodes can be corroborated in other studies is not known. It is counterintuitive that the FN rate would be so low in normal-sized nodes if it has generally been found to be around 25% with this technique in studies that have primarily included patients with enlarged nodes. Until this is better defined, it is suggested that negative EBUS-NA biopsy results in most centers be confirmed by additional staging modalities.

### TTNA

TTNA or biopsy for the diagnosis and staging of the mediastinum is distinct from TTNA of parenchyma

**Table 6—EBUS-NA of the Mediastinum in Lung Cancer Patients\***

Study/Year	Patients, No.	Patient Type	Technique	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Herth et al <sup>46</sup> /2006	502	cI-III	RT-US bronch (22 ga)		94	100	0	(89)†	98	25% SCLC
Yasufuku et al <sup>101</sup> /2005	108	cII-III	RT-US bronch (22 ga)	100	95	100	0	11	69	16% SCLC
Yasufuku et al <sup>102</sup> /2004	70	cII-III	RT-US bronch (22 ga)	100	95	100	0	10	67	14% SCLC, 22% other cancers
Vilmann et al <sup>103</sup> /2005‡	31	cII-III	RT-US bronch (22 ga)	100	85	100	0	28	65	‡% of SCLC
Rintoul et al <sup>112</sup> /2005	20	cII-III	RT-US bronch (22 ga)	100	79	100	0	30	70	14% SCLC
Kanoh et al <sup>104</sup> /2005	54	cII-III	Catheter probe (19 ga)	100	86	100	0	37	81	30% SCLC
Plat et al <sup>105</sup> /2006	33	cII-III	Catheter (histo needle)		93	100	0	25	82	19% SCLC
Herth et al <sup>47</sup> /2006	100	cI	RT-US bronch 22 ga		94	100	0	1	17	
Summary	918				90	100	0	20	68	

\*RT-US bronch = real-time ultrasound bronchoscope. See Tables 3 and 5 for abbreviations not used in the text.

†Excluded from calculations because NPV is relatively less reliable with a prevalence of > 90%.

‡Both EBUS-NA and EUS-NA were performed in each patient. Only values from EBUS-NA were used in calculating the summary statistics.

**Table 7—TTNA of the Mediastinum in Lung Cancer Patients\***

Study/Year	Patients, No.	Patient Type	Technique	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Westcott <sup>106</sup> /1981	72	cN2,3†	CT scan-guided (20–22 ga)		94	‡	‡	‡	‡	?% SCLC
de Gregorio et al <sup>107</sup> /1991	48	cN2,3†	Fluoro-guided (18–22 ga)	92	72	100	0	(58)§	90	SCLC + other cancer
Moinuddin et al <sup>108</sup> /1984	40	cN2,3†	CT scan-guided (18–20 ga)	91	100	100	0	0	78	48% SCLC
Protopapas and Westcott <sup>109</sup> /1996	32	cN2,3	CT scan-guided (20 ga)		100	100	0	(0)§	91	16% SCLC
Böcking et al <sup>110</sup> /1995	23	cN2,3	CT scan-guided (22 ga)	87	80	100	0	0	65	
Summary	215				89	100	0		81	

\*See Tables 3 and 5 for abbreviation not used in the text.

†Bulky masses, corresponding to radiographic group A.

‡Not defined because all subjects had mediastinal disease.

§Excluded from calculations because NPV is relatively less reliable with a prevalence of > 90%.

mal masses to achieve a diagnosis. The ability to carry out TTNA for the diagnosis and staging of cancer in the mediastinum has generally been reported to be high (*ie*, > 90%), although approximately 10% of patients require the placement of a catheter for the evacuation of a pneumothorax.<sup>32</sup> The sensitivity has generally been reported to be approximately 90% (see Table 7).<sup>106–110</sup>

Patients selected for this procedure have generally had quite extensive mediastinal involvement (patients in radiographic group A, with some patients in group B). The mediastinal lymph nodes have generally been at least 1.5 cm in size. This is also supported by the fact that the prevalence of cancer in the mediastinal nodes was very high (*ie*, > 80%). Furthermore, only about 75% of the patients had lung cancer (despite excluding studies in which only a minority of patients had lung cancer). Therefore, these results are most applicable to patients with mediastinal infiltration or bulky mediastinal involvement, in whom the purpose of the procedure was probably primarily to confirm the diagnosis and less likely to confirm the stage. Extrapolation of these results to patients with lesser amounts of mediastinal spread for staging purposes may be inappropriate. Furthermore, the practical aspects of TTNA make this test unsuited for the biopsy of multiple mediastinal nodes such as would be needed in patients in radiographic groups C, D, and even B.

