EBUS-TBNA/Staging of Lung Cancer

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KEYWORDS
- Endobronchial ultrasound
- Transbronchial needle aspiration
- Positron emission tomography/computed tomography
- Lung cancer

KEY POINTS
- In the staging of mediastinal lymph nodes before lung cancer surgery, endobronchial ultrasound transbronchial needle aspirations (EBUS-TBNA) has proven to be highly sensitive and specific as well as safe.
- Although positron emission tomography/computed tomography (PET/CT) has been a major development in the preoperative workup of patients with lung cancer, EBUS-TBNA has superior test performance and PET/CT cannot be regarded as a substitute for tissue sampling with EBUS-TBNA.
- In general, EBUS-TBNA staging is needed for any patient with CT nodes greater than 1 cm in short axis, or PET-positive mediastinal nodes.
- Large studies of EUS staging have confirmed the place of sampling mediastinal nodes via the esophagus, giving complementary access to posterior and inferior lymph node stations.
- EBUS-TBNA can detect micrometastatic disease in CT-negative and PET-negative mediastinal nodes.

RADIOLOGY INVESTIGATIONS AND STAGING—COMPUTED TOMOGRAPHY, POSITRON EMission TOMOGRAPHY, POSITRON EMission TOMOGRAPHY/COMPUTED TOMOGRAPHY

By convention, computed tomography (CT) of mediastinal lymph nodes regarded nodes greater than 1 cm in the short axis to be abnormal.\textsuperscript{1–4} It is widely known that this criterion lacks both sensitivity and specificity. Reported predictive ability of CT for mediastinal lymph node metastasis shows sensitivity ranges of 57% to 68% and specificity range of 76% to 82%. The advent of positron emission tomography (PET) scanning radically improved mediastinal node staging. Using the fluorine-18 fluorodeoxyglucose (FDG) tracer, positron emission tomography (PET) demonstrates abnormal metabolic uptake, which often precedes change in node size, providing a sensitivity of 79% to 85% and a specificity of 87% to 92%.\textsuperscript{1–4}

Further studies over the last 10 years have demonstrated the additional benefits of PET/CT, which was an advantage because of the poor anatomic detail of PET.\textsuperscript{5,6} An early study by Antoch and coworkers showed in 27 patients that PET/CT findings led to a treatment change for 4 patients (15%) when compared with PET alone.\textsuperscript{7} Differences in the accuracy of overall tumor staging between PET/CT and PET (\(P = .031\)) were significant.

Another study showed that in 129 patients integrated PET-CT is a better predictor than PET for N status (78% vs 56%, \(P = .008\)). It was more accurate for the total N2 nodes (96% vs 93%, \(P = .01\)) and for the total N1 nodes (90% vs 80%, \(P = .001\)).

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Integrated PET-CT was significantly more sensitive at the 4R, 5, 7, 10L, and 11 stations and more accurate at the 7 and 11 lymph node stations than dedicated PET. A more recent study by Bille and colleagues\(^9\) studied 1001 nodes in 159 patients before lung resection who were clinically N0 in the mediastinum. Of 71 nodes that were ultimately found to be positive histologically, PET/CT correctly identified 41 metastatic lymph node stations (57.7%; 19 N1, 22 N2). False negative results were obtained in 30 nodal stations (5 N1, 24 N2, 1 N3), and false positive results in 14 (5 N1, 9 N2). The most common lymph node station for occult metastatic involvement was in the subcarinal level (8 of 30 [26.6%]) followed by right upper and lower paratracheal and hilar levels (4 each of 30). Through systematic pulmonary and mediastinal lymph node dissection, 22 patients (13.8%) were falsely understaged and 9 patients (5.7%) were falsely overstaged. These authors concluded, “PET/CT was well below the threshold of 95% at which the test could replace invasive staging procedures.”

A recent meta-analysis has explored the negative predictive value of PET/CT in evaluating the mediastinum in clinical T1 and T2 tumors with no enlarged mediastinal nodes on CT\(^{10,\text{11}}\). Ten studies were analyzed and all used mediastinoscopy and/or surgical staging to confirm nodal status. Negative predictive value of PET/CT ranged from 94% in T1 to 89% for T2 tumors.

