In patients with non-small cell lung cancer (NSCLC), accurate mediastinal staging is relevant to determine treatment options, estimate prognosis, and provide a common language when communicating about patients and enrolling them in clinical trials. For the last 4 decades, several lymph node maps have been used to define the clinical and pathologic lymph node involvement in patients with lung cancer by labeling intrathoracic lymph node regions using either anatomic descriptions (eg, right lower paratracheal) or numerical levels (eg, 4R). These maps include those by Naruke, American Thoracic Society (ATS), and Mountain Dressler-ATS (MD-ATS), a modification of the ATS map. The Naruke map had been used by Japanese surgeons and oncologists, whereas the MD-ATS was widely adopted in North America. The International Association for the Study of Lung Cancer (IASLC) has proposed a revision of the TNM staging system in which the N descriptors reconcile the discrepancies between the Naruke and the MD-ATS maps. The most striking discrepancy between the two systems was that level 7 subcarinal lymph nodes in the MD-ATS map corresponded...
Recent Advances in Chest Medicine

Relevance and Impact of Adequate Staging

The distinct treatment options and prognosis for any given tumor stage make accurate staging the most relevant step in the management of patients with lung cancer. Staging sequence and completeness prior to curative-intent treatment remain suboptimal. In one study, single (CT scan), bimodality (CT scan plus PET scan or CT scan plus invasive), or trimodality (CT scan, PET scan, and invasive) tests were used to assess for mediastinal metastases. Only 30% of patients had bimodality and 5% had trimodality staging, despite the guidelines recommending for bimodality or trimodality strategies, which have a significantly lower risk of death.1

The Institute of Medicine recommends that patient care should be "STEEEP": safe, timely, effective, efficient, equitable, and patient-centric. For efficiency, access, and timeliness of an initial procedure in the management of patients with suspected lung cancer, concomitant diagnosis and staging is beneficial because it avoids additional procedures. It is preferable to perform a biopsy at the site that would confer the highest stage (ie, to perform a biopsy of a suspected metastasis or mediastinal lymph node rather than the primary pulmonary lesion).2 Timely staging is relevant, as negative outcomes result from delaying therapy. Distant metastases may become evident on serial CT scans or PET scans in 3% of untreated patients at 4 weeks and in 13% at 8 weeks. Complete restaging, therefore, should be considered if therapy is delayed for 4 to 8 weeks after the diagnosis.3

Safety and effectiveness can be ensured by adherence to the guidelines, which recommend mediastinal lymph node sampling as the first invasive test in patients with suspected lung cancer and mediastinal lymph node involvement without distant metastases. Guideline-consistent care with initial mediastinal sampling results in fewer tests and complications.4 One study compared outcomes of diagnostic strategies in patients with lung cancer with regional spread without distant metastases.4 If the first invasive test involved mediastinal sampling, patients were classified as guideline consistent; otherwise, they were classified as inconsistent. Only 21% of patients had guideline-consistent diagnostic evaluations, and 44% never had mediastinal sampling. Patients who had guideline-consistent care required fewer tests than patients with guideline-inconsistent care, including thoracotomies and CT scan-guided biopsies, although they had more transbronchial needle aspirations. As a consequence, patients with guideline-consistent care had fewer pneumothoraces, chest tubes, hemorrhages, and respiratory failure events.4 Three quality gaps are in fact identified in the care of patients with lung cancer: failure to sample the mediastinum first, failure to sample the mediastinum at all, and overuse of thoracotomy. Furthermore, out of the seven process of care quality indicators related to the evaluation of patients with lung cancer, four are related to staging alone and include mediastinal sampling prior to curative-intent surgery for stage IB or higher.5 Performing a safe, timely, effective, and patient-centric staging requires a coordinated effort. Guidelines recommend a multidisciplinary lung cancer team involvement early in a patient’s care, which coordinates the optimal approach to staging and specimen acquisition to expedite diagnostic and molecular testing.2,6,7