### VATS

Thoracoscopy, also known as VATS, can be used to access mediastinal nodes. This is done under general anesthesia and in general is limited to an assessment of only one side of the mediastinum. Access to the

R-sided nodes is straightforward, but access to the L paratracheal nodes is more difficult. Several series have shown the feasibility of this technique. No mortality has been reported from VATS for mediastinal staging, and complications were noted in only 12 of 669 patients (average, 2%; range, 0 to 9%).<sup>48–55</sup>

The performance characteristics of VATS mediastinal node biopsy for N2 node staging are shown in Table 8. The sensitivity varies widely, from 37 to 100%. The reason for this variation is not entirely clear. Even if the studies are restricted to patients with enlarged nodes, the sensitivity still ranges from 50 to 100%. The low sensitivity comes primarily from a study by Sebastian-Quetglas et al<sup>49</sup> This study is the only prospective, multiinstitutional study, and may perhaps be more generally applicable than the results from single institutions with a focused interest and extensive experience. It should be noted that VATS staging was feasible in only 75% of patients in this series. The performance characteristics recorded here are those that apply specifically to determination of mediastinal node status. The FN rate is 15% both in enlarged and normal-sized nodes. In all reports, the specificity is reported as 100% and the FP rate as 0%, but this is technically not evaluable because no further testing was done in the event of a positive VATS result.

VATS can also be useful for further evaluation of the T stage as determined radiographically. This is primarily useful in detecting or ruling out T4 lesions that preclude resection. In patients with radiographically suspected T4 involvement this has been shown to be absent in 38% of patients (29 to 50%) in three studies.<sup>49,50,55</sup> Furthermore, in patients with a cytologically negative pleural effusion, 40% were shown

**Table 8—Thoracoscopic (VATS) Assessment of the Mediastinal Nodes in Lung Cancer Patients**

Study/Year	Patients, No.	Patient Type	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Sebastian-Quetglas et al <sup>49</sup> /2003	105	All	75	37	100	0	20	29	
Roberts et al <sup>53</sup> /1999	50	All	100	38	100	0	11	16	All had negative mediastinoscopy results
Subtotal	155			38	100	0	15	25	
Sebastian-Quetglas et al <sup>49</sup> /2003	30	cN2	63	50	100	0	58	73	
Eggeling et al <sup>50</sup> /2002	73	cN2, cT4	100	99	100	0	4	70	VATS combined with medication
Massone et al <sup>48</sup> /2003	53	cN2		100	100	0	0	64	
Landreneau et al <sup>52</sup> /1993	33	cN2		100	100	0	0	42	All had negative mediastinoscopy results
Subtotal	189			87	100	0	15	64	
Sebastian-Quetglas et al <sup>49</sup> /2003	75	cN0	80	0			32	11	
Total*	419			75	100	0	7	44	

\*Patients depicted in several different rows from the same study were not counted twice in the calculations.

not to be due to malignant involvement by VATS.<sup>55</sup> On the other hand, routine VATS found unsuspected pleural studding in 4% of patients (0 to 5%) in several studies.<sup>48–51,54,56</sup> An unsuspected malignant pleural effusion was also found in 6% of patients in one study.<sup>53</sup> Most of the patients in these studies regarding pleural involvement had CT scan evidence of discrete node enlargement.

#### Assessment of APW Lymph Nodes

Cancers in the left upper lobe (LUL) have a prediction for involvement of the nodes in the APW (station 5). These nodes are classified as mediastinal nodes and represent the most important group of N2 nodes that are not accessible by standard cervical mediastinoscopy. It has been suggested<sup>57</sup> that nodes in this region should not be viewed as mediastinal nodes and that the resection of patients should be performed regardless of APW node involvement, making the assessment of these nodes superfluous. This was based

on a selected subgroup of 23 completely resected patients who had APW node involvement as the only site of N2 disease. However, the analysis of all of the data in this regard shows that the survival of patients with only APW node involvement is not substantially different than that of patients with involvement of only a single N2 node station in another location.<sup>58</sup> Therefore, the issue is more a matter of whether patients with involvement of a single mediastinal node station should undergo surgical resection, and not whether APW nodes should be classified as N2 nodes.