**MEDIASTINOSCOPY**

In 2003 Toloza and colleagues\(^{11}\) published a meta-analysis of mediastinoscopy for lung cancer staging in 5687 patients. Results are as shown in Table 1. Major morbidity was seen in 2% including recurrent laryngeal nerve paresis (0.55%), hemorrhage (0.32%), tracheal injury (0.09%), and pneumothorax (0.09%). Mortality occurred in 0.08%. Results for a large, single-center experience by Lemaire and coworkers are also shown.\(^{12}\)

### Table 1

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<th>Patients with lung cancer mediastinoscopy results</th>
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LEUKOCYTES STUDIED 61 PATIENTS WITH KNOWN OR SUSPECTED EXPERIENCE OF HERTH AND COLLEAGUES. 15

Ernst and colleagues used 2-step balloon EBUS and standard TBNA for the presurgical staging of operable patients with lung cancer, as shown in Table 1.13,14 All of the studies reported on the convex probe bronchoscopy but in the report of Adams and coworkers,13 2 early studies that used 2-step balloon EBUS and standard TBNA are included. Table 1 also shows the single-center experience of Herth and colleagues.15

They performed EBUS-TBNA in 97 patients with presumed or known non-small-cell lung cancer (NSCLC) and PET and CT-negative mediastinum. They sampled 156 nodes, with a diameter of 7.9 ± 0.7 mm, and all patients had node tissue confirmed by mediastinoscopy or node dissection. There was a prevalence of malignancy of 9 patients, 8 of which were detected by EBUS. The node that was missed was at station 10.

Studies directly comparing EBUS-TBNA staging and mediastinoscopy have shown no advantage to mediastinoscopy and excellent diagnostic performance of EBUS-TBNA.16 Ernst and colleagues studied 61 patients with known or suspected lung cancer; a final diagnosis of cancer was made in 57 patients. Comparison was made for nodes larger than 1 cm at stations 2, 4, and 7. A total of 120 nodes were sampled, with a mean diameter of 15 mm in the short axis. The diagnostic yield of EBUS-TBNA was 109/120 compared with 94/120 for mediastinoscopy (P = .007). The combination of EBUS and mediastinoscopy gave a yield of 115/120, which was not significantly better than EBUS alone. These authors therefore concluded that a normal EBUS-TBNA could allow a patient to proceed to surgery without mediastinoscopy.

A comparison to PET was important given the potential of this technique in stratifying risk of mediastinal involvement. In an important study, Yasufuku and colleagues performed a direct comparison of CT, PET, and mediastinal node sampling by EBUS-TBNA. They studied 102 patients with 147 mediastinal and 53 hilar lymph nodes of whom EBUS-TBNA proved malignancy in 37 lymph node stations in 24 patients. The sensitivities of CT, PET, and EBUS-TBNA for the correct diagnosis of mediastinal and hilar lymph node staging were 76.9%, 80.0%, and 92.3%, respectively; specificities were 55.3%, 70.1%, and 100%, and diagnostic accuracies were 60.8%, 72.5%, and 98.0%. All values for EBUS-TBNA were significantly better than both CT and PET.

Cerfolio and colleagues reported a retrospective series of EBUS (and EUS) staging in suspicious enlarged N2 nodes. Of 234 patients, 72 patients had an EBUS. Sixteen were true positive for N2 disease; however, 12 were false negative. The median diameter of the false-negative nodes was 12 mm. Four passes of the node were performed and rapid on-site evaluation of samples was made. The authors state the series was relatively early in their EBUS experience and the results do not state whether adequate lymph node material was obtained at EBUS. As expected, they concluded that negative sampling in suspicious nodes should be followed by mediastinoscopy or surgical staging. In an article supporting the preoperative staging of the mediastinum by surgeons using EBUS and EUS, Groth and Andrade also recommended that nonmalignant EBUS or EUS cytologic findings should be confirmed with mediastinoscopy or thoracoscopy if the pretest probability of malignancy is high.