Normal and Pathologic Mediastinum on CT Scan and PET Scan: Implications for Staging

Contrast-enhanced chest and upper abdominal CT scan is recommended as an initial step for all patients with suspected or confirmed diagnosis of lung cancer suitable for treatment.7,18 The revised IASLC system is clinician oriented and should be used for staging,8 as it unifies previously used systems and defines the borders of the mediastinal, hilar, and interlobar lymph nodes based on CT scan landmarks.11 To further help clinicians in their routine practice, the American College of Chest Physicians proposed that patients with lung cancer be separated into four categories with respect to the radiographic characteristics of the primary tumor and the lymph nodes based on CT scan findings12 (Fig 1). For group A, tissue diagnosis suffices, as mediastinal involvement is implied. Group B patients need pathologic confirmation of their lymph nodes prior to curative-intent treatment. Groups C and D involve patients with normal mediastinal nodes on CT scan. In group C, the presence of a central tumor or suspected N1 disease on CT scan or PET scan (hilar, interlobar nodes) makes the risk of mediastinal (N2, 3) nodal involvement high (20%–25%) despite normal-sized mediastinal nodes negative on PET scan; thus, further tissue confirmation is needed for this group. For group D, invasive staging is currently not routinely recommended prior to thoracotomy.
but may be warranted to rule out N1 disease for non-
surgical candidates who will undergo stereotactic body
radiation therapy (SBRT). The European Society of
Thoracic Surgeons guidelines also recommend invasive
staging in patients with the primary tumor size > 3 cm,
based on higher probability of N2 disease, even when
the CT and PET scans are negative for mediastinal
lymph node involvement. Spanish Society for Pulmo-
nology and Thoracic Surgery (SEPAR) guidelines recom-
mend invasive staging in patients with low metabolic
activity in the primary tumors, as in some adenocarci-
nomas, since these tumors may be associated with
occult N2 disease (ie, pathologic involvement with a
negative CT scan and PET scan).

The term “normal mediastinum” by CT scan criteria is
used to define the absence of visualized mediastinal
lymph nodes or the presence of nonpathologic-size
lymph nodes. CT scan criteria have been used to define
the probability of malignant involvement of the medias-
tinal lymph nodes. The most widely used criterion is a
short-axis lymph node diameter ≥ 1 cm on a transverse
CT scan. There is no universal agreement on these
definitions, however, and different organizations use
slightly different cutoff values to define discrete suspi-
cious mediastinal lymph nodes. SEPAR defines these as
nodes whose smallest diameter is > 15 mm on CT scan
with contrast, whereas National Institute for Health
and Care Excellence defines them as lymph nodes
between 10 and 20 mm maximum short axis on
CT scan. Overall, however, the median sensitivity and
specificity of CT scanning for identifying mediastinal
lymph node metastasis are 55% and 81%, respectively
(Table 1). Therefore, lymph nodes < 1 cm seen on the
CT scan or nodes that may not be visualized at all may
have metastatic involvement once sampled by surgical
or needle-based techniques.

PET scanning has a higher accuracy than CT scan for
the evaluation of mediastinal lymph node involvement
from lung cancer. Lymph nodes with higher fluorode-
oxylucose uptake than that of the surrounding normal
mediastinal structure are considered as positive. Lymph
nodes with equivocally increased fluorodeoxyglucose
uptake to a level similar to that of the surrounding nor-
mal mediastinal structure are interpreted as negative. This
defines a “normal mediastinum” by PET scan criteria.

PET scanning also provides information regarding met-
astatic disease outside the thorax, except for the brain.
Guidelines recommend the use of PET scan and PET-
CT scan for staging in patients who are potential candi-
dates for radical treatment (clinical stage IA-III).