The classic way of invasively assessing this area is a Chamberlain procedure (also known as an *anterior mediastinotomy*), which involves an incision in the second or third intercostal space just to the left of the sternum. Traditionally, an overnight hospital stay has been necessary, but in many institutions this is no longer found to be necessary, especially as surgeons have used visualization between the ribs more frequently as opposed to removal of a costal cartilage.

**Table 9—Anterior Mediastinotomy in Lung Cancer Patients**

Study/Year	Patients, No.	Patient Type	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Anterior mediastinotomy alone									
Best et al <sup>60</sup> /1987	39	cIII		63	100	0	0	77	> 21% SCLC
Pagé et al <sup>86</sup> /1987	45	cII–III		86	100	0	11	47	18% SCLC
Standard cervical mediastinoscopy alone									
Pagé et al <sup>86</sup> /1987	345	cII–III		73	100	0	20	48	18% SCLC
Deneffe et al <sup>84</sup> /1983	124	cII–III	100	68	100	0	12	31	NSCLC only
Anterior mediastinotomy + standard cervical mediastinoscopy									
Pagé et al <sup>86</sup> /1987	32	cII–III		87	100	0	11	47	18% SCLC
Deneffe et al <sup>84</sup> /1983	39	cII–III	100	87	100	0	8	38	NSCLC only

The reliability of this procedure has not been extensively documented, despite its common use. The sensitivity of a Chamberlain procedure in addition to standard cervical mediastinoscopy in patients with LUL tumors is approximately 87%, and the FN rate is approximately 10% (Table 9). Two additional studies<sup>59,60</sup> regarding this procedure have not really addressed the reliability of the procedure for the staging of NSCLC. In one study,<sup>59</sup> no actual biopsies were performed in most patients, and the procedure was used to assess resectability (in this series, resectable patients included those with bulky APW nodal involvement). The other study<sup>60</sup> used anterior mediastinotomy primarily for diagnosis (not staging), and included pulmonary biopsies and evaluation of patients with mediastinal masses. In fact, only a minority of patients included in this study had lung cancer.

Extended cervical mediastinoscopy offers an alternative method for the invasive assessment of APW nodes, but it is used in only a few institutions (see Table 10). With this procedure, a mediastinoscope is inserted through the suprasternal notch and is directed lateral to the aortic arch.<sup>61</sup> In 100 consecutive patients with LUL cancers, standard mediastinoscopy and extended mediastinoscopy were found to have a sensitivity of 69% and an FN rate of 11% for the detection of N2,3 disease (prevalence, 29%).<sup>61</sup> Similar results (sensitivity, 81%; FN rate, 9%) were reported in another series<sup>62</sup> of 93 such patients, all of whom had enlarged APW nodes. In approximately 550 patients who were undergoing extended cervical mediastinoscopy, two major complications (stroke, 1 patient; aortic injury, 1 patient) have been reported.<sup>61–65</sup>

Thoracoscopy has been used to assess APW lymph nodes. The general results for this technique are reported in Table 8. Specific results for stations 5 and 6 have not been reported, but are likely to be better because these node stations are much easier to access

than any of the other mediastinal node stations. EUS-NA also provides an alternative method of sampling APW nodes (see previous “EUS-NA” subsection). Data addressing the reliability of this procedure specifically for APW nodes in patients with LUL tumors are not available. In general, however, the sensitivity of this test is very high, although the FN rate is high enough to potentially be an issue.

The patients included in these series of Chamberlain procedure or extended cervical mediastinoscopy have had potentially operable lung cancer with very few exceptions. These patients are primarily from radiographic group B, with probably a few from group C. The reported results provide data regarding the reliability of these tests for the staging of mediastinal nodes compared to thoracotomy in patients with lung cancer.