In 2011 Yasufuku and coworkers reported a large series of 153 patients with lung cancer undergoing surgical staging. These cases were mostly radiological N0 or N1 (64% of cases), and the short-axis diameter of nodes sampled was only 6.9 ± 3 mm. In the same anaesthetic, patients had EBUS-TBNA by 1 of 3 operators followed by mediastinoscopy. The average number of nodes sampled by EBUS was 3 and by mediastinoscopy was 4. The sensitivity, specificity, negative predictive value, and diagnostic accuracy of EBUS-TBNA were 81%, 100%, 91%, and 93%, respectively. The results for mediastinoscopy were 79%, 100%, 90%, and 93%, respectively. There were 8 false negative lymph node stations on EBUS-TBNA compared with 14 false negative lymph node stations on mediastinoscopy. Inadequate lymph node sampling was seen in 122 lymph nodes on EBUS-TBNA; these nodes were mostly less than 5 mm, and none were subsequently shown to have metastatic cancer at mediastinoscopy or thoracotomy. Conversely 10 lymph node stations were thought to have inadequate sampling on mediastinoscopy (lacking lymphoid tissue). This very detailed study demonstrates a great deal of skill on the part of the EBUS operators sampling very small nodes. However, by including these small nodes, the authors have shown the maximal capability of the technique. Others doing EBUS-TBNA for staging may not necessarily attempt such detailed staging of small nodes in CT and PET-negative cases except in a relatively select group of patients, as mentioned above.

EBUS-TBNA has also been reported in several studies as restaging after preoperative therapy.
for lung cancer. Herth and colleagues\textsuperscript{21} reported a series of 124 patients restaged with EBUS-TBNA after induction chemotherapy. Of these, 66 had a partial response by CT criteria. Overall the sensitivity by EBUS-TBNA for detecting persistent disease was 76%; however, the negative predictive value was only 20%, indicating the need for surgical restaging in EBUS-TBNA-negative samples in this group of patients. The lower sensitivity was attributed to nodes being altered by necrosis and fibrosis from chemotherapy.

**EUS COMBINED WITH EBUS IN STAGING**

Numerous studies investigated EUS as a staging and diagnostic tool for mediastinal nodes.\textsuperscript{22,23} In one large study by Annema and colleagues,\textsuperscript{22} operable patients were randomized to either surgical staging or EUS plus surgical staging. Node metastases were found in 41 and 56 patients, respectively; sensitivity for surgical staging alone was 79% compared with 85% with the addition of EUS. Unnecessary thoracotomy occurred in significantly fewer patients with the addition of EUS (21 vs 9, \( P = .02 \)).

In view of the clear complementary anatomic reach of EBUS and EUS, studies combining the 2 modalities were undertaken. Vilmann and Pur\textsuperscript{24} demonstrated the concept in a 2005 study in 33 patients. Twenty patients had abnormal nodes and 13 had masses. EUS sampled 59 lesions, and EBUS sampled 60 lesions. With combined EUS-fine needle aspiration [FNA] plus EBUS-TBNA in 28 of the 31 patients in whom a final diagnosis was obtained in the evaluation of mediastinal cancer, 20 patients were found to have mediastinal involvement, whereas no mediastinal metastases were found in 8 patients. The accuracy of EUS-FNA and EBUS-TBNA, in combination, for the diagnosis of mediastinal cancer was 100% (95% CI, 83%–100%). With EBUS-TBNA, 11 additional cancer diagnoses were made compared with EUS, and 3 had “suspicious cells” that had not been obtained by EUS-FNA. Conversely, with EUS-FNA, 12 additional cancers were found compared with EBUS, as well as one “suspicious cells” case and 1 sarcoidosis in addition to EBUS-TBNA.

Rintoul and colleagues\textsuperscript{25} studied EBUS and EUS-FNA for mediastinal staging in 18 patients with 26 lymph nodes. All had EBUS-TBNA. An additional EUS examination was performed in patients in whom the staging CT scan had demonstrated enlarged lymph nodes inaccessible by EBUS (ie, stations 5, 8, and 9, and posteroinferiorly placed lymph nodes in station 7). Seven patients had both procedures, and of these 5 patients had additional pathologic abnormality detected on EUS compared with EBUS (3 true positive, 2 true negative).

Ohnishi and colleagues\textsuperscript{26} showed that in 110 patients the combination of EBUS and EUS had a combined sensitivity and negative predictive value of 72% and 89%, compared with PET/CT, which had results of 47% \((P < .0001)\) and 76%.