Figure 1 – Radiographic characteristics of the primary tumor and associated interlobar, hilar, and mediastinal lymph nodes. The American College of
Chest Physicians defines these groups based on CT scan findings; for the purpose of this article, the integrated CT-PET scan findings are illustrated. A, Group A involves patients with mediastinal infiltration; discrete lymph nodes can no longer be discerned or measured. Diagnosis is necessary, but medi-
stinal involvement is implied, and thus a mediastinal staging procedure is not indicated. B, Group B involves patients with mediastinal node enlarge-
ment, in whom the size of the discrete nodes can be measured. These patients require pathologic confirmation (ie, invasive staging). C, D, In Group C,
the mediastinal lymph nodes are normal, but there is a high risk for occult N2/N3 disease based on the presence of suspected N1 disease (C) or a central
tumor (D). These patients also need invasive staging prior to surgery. E, Group D is composed of patients with a peripheral clinical stage I tumor (the
mediastinal, hilar, and interlobar nodes are normal on PET-CT scan). Invasive staging prior to surgery is not recommended in this group unless these
patients are considered for stereotactic ablative surgery.
PET scan, however, is less sensitive for lymph nodes with diameters between 7 and 10 mm, which in fact, by convention, may be called “normal” on chest CT scan. Mediastinoscopy, endobronchial ultrasound (EBUS), and esophageal ultrasound (EUS)-guided sampling have identified unsuspected mediastinal metastases in patients with normal-sized lymph nodes without increased PET activity (ie, normal mediastinum on CT scan and PET scan).\(^{14}\) Overall, the sensitivity and specificity of PET scan for identifying mediastinal metastasis are approximately 77% and 86%, respectively (Table 2\(^{15-18}\)).\(^{12}\) Thus, tissue sampling is still required to confirm PET scan-positive findings. False positives are seen in patients with active infection and inflammation where there is increased glycolysis. Sarcoidosis, anthracosis, infections, and reactive lymph nodes lead to nodes that are positive on PET scan.\(^{2,7-10,19}\) In cases of recent lymph node sampling, PET scan may be falsely positive (Fig 2). False-negative PET scans occur when there is impaired blood flow (ie, necrosis) and minimal radiotracer can reach the area or in processes with a low metabolic activity (eg, carcinoid, some adenocarcinomas).

Therefore, PET scanning is not a definitive test. Lymph node sampling improves staging accuracy beyond the ability of PET scanning.\(^{12}\) In the absence of M1 extrathoracic disease, a PET scan showing hypermetabolism in the mediastinal nodes requires confirmation.\(^{2,7-10,13}\) If the PET scan is negative, tissue confirmation is recommended prior to surgery in any of the following circumstances (Fig 1):

1. Discrete mediastinal lymph nodes is seen on CT scan.\(^{2,8,10,13}\)
2. Central tumor, usually in contact with the mediastinum\(^{2,8,13}\) (A central tumor was defined as existing within the proximal one-third of the hemithorax, and a peripheral tumor was defined as existing outside the proximal one-third of the hemithorax.)
3. The tumor has low maximum standard uptake value.\(^{8}\)
4. There is suspicion for N1 disease.\(^{7,8,13}\)
5. Tumor size is > 3 cm.\(^{13}\)