### Other Staging Procedures

In patients with signs of advanced disease, clinical scenarios often occur that indicate the need for other invasive procedures to be performed, such as NA of a supraclavicular lymph node, thoracentesis or thoracoscopy of a pleural effusion, or NA or biopsy of a metastatic site such as an enlarged adrenal or hepatic mass. The indications for such procedures are covered in more detail in the chapters on diagnosis<sup>9</sup> and noninvasive staging,<sup>12</sup> and specific recommendations regarding such procedures can be found in these chapters as well. In brief, if an enlarged supraclavicular lymph node or a pleural effusion is present, it is generally prudent to pursue a diagnosis of these lesions. When the clinical presentation is entirely consistent with locally advanced disease (stage IIIb), these procedures are usually indicated because they represent the easiest way to confirm the diagnosis of lung cancer. When the clinical presentation is otherwise not consistent with locally advanced disease,

**Table 10—Extended Cervical Mediastinoscopy in Lung Cancer Patients\***

Study/Year	Patients No.	Patient Type	Feasibility, %	Sensitivity, %	Specificity, %	FP, %	FN, %	Prevalence, %	Notes
Anterior mediastinotomy alone									
Freixinet Gilart et al <sup>62</sup> /2000	106	cII,III	NR	33	100	0	38	0.48	5% SCLC
Ginsberg et al <sup>61</sup> /1987	100			52	100	0	16	0.29	LUL NSCLC only
Standard cervical mediastinoscopy alone									
Freixinet Gilart et al <sup>62</sup> /2000	106	cII,III	NR	51	100	0	31	0.48	5% SCLC
Ginsberg et al <sup>61</sup> /1987	100			45	100	0	18	0.29	LUL NSCLC only
Anterior mediastinotomy + standard cervical mediastinoscopy									
Freixinet Gilart et al <sup>62</sup> /2000	106	cII,III	NR	76	100	0	18	0.48	5% SCLC
Ginsberg et al <sup>61</sup> /1987	100			69	100	0	11	0.29	LUL NSCLC only

\*See Table 9 for abbreviation not used in the text.

the etiology of these lesions must be established in order to accurately define the stage. However, the procedures used to diagnose an enlarged supraclavicular node (*ie*, NA or surgical biopsy) are the same regardless of whether the issue is to confirm the diagnosis or to define the stage. Similarly, in patients with a clinical presentation that is consistent with advanced disease (stage IV), an invasive procedure may be indicated as the easiest way to confirm the diagnosis and establish the cell type of the lung cancer. In patients with a solitary site that is suspicious for a distant metastasis or in patients with a clinical presentation that seems inconsistent with advanced disease, an invasive procedure is indicated to accurately define the stage. The procedures used to assess possible distant sites are the same regardless of the clinical presentation, and are dictated primarily by technical and anatomic factors that are specific to the particular patient.

No data are available to assess the sensitivity, specificity, and FN and FP rates of NA of a supraclavicular node. General experience indicates that this procedure is usually successful; in addition, surgical biopsy of such a node is easily accomplished if a NA procedure is not diagnostic. The reliability of procedures to diagnose a pleural effusion is covered in the chapter on diagnosis. Thoracentesis has a sensitivity of approximately 60%; thoracoscopy has a sensitivity of > 95%. Procedures to diagnose suspected distant metastatic sites are too varied to discuss in detail; furthermore, no data are available that expressly assesses the reliability of these tests in patients with lung cancer.

## APPROACH TO PATIENTS

### *Mediastinal Infiltration*

In patients with extensive mediastinal infiltration, the radiographic evidence of mediastinal involvement is quite universally considered adequate. There are no data to prove this, because invasive confirmation is not done. However, even though staging is not an issue, tissue is needed to confirm the diagnosis and to establish what type of cancer is present (*eg*, NSCLC vs SCLC). In this case, it does not matter whether tissue is obtained from the primary tumor or from a mediastinal site.

In patients in whom the diagnosis is the primary issue, tissues should be obtained by whatever method is easiest to perform. In other words, the choice of procedure will be governed primarily by patient-specific factors (*ie*, anatomic, convenience, and comorbidity factors) instead of the performance characteristics of a test. For example, it is still likely that a test of relatively low sensitivity such as sputum

cytology or cytology of a pleural effusion will be chosen first simply because it is easiest to perform. It is rare that such a patient will undergo TBNA, EUS-NA, or mediastinoscopy. Details of the performance characteristics of diagnostics tests of the primary tumor are summarized in chapter 9, and performance characteristics of the invasive mediastinal tests are summarized in the tables here. However, as noted above, the determining factor concerning which test to choose will be governed primarily by patient-specific issues.