EBUS and EUS-FNA combined have been studied in the radiologically normal mediastinum in NSCLC staging. In a study by Szlubowski and colleagues\textsuperscript{27} of 120 patients clinically CT N0, nodes were abnormal for malignancy by FNA in 31/318 nodes (10%). Extensive mediastinal node dissection with TEMLA (transcervical extended bilateral mediastinal lymphadenectomy) was performed as confirmation in aspirate negative cases; 99 patients with negative FNA had TEMLA with 9 patients positive (8%). This low figure of false negative sampling for the combined technique in micrometastatic disease demonstrates its sensitivity. These authors had a sensitivity of 68%, which is understandable given the low prevalence of positive cases in this series. They concluded, “In the radiologically normal mediastinum, EBUS/EUS is a highly effective and safe technique in NSCLC staging and, if negative, a surgical diagnostic exploration of the mediastinum may be omitted.”

In a large randomized series conducted at 4 centers, Sharples and colleagues\textsuperscript{28} have reported results of surgical staging alone \((n = 118)\) compared with endosonography (EBUS plus EUS) followed by surgical staging if endosonography was negative \((n = 123)\). Sensitivity for detecting N2/N3 metastases was 79% \((41/52; 95\% \text{ confidence interval [CI]} 66\%-88\%)\) for the surgical arm compared with 94% \((62/66; 95\% \text{ CI } 85\%-98\%)\) for the endosonography strategy \((P = .02)\). In the sonography arm it was possible to separate out sensitivity and negative predictive value for sonography alone \((85\% \text{ and } 85\%)\) versus surgical staging alone \((79\% \text{ and } 86\%)\).

The ASGE recommendations for EUS staging and combined EBUS/EUS staging are as follows\textsuperscript{29}:

- EUS-FNA in patients with paraesophageal, posterior, and inferior mediastinal adenopathy, if the expertise if available.
- EBUS-FNA in patients with paratracheal mediastinal adenopathy if this information adds to the staging of the lung cancer.
- EUS-FNA and EBUS-FNA have been shown to be safe and potentially cost-effective compared with mediastinoscopy, although individually each has a high false negative rate that warrants surgical confirmation before proceeding with resection.
In patients with known or suspected potentially resectable lung cancer whose imaging shows no evidence of mediastinal adenopathy, the authors suggest combined EUS-FNA/EBUS-FNA for staging.

Combined EUS-FNA/EBUS-FNA has been shown to have a negative predictive value comparable to that of mediastinoscopy. However, expertise in both modalities is not readily available at most institutions.

**EUS USING A CONVEX PROBE BRONCHOSCOPE**

Pulmonologists have used an EBUS-TBNA scope in the esophagus to perform sampling that had previously only been performed by EUS endoscopes.\(^{30,31}\) This method is known as either EUS-B-FNA or EBUS TENA (Trans Esophageal Needle aspiration). The potential advantages are that only one scope needs to be used per case, no additional training in using the scope is required and it builds on the experience of other specialties accessing organs through the esophagus such as trans-esophageal echo by cardiologists and anesthetists. Herth and colleagues\(^{30}\) studied 139 consecutive patients, with a primary lung cancer with nodes larger than 1 cm needing evaluation with PET having been performed as clinically indicated. EBUS and EBUS-TENA were performed in all patients with a mean of 1 to 2 nodes sampled by each method. From 71 patients with malignant nodes, the numbers positive by the bronchus, esophagus, and combined were as follows: 65, 63, and 68 (96% sensitivity), which meant that by adding the esophageal examination, an additional 3 patients were found abnormal.

A contemporaneous study was performed by Hwangbo and coworkers.\(^{31}\) In 150 patients with lung primary, following PET scan, staging EBUS-TBNA was performed followed by EUSB-FNA on nodes that were inaccessible or difficult. EBUS sampled 310 lesions (mostly nodes), and then EUSB-FNA was performed in 64 lesions in 54 patients. The reasons were as follows: 12 nodes were inaccessible by EBUS, 47 nodes were technically difficult by EBUS, and 5 had poor sampling by EBUS. By patient, overall there were also 3 patients where EUSB FNA was abnormal when EBUS was normal or impossible. One of the EBUS-negative and EUS-positive cases was 4L; it was accessible by EBUS but easier to sample by EUS. The overall success of sampling was high (41 of 45 nodes); 2 of the 4 negative nodes in the series were in sites unreachable by either method (stations 3 and 6).