**Staging the PET-CT Scan Normal Mediastinum Prior to Curative-Intent Therapy**

**Curative-Intent Surgery**

For patients with peripheral clinical stage I tumors with negative nodal involvement by CT and PET scan (Fig 1), invasive preoperative evaluation of the mediastinal nodes is not recommended,\(^{7,13}\) based on the evidence that PET scan has a false-negative rate of only 3% to 6% in this population.\(^{12}\) One study, for example, evaluated the role of mediastinoscopy and EUS-fine-needle aspiration (FNA) in patients with no mediastinal nodal disease on PET-CT scan.\(^{20}\) The incidence of unsuspected pathologic N2 (pN2) disease was 2.9% for mediastinoscopy and 3.7% for EUS-FNA. Patients with clinical N1 (cN1) disease suspected on PET-CT scan had a high incidence of unsuspected pN2 disease (17.6% after mediastinoscopy and 23.5% after EUS-FNA).
and it was concluded that cytohistologic confirmation is not recommended for cN0, but it is necessary for cN1. Studies demonstrate that preoperative EBUS could upstage patients with small, peripheral tumors and PET-CT scan-negative mediastinum. In these trials, the overall rate of N2 disease that was not detected by PET or PET-CT scan ranged from approximately 5% to 17%. These higher rates of detected occult N2 disease in the more recent studies may be partially explained by histologic differences in the study populations and by the changes in the lymph node map in which the area of lymph node station 7 has been widened, allowing detection of additional diseased N2 nodes (Fig 3). Future algorithms for staging the normal PET-CT scan mediastinum may also need to take into account biomarkers (eg, carcinoembryonic antigen, carbohydrate antigen 19-9, carbohydrate antigen 125, or cytokeratin 19 fragment), as these may be useful indicators for nodal staging. They may impact the decision to proceed with invasive

### TABLE 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Rationale</th>
<th>Comments</th>
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<tbody>
<tr>
<td>F: frequency</td>
<td>Fast 1-2 downstroke movements of the needle per s</td>
<td>Cut the nodal tissue</td>
<td>Cells are conducted into the needle by capillary forcea</td>
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<tr>
<td>A: amplitude</td>
<td>Move the needle from capsule to capsule</td>
<td>Assure sampling of all intranodal regions (subcapsular, hilar)</td>
<td>In adenocarcinoma, subcapsular nodal involvement may be the only site of malignant cells15</td>
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<tr>
<td>S: suction</td>
<td>No suction technique</td>
<td>Suction may not increase the yield and may result in bloodier specimens16</td>
<td>When nonsuction technique fails to yield an adequate sample (as in fibrotic nodes), the conventional aspiration with suction may be used and vice versa17</td>
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<tr>
<td>T: time</td>
<td>Spend little time (&lt;6 s) inside the node</td>
<td>FNAs from thyroid/breast suggest that the less time spent in the node, the better the specimen purity17</td>
<td>For hypervascular and densely fibrotic nodes, smaller needles (25-gauge) may perform better17</td>
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<tr>
<td>E: edge</td>
<td>Keep the needle inside the node at all times during the aspiration</td>
<td>Rarely, complications can occur: pericarditis, mediastinitis, pneumothorax, pneumomediastinum, bleeding18</td>
<td>Aspiration of extra nodal tissues will also likely result in a nondiagnostic specimen</td>
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<tr>
<td>R: route</td>
<td>Change the direction of the needle inside the node by flexing or extending the lever of the bronchoscope handle</td>
<td>Cut into previously nontraumatized lymph node tissue</td>
<td>Easier to perform with the 25-gauge than with the 21- or 22-gauge needles</td>
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<tr>
<td></td>
<td></td>
<td>Potentially increase the quantity and quality of the aspirated material</td>
<td>This element remains to be further studied</td>
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</table>

FNA = fine-needle aspiration. See Table 1 legend for expansion of other abbreviation.

Capillary force or action refers to the ability of a medium (usually liquid) to flow in a narrow space (eg, small-gauge needle) against gravity. The medium is lifted up inside the needle as a result of cohesion and adhesive forces between the medium and the inner aspect of the needle. The height of the medium column inside the needle is inversely proportional to the radius of the needle, suggesting that the smaller the needle gauge, the more specimen is collected through the capillary action. The specimen is collected in the needle by nonsuction fine-needle sampling; this results in less nodal trauma and less blood in the smear without compromising specimen cellularity necessary for cytology diagnosis.
staging. For instance, if the N2/N3 node is negative by EBUS but the markers are elevated, surgical staging may be warranted. Although it remains to be determined which marker is most suitable for a specific histologic subtype, biomarker-driven risk stratification of PET-CT scan-normal mediastinum is promising and needs further investigation.