## RECOMMENDATION

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

### *Discrete Mediastinal Lymph Node Enlargement*

Many patients present with a CT scan demonstrating the enlargement of discrete mediastinal (N2,3) lymph nodes. An extensive literature<sup>32</sup> demonstrates that enlargement seen on CT scan alone carries an FP rate of approximately 40% (see chapter 12). The PET scan literature has only recently become detailed enough to begin to define FN and FP rates in subgroups of patients such as those with discrete nodal enlargement seen on a CT scan. The FP rate for PET scanning in the mediastinum has been widely shown to be around 15 to 20%, although this has not been defined for this particular subgroup of patients. Two metaanalyses<sup>66,67</sup> have estimated the PET FN rate to be 13 to 25% in patients with nodal enlargement detected by CT scan, although these estimates are not based on direct data or clearly defined patients. Direct data from studies<sup>68,69</sup> in patients with mediastinal or hilar nodal enlargement (radiographic groups B and C combined) have found a PET FN rate of 20 to 28% for N2,3 involvement. Thus, it appears that in patients with enlarged mediastinal nodes detected by CT scanning, the CT scan alone cannot be relied on, and invasive biopsy is needed whether a PET scan finding is positive or negative.

In choosing an invasive staging test, several issues must be considered. First is the availability of different procedures. All of the invasive tests require some specialized experience and skill, and people who perform these procedures only occasionally may not be able to achieve the performance characteristics published in studies performed at high-volume institutions. Second, the location of the suspicious nodes is important, because nodes in one location may be

accessible only by a particular approach. There may be factors related to patient comorbidity that may argue against certain approaches, such as mediastinoscopy, which usually requires general anesthesia. However, patients who are unable to tolerate a general anesthetic for such a small procedure as mediastinoscopy are likely not to be well enough to tolerate definitive treatment for lung cancer anyhow. The morbidity and mortality of invasive procedures may be a consideration, although all of the available procedures generally have an excellent safety profile. Finally, cost may be a consideration.

The sensitivity of various invasive mediastinal staging tests in cN2,3 patients appears to be similar. A strict comparison is not justified because the patients undergoing these procedures are not comparable due to differences in how they are selected for a particular procedure (eg, the location of the nodes). The primary issue is the variability in FN rates. If a NA technique is chosen, it must be remembered that a negative result is not very reliable. A NA procedure may well be a good first choice because these procedures are less invasive than mediastinoscopy. However, a negative needle biopsy finding should be followed up in general with mediastinoscopy.

An option for the treatment of patients with stage III NSCLC is induction therapy followed by surgery (see chapter 17). If this approach is chosen, the role of mediastinal restaging after induction therapy is very unclear. However, some people have argued that the approach should include surgery only in those patients who have a response in the mediastinum to induction therapy. It has been shown repeatedly<sup>70</sup> that CT scan evidence of tumor shrinkage is notoriously misleading. PET scanning for mediastinal restaging has also been shown to have high FP and FN rates.<sup>70</sup> A repeat mediastinoscopy is generally safe and feasible (82 to 100%) but has mediocre results (sensitivity, 70 to 82%; FN rate, 15 to 25%),<sup>13,71–73</sup> and most surgeons are uncomfortable with this procedure. Because a first-time mediastinoscopy is probably the best way to accomplish mediastinal restaging, an argument can be made to use a NA technique initially to document N2,3 involvement and to save mediastinoscopy for the restaging procedure after induction therapy. All of this only applies if the adopted treatment policy is one of induction therapy, with subsequent therapy to be determined by the results of mediastinal restaging (despite the lack of data defining the role of surgery and restaging).

## RECOMMENDATIONS

### **2. For patients with discrete mediastinal lymph node enlargement (and no distant metastases),**

**invasive confirmation of the radiographic stage is recommended (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes).** Grade of recommendation, 1B

**3. For patients with discrete mediastinal lymph node enlargement (and no distant metastases), many invasive techniques for the confirmation of the N2,3 node status are suggested as reasonable approaches (eg, mediastinoscopy, EUS-NA, TBNA, EBUS-NA, or TTNA), given the appropriate experience and skill (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes).** Grade of recommendation, 1B

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

### *Central and Clinical N1 Tumors*

Patients with no evidence of mediastinal node enlargement but with a central tumor or N1 node involvement represent another distinct group (group C). It is reasonable to consider patients with central tumors together with those with N1 node enlargement, because it is usually difficult to assess the N1 nodes in the case of a central tumor. Extensive data indicate that the FN rate of a CT scan with respect to the mediastinal nodes is 20 to 25% (see chapter 12 on noninvasive staging).<sup>32</sup> More limited data demonstrate that the FN rate for PET scanning in the mediastinal nodes in this situation is similarly high (24 to 83%).<sup>68,69,74,75</sup> Thus, invasive staging is required in these patients despite the negative CT scan result and even a negative PET scan result.

In patients with normal-sized mediastinal lymph nodes in whom invasive staging is needed, mediastinoscopy remains the “gold standard.” The general experience with mediastinoscopy suggests that the FN rate (approximately 10%) is low in these patients, and those studies<sup>15,16</sup> that have specifically reported on these patients substantiate this. Although it cannot be directly compared to mediastinoscopy, the FN rate (20%) of EUS-NA demonstrates that a significant number of patients with negative EUS-NA finding may still harbor metastases. Subgroup analysis in the study by Wallace et al<sup>24</sup> has suggested that approximately one half of these FN cases were due to malignant lymph nodes in the anterior mediastinum, which may be more accessible by mediastinoscopy or, theoretically, EBUS-NA, although to date this area has not been carefully

studied. The other half of FN cases were often due to very small deposits that may be more subject to sampling error of the needle or small biopsy methods.

Other methods of mediastinal staging have generally not been used much in this patient population (*ie*, TTNA, TBNA, and EBUS-NA). However, the performance characteristics of these tests, especially the FN rates, in patients with enlarged mediastinal nodes would suggest that TTNA, TBNA, and EBUS-NA are likely not to perform as well as mediastinoscopy in patients with normal-sized nodes. This is particularly true with regard to the FN rates. Because the goal of invasive staging in this situation is to confirm the absence of mediastinal disease, the FN rate is the parameter of greatest importance. It does not appear that the NA techniques can confirm a negative mediastinum finding with sufficient reliability. EBUS-NA may turn out to be sufficiently reliable to rule out mediastinal node involvement in small nodes, but the data are too preliminary to justify a firm recommendation.<sup>47</sup>

#### RECOMMENDATIONS

**5. For patients with a radiographically normal mediastinum (by CT scan) and a central tumor or N1 lymph node enlargement (and no distant metastases), invasive confirmation of the radiographic stage is recommended (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes).** Grade of recommendation, 1C

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

#### *Peripheral Clinical Stage I Tumors*

Patients with peripheral tumors in whom there is no enlargement of N1 or N2,3 nodes seen on CT scans, the FN rate of this radiographic assessment in the mediastinum is approximately 10%.<sup>32</sup> The incidence is lower in patients with T1 tumors (9%) than in those with T2 tumors (13%).<sup>32</sup> Whether this incidence is viewed as being high enough to justify performing mediastinoscopy or PET scanning is a matter of judgment. A negative PET scan finding in the mediastinum carries a FN rate of approximately 5% (range, 3 to 6%) in this group of patients.<sup>68,74-76</sup> Thus, invasive staging is probably

not needed in this patient group if the findings of a PET scan of the mediastinum are negative. A PET scan is generally not needed in the case of a cT1N0M0 tumor (see chapter 12). Invasive staging of the mediastinum is also generally not indicated in these cases.

If invasive staging is deemed to be necessary, it appears that mediastinoscopy is the best choice because of a low FN rate compared to techniques involving NA. The arguments raised concerning the invasive staging of normal mediastinal nodes in cN1 or central tumors (group C) applies to this group (group D) as well, since these arguments are a function primarily of the size of the mediastinal nodes.