**Stereotactic Body Radiation Therapy**

Open surgery is not feasible in 25% to 35% of patients with stage I NSCLC, and external-beam radiation is offered as a standard treatment. Conventionally fractionated radiotherapy has been the traditional radiation treatment of these patients, but SBRT, also known as stereotactic ablative radiotherapy, is an alternative. SBRT may be more cost effective than conventionally fractionated radiotherapy, wedge resection, or lobectomy for marginally operable patients. Regional failures, however, occur in up to 15% of patients treated with SBRT. This may be because prior to SBRT, patients with medically inoperable NSCLC generally have limited, noninvasive staging. At a minimum, however, until more data become available, mediastinal interrogation with EBUS should be performed before patients undergo SBRT. Indeed, mediastinal lymph nodes were found to be positive for metastatic disease in 16% of patients who underwent EBUS prior to SBRT and had no previous radiographic evidence of disease. A prospective study is currently testing whether there is a difference in accuracy between CT-PET scan and EBUS-transbronchial needle aspiration (TBNA) for mediastinal staging in patients with NSCLC prior to SBRT.

**Sampling Techniques and Sequence for Mediastinal Staging**

The staging technique should be chosen that is most cost efficient, least invasive, and has the least delay in care. Each center should plan the sequence of tests so the initiation of treatment is not delayed. Communication among the oncologist, practitioner performing the biopsy, and the pathologist is important to ensure that sufficient tissue is obtained and processed for diagnosis, staging, and genetic alterations.

Needle-based techniques currently proven to be accurate for mediastinal staging include EBUS, EUS, and combined EUS/EBUS, with sensitivities of approximately 89%, 89%, and 91%, respectively. These are the tests of first choice to confirm mediastinal involvement in accessible lymph node stations. If negative, as of this writing, they should be followed by surgical biopsy. This recommendation is based on the studies of EBUS vs mediastinoscopy and applies to patients with enlarged mediastinal lymph nodes on CT scan or high uptake on PET scan (Fig 4). The preferred first needle technique is EBUS-TBNA, because its diagnostic yield is comparable to that of mediastinoscopy. In fact, EBUS has several advantages over mediastinoscopy: reduced invasiveness; ease of restaging; ability to routinely reach posterior subcarinal, hilar, and interlobar nodal stations (Table 1); and, in some practices, the lack of requirement for general anesthesia. National Institute for Health and Care Excellence guidelines recommend that every cancer network should have at least one center with EBUS and/or EUS and that the local test performance of EBUS and EUS-guided FNA should be the subject of audit.
and 9, the only ones not accessible by EBUS but accessible by EUS (Table 1), did not contribute to the increased yield of EUS-FNA. In addition, it is extremely rare that stations 8 and 9 are involved without concurrent involvement of upper mediastinal nodes (stations 2, 4, or 7). In one study of 621 patients who underwent staging according to the European Society of Thoracic Surgeons guidelines, only one of 30 patients with unexpected (ie, negative PET-CT scan) pN2 had involvement in the inferior mediastinum (in station 8). These data do not justify routine exploration of the inferior mediastinum prior to thoracotomy and questions the value of routinely performing EUS in addition to EBUS for staging.