#### RECOMMENDATIONS

**7. For patients with a peripheral clinical stage I tumor in whom a PET scan shows uptake in mediastinal nodes (and not distant metastases), invasive staging is recommended. In general, mediastinoscopy is suggested, but EUS-NA or EBUS-NA may be a reasonable alternative if nondiagnostic results are followed by mediastinoscopy.** Grade of recommendation, 1C

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

#### *Patients With LUL Tumors*

Patients with tumors in the LUL deserve special mention because the aortic arch raises technical issues of access to the mediastinal nodes in the APW (station 5). This node station is the most likely mediastinal nodal area to be involved in the case of an LUL tumor, whereas it is extremely unlikely to be involved in patients with a tumor in any of the other lobes. Of course, mediastinal nodal involvement from an LUL tumor can also extend to other node stations such as the subcarinal (station 7) or paratracheal areas (stations 4L, 4R, 2L, and 2 R). A full assessment of potentially involved mediastinal node stations in the case of an LUL tumor requires investigation of the paratracheal and subcarinal nodes, as well as a separate procedure to access the APW area. The technical issues of access to the APW nodes raises questions about whether a separate invasive test for the assessment of these nodes is really necessary.

The definition of radiographic groups (groups A, B, C and D) is the same no matter which lobe of the lung is involved. In addition, the indications for invasive staging of the mediastinum in patients with

LUL tumors should follow the same guidelines as in patients with a tumor in a different lobe (patients with enlarged mediastinal nodes, a central tumor or N1 nodal enlargement and a normal mediastinum, or with evidence of PET scan uptake in mediastinal areas should undergo invasive mediastinal staging).

If the usual mediastinal node stations are found to be negative (stations 2R, 4R, 7, 2L, and 4L), it is controversial whether a separate procedure to assess the station 5 area is needed. However, given the lack of clear data that involvement of only this station carries a different prognosis than involvement of a different single mediastinal node station, and with the availability of techniques of assessing the APW area that are easier for patients to undergo (*eg*, EUS-NA, EBUS-NA, extended cervical mediastinoscopy, and VATS), the guidelines committee favors pursuing an invasive assessment of the APW nodes. A finding of involvement in one mediastinal area may preclude the necessity of biopsying other areas, especially if an additional procedure would be necessary (*eg*, a positive EUS-NA finding for station 5 may preclude the assessment of paratracheal nodes, or a positive mediastinoscopy result would obviate the need for an anterior mediastinotomy).

A comparative assessment of different invasive tests for APW nodes is not possible. A reasonable extrapolation from the data for other node stations would be to pursue a needle technique for enlarged APW nodes and a surgical biopsy (*eg*, Chamberlain procedure, VATS, or extended cervical mediastinoscopy) for normal-sized APW nodes. However, it is also a reasonable compromise to accept a negative NA finding without adding an additional surgical biopsy, given the controversy over the need to assess the APW nodes. Modification of these suggestions may be necessary due to the availability of expertise with the invasive procedures. However, it is suggested that referral to a larger center be considered if there is not a fair amount of expertise with at least one invasive APW staging procedure.

#### RECOMMENDATION

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

#### CONCLUSION

Accurate mediastinal staging is crucial to the selection of the optimal therapy for patients without distant metastases. Imaging studies are not sufficiently reliable in many situations, making invasive staging tests an important part of appropriate staging. Many different invasive staging tests, which should be viewed as complementary to one another because they are applicable to particular nodal stations and patient groups, are available. It is helpful to separate patients into different groups based on the extent of mediastinal involvement by CT scan and whether the primary tumor is central or peripheral. In general, needle techniques are most useful in patients with enlarged mediastinal nodes, while mediastinoscopy remains the “gold standard” in patients with normal-sized nodes.

#### SUMMARY OF RECOMMENDATIONS

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

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

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

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

**5. For patients with a radiographically normal mediastinum (determined by CT scan) and a**



**central tumor or N1 lymph node enlargement (and no distant metastases), invasive confirmation of the radiographic stage is recommended (regardless of whether the findings of a PET scan of the mediastinal nodes are positive or negative). Grade of recommendation, 1C**

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

**7. For patients with a peripheral clinical stage I tumor in whom a PET scan shows uptake in the mediastinal nodes (and no distant metastases), invasive staging is recommended. In general, mediastinoscopy is suggested, but EUS-NA or EBUS-NA may be a reasonable alternative if nondiagnostic results are followed by mediastinoscopy. Grade of recommendation, 1C**

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

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

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