Surgical techniques (mediastinoscopy, video-assisted thoracic surgery [VATS]) are used when the suspicion is high (CT or PET scan-positive hilar or mediastinal nodes) and needle techniques are negative. Figure 4. SEPAR recommends mediastinoscopy when three needle-based samples fail to provide a cytopathologic diagnosis or normal lymphatic tissue. In most studies, surgical staging consists of a standard videomediastinoscopy performed in the operating room, under general anesthesia, and patients are discharged to home the same day. The median sensitivity of standard cervical mediastinoscopy is 78%, and median negative predictive value (NPV) is 91% (Table 1). The false-negative rate at mediastinoscopy is influenced by: lymph node accessibility, number of stations sampled (3 or 5), and diligence with which the nodes are dissected or sampled. In this regard, lymphadenectomy and videomediastinoscopy have better results than traditional mediastinoscopy, with a median sensitivity of 94%, 89%, and 78%, respectively. A surgical staging technique, however, may be the first step for patients with left upper lobe (LUL) tumors because of the predilection for involvement of the aorto-pulmonary window (APW) nodes (station 5). Invasive assessment of the APW nodes should be performed via Chamberlain, VATS, or extended cervical mediastinoscopy (ECM) if other mediastinal stations are found to be uninvolved. These nodes represent the most important group of N2 nodes not accessible by standard cervical mediastinoscopy (Table 1). ECM can be added to explore the subaortic and the paraaortic nodal stations if videomediastinoscopy is deemed to be negative by macroscopic inspection of the biopsied or removed lymph nodes or by frozen section examination of macroscopically suspicious lymph nodes. If videomediastinoscopy reveals N2 or N3 disease in other stations, ECM for

Studies suggest that the combination of EBUS and EUS allows complementary and near-complete access to all mediastinal lymph node stations (Table 1). The sensitivities of surgery, endosonography (EBUS and EUS), and endosonography followed by surgery if the needle technique was negative were 79%, 85%, and 94%, respectively. A better understanding of the published data and recent evidence, however, challenge the value of combined EBUS and EUS. EUS must be followed by EBUS for complete staging. Lymph node stations 2

Figure 3 – Diagram illustrating the mediastinal, hilar, and interlobar lymph node stations relevant for staging and accessible by endobronchial ultrasound transbronchial needle aspiration (stations 2, 4, 7, 10, and 11). The upper and lower borders are based on the revised International Association for the Study of Lung Cancer lymph node map. Station 2R includes nodes extending to the left lateral border of the trachea. The upper border is the apex of the right lung and pleural space and, in the midline, the upper border of the manubrium, and the lower border is the intersection of caudal margin of innominate vein with the trachea. Station 2L includes nodes extending to the left of the left lateral border of the trachea. The upper border is the apex of the left lung and pleural space and, in the midline, the upper border of the manubrium, and the lower border is the superior border of the aortic arch. Station 4R includes right lower paratracheal nodes and pretracheal nodes extending to the left lateral border of trachea. The upper border is the intersection of caudal margin of innominate vein with the trachea, and the lower border is the lower border of the azygos vein. Station 7 is the subcarinal nodal station with the upper border composed of the carina of the trachea and the lower border composed of the upper border of the lower lobe bronchus on the right and the lower border of the bronchus intermedius on the right. Station 4L includes nodes to the left of the left lateral border of the trachea, mediastinum prior to thoracotomy and questions the value of routinely performing EUS in addition to EBUS for staging. In one study of 621 patients who underwent staging according to the European Society of Thoracic Surgeons guidelines, only one of 30 patients with unexpected (ie, negative PET-CT scan) pN2 had involvement in the inferior mediastinum (in station 8). The data do not justify routine exploration of the inferior mediastinum prior to thoracotomy and questions the value of routinely performing EUS in addition to EBUS for staging.

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station 5 and 6 is not recommended. With this procedure, a mediastinoscope is inserted through the suprasternal notch and directed lateral to the aortic arch. In a study of 456 patients with LUL cancers, standard mediastinoscopy accompanied by ECM was found to have a median sensitivity of 71% for identifying station 5, 6 nodal involvement, with a median NPV of 91%. VATS has also been used to assess APW lymph nodes, but specific results for stations 5 and 6 have not been reported.

EBUS Sampling Techniques and Novel Processor Functions

Most studies on EBUS-TBNA showed a high yield for diagnosis and staging of lung cancer using a sampling technique that involved several (approximately 10-15) needle revolutions inside the node and the use of suction. The current understanding of optimal fine-needle sampling techniques, however, include capillary action and minimal intranodal trauma (Fig 5), methods that may increase the purity of the acquired specimens and, thus, their quality, relevant for molecular analysis (Table 2).

Elastography and vascular imaging may be able to further improve the sensitivity in detecting malignant lymph nodes. The power/color Doppler mode allows vascular image pattern classifications of the lymph nodes, which could predict metastatic lymph node involvement. Elastography is an imaging modality already available on certain EBUS processors, which permits the evaluation of the relative stiffness of the tissues. It has already been used in EUS studies for differentiating benign from malignant disease, and the data in EBUS are emerging. Although in the era of biomarker-driven lung cancer treatment tissue acquisition is still required, these processor functions may allow for selecting the intranodal region that lacks necrosis or has greatest amount of malignant tissue to further increase diagnostic yield, specimen quality, and quantity. In addition, the presence of certain sonographic characteristics may predict the lack of, or the presence of, malignant involvement. Evidence and clinical experience suggest that the presence of a “central hilar structure” on EBUS predicts a benign diagnosis (granulomatous inflammation, reactive lymph node), whereas the “coagulation necrosis sign” predicts malignancy (Fig 5). Research is needed to clarify how image patterns can alter posttest probability in cases of nondiagnostic EBUS specimens.

EBUS-TBNA Staging Strategies: Implications for Practice

Should the Contralateral (N3), Hilar (Station 10), and Interlobar (Station 11) Nodes Be Sampled During Routine EBUS Staging?

In most trials comparing EBUS with mediastinoscopy for staging NSCLC, stations 2, 4, and 7 were evaluated and sampled by EBUS if they were > 5 mm on the short axis, starting with N3 and ending with N1 nodes. However, contralateral hilar and interlobar (station 10, 11)
nodes were not sampled. In one trial of EBUS-TBNA performed in patients with mediastinum negative on PET-CT scan that reports results on stations 10 and 11, none of the patients with confirmed lymph node involvement on EBUS had disease in a contralateral station 10 or 11. It is unclear, however, whether the contralateral station 10 and 11 were even sampled. Routinely sampling these stations may not be warranted for the following reasons: (1) in surgical staging, operators routinely sample only contralateral mediastinal (stations 2, 4) and not contralateral hilar and interlobar nodes (stations 10, 11); (2) sampling contralateral station 10 and 11 does not impact staging if a contralateral mediastinal (station 2 or 4) nodes are positive (ie, N3 disease is confirmed by sampling a mediastinal node). If the contralateral mediastinal stations are negative, and EBUS identifies a contralateral node > 5 mm (as it is often the case in station 11L or 11Rs, even when the CT and PET scans are negative), it is unknown whether these nodes should be routinely sampled. Two arguments favor this strategy: (1) the extremely rare possibility of identifying skipping metastasis to the contralateral hilum/interlobar nodes, and (2) the knowledge of hilar and interlobar N3 disease may affect the radiation field in stage IIIB. Specifically, the dose of radiation and pneumonitis risk are different when these nodes are included in planning. Research is needed to determine the value of this practice.

Should N1 Nodes Be Sampled During Routine EBUS Mediastinal Staging in Surgical Candidates?

Surgical series report that hilar pN1 disease has a worse prognosis than the more peripheral pN1. Intralobar pN1 could behave as pN0, and hilar pN1 could have similar prognosis as single-station pN2. Since it affects prognosis, this subdivision of the pN1 group justifies sampling of N1 nodes preoperatively, which is possible via EBUS. In patients with potentially resectable clinical N0 or N1 NSCLC based on CT and PET scan, EBUS demonstrated a sensitivity, specificity, diagnostic accuracy, and NPV to accurately differentiate between N0 and N1 disease of 76.2%, 100%, 96.6%, and 96.2%, respectively. These findings highlight the importance of exploring hilar nodes preoperatively either by EBUS or surgically for prognosis and potential induction therapy to cN1 disease confirmed pathologically.

Figure 5 – A-C, Lymph node EBUS image patterns. D-G, Images obtained during EBUS-guided TBNA. A, Hypervascular node detected on Doppler mode; this finding may guide the operator to avoid using suction during TBNA to potentially prevent a bloody specimen. B, “Central hilar structure,” defined as a hyperechoic area in the center of the node (arrow), is a sonographic sign that may predict a benign etiology. C, Coagulation necrosis sign is characterized by hypoechoic areas (arrows) inside the node without blood flow (Doppler negative). Sometimes this can occupy the entire node. The presence of coagulation necrosis sign has a high specificity and hazard ratio for prediction of malignancy. D, EBUS-TBNA of the 4L lymph node; the needle is seen at the proximal aspect of the node. E, During the same maneuver, the needle is advanced to the distal capsule of the node; this back-and-forth movement from capsule to capsule is warranted, as malignant cells may cluster in subcapsular zones. EBUS-TBNA using a 25-gauge pro-core needle from a large mass. G, During the same maneuver, by extending the lever of the bronchoscope, the needle direction is changed to sample different areas of the node. See Figure 4 legend for expansion of abbreviations.
Restaging the Mediastinum

Induction therapy followed by surgery is an option for treating patients with stage IIIA NSCLC with discrete mediastinal node involvement. Studies demonstrate the benefit of induction chemotherapy to surgical resection for patients with clinical N2 disease. If this approach is chosen, the role of mediastinal restaging after induction therapy remains unclear, but downstreaming and complete pathologic response are good prognostic factors. Some authorities suggest that surgery should only be performed in those patients who have a response in the mediastinum to induction therapy. In this regard, both CT and PET imaging for restaging have been shown to be inaccurate.

Invasive restaging, therefore, is warranted if restaging is to be performed. Restaging of the ipsilateral N2 nodes by VATS has been done, but this is limited by radiation and sometimes anatomy (ie, 4R station), resulting in a sensitivity of only 67% and NPV of 73%. A repeat mediastinoscopy has a sensitivity of about 70% to 82% but may pose a technical challenge, and in some series the sensitivity was as low as 30%. As a general concept, the less invasive the staging is, the easier the restaging. Because a first-time mediastinoscopy may be the optimal way to accomplish mediastinal restaging, an argument can be made to always use a needle-based technique initially to document N2/3 involvement, as suggested by current guidelines, and to save mediastinoscopy, if needed, for restaging after induction therapy (Fig 6). Two studies, however, show that EBUS has a sensitivity of 64% and 76%, respectively, for restaging, so that EBUS may be attempted as a first restaging technique. There is still no reliable way of restaging the mediastinum, and none of the above-mentioned methods can be considered preferred. The choice may depend on the availability of EBUS, surgical expertise, and the invasive method used for the initial staging.

Conclusions

Accurate assessment of mediastinal lymph node involvement in NSCLC is relevant for treatment and prognosis. Recently updated lung cancer guidelines recommend EBUS over surgical staging as a best first test for patients with intermediate and high suspicion of N2, 3 lymph node involvement. These include patients with discrete mediastinal lymph node enlargement on CT or PET scan uptake and patients with radiographically normal mediastinum (by CT and PET scan) and a central tumor, N1 lymph node enlargement, or tumor size > 3 cm. Preoperative invasive staging for clinical stage IA is not currently recommended, but EBUS staging may be warranted in nonsurgical candidates to confirm N0 disease prior to SBRT. EBUS-TBNA is a coordinated sequence of events that includes collection of relevant clinical information, optimal lymph node sampling, specimen preparation and staining, interpretation, communication, and reporting. Advancements in sampling techniques, ultrasound, and needle technology may further improve the diagnostic yield of EBUS and the quality of the samples to guide biomarker-driven lung cancer therapy.

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