In a 2012 study Szlubowski and coworkers compared a sampling of the esophageal route by EBUS scope with EUS scope.\(^{32}\) It was a non-randomized study of 214 patients undergoing preoperative staging. EUS-FNA was performed in 110 patients (CUS), whereas 104 patients had EUS-B-FNA plus EBUS-TBNA (CUSb). In patients with normal results, an appropriate pulmonary resection with the systemic lymph node dissection (SLND) of the mediastinal nodes was performed. Overall, no significant differences were observed with sensitivity and specificity for the EUS scope being 92% and 98% and with the EBUS scope being 85% and 93%, respectively. In 55 CUS-negative (50%) and 53 (51%) CUSb-negative patients with NSCLC, the subsequent SLND revealed metastatic nodes in 5 patients (4.5%) and in 9 patients (8.7%), respectively \((P = NS)\). There was “minimal N2” in 11 of these 14 patients (5 in the CUS group and 6 in the CUSb group)—with no predominance for any nodal station (except 3 patients with right upper lobe tumor, all with false negative results in station 2R/4R). In 3 patients with false negative results of CUSb, a multilevel N2 was diagnosed by means of SLND. This interesting study, although not randomized, shows promise for the use of the EBUS-TBNA bronchoscope in this way. The authors were surgeons and adept at use of both endoscope and bronchoscope, which supports such a comparison being done.

The EUS endoscope has a better radial range of imaging: 120° to 180° compared with 70° of the EBUS scope.\(^{32}\) Furthermore, it is reported to be easier to orient and allows deeper penetration of both the ultrasound image and the needle, also allowing sampling of the adrenal gland in selected cases. As an editorial commenting on the EBUS/esophageal studies stated, “If only an EBUS scope is available for the detection of mediastinal nodes, a transesophageal (EUS) investigation should be performed with it as well to improve preoperative tumor staging. That said, we still believe that a dedicated EUS scope has additional benefit and should be part of a complete diagnostic unit.” That is, gastroenterologists in mediastinal staging support the use of the EUS scope, although the studies suggest in practice the EBUS scope gives satisfactory sampling.

Although it is possible to use an EBUS scope in this way, authors have questioned whether it is worthwhile given the relatively few extra cases it picks up (3 extra from 150 cases).\(^{34}\) Also, although EUS accesses station 5 well, if that node is enlarged, 4L usually is as well, and accessible by EBUS. Furthermore, it is very uncommon to see
isolated station 8 or 9 nodes without, for example, associated station 7 nodes.

Overall, in mediastinal staging there are real but small benefits to staging by adding EUS. It could well be possible to anticipate those cases whereby EUS-FNA was needed (predominantly low and posterior lymph nodes on preprocure PET/CT), or to use rapid on-site assessment of specimens and move between modalities in difficult node stations such as 2L or 4L. Also, it seems using an EBUS scope seems to have the same benefits as a full EUS scope; however, different training expectations in different countries are likely to affect uptake of the method.

WHICH PATIENTS NEED MEDIASTINAL NODE TISSUE SAMPLING FOR STAGING?

Given the previous considerations, it is clear that where a patient is operable, a positive PET scan requires tissue confirmation of mediastinal nodes with abnormal uptake. If a PET scan is normal, there are some situations whereby node staging should be performed. These situations include if the tumor is central, if positive N1 nodes on CT or PET are seen, if mediastinal nodes larger than 1 cm on CT are seen, and in the setting of low FDG uptake in the primary tumor. If a PET scan is normal, there are some situations whereby node staging should be performed. These situations include the following:

- If the primary tumor is central; in a study of the role of preoperative PET/CT, test performance of PET/CT was relatively poorer in central tumors in predicting N stage, with Cohen’s kappa statistic of 0.39, only a fair correlation with tissue sampling.
- If positive N1 nodes on CT or PET are seen.
- If mediastinal nodes larger than 1 cm on CT are seen, with negative PET uptake; in the study by Fischer and colleagues, there was a lower negative predictive value for larger lymph nodes than those less than 1 cm (70% compared with 96% for small nodes). This lower negative predictive value could be accounted for by a higher overall prevalence of tumor cells in larger nodes; with similar sensitivity and specificity it meant there were more falsely negative nodes by PET/CT in the larger nodes. Although there is value in a negative PET/CT in normalized mediastinal lymph nodes, the risk of a false negative diagnosis is 30% in enlarged lymph nodes without FDG uptake.
- In the setting of low FDG uptake in the primary tumor.

PRACTICAL ASPECTS OF EBUS-TBNA STAGING AND TIPS

Before the procedure, it is important to consider which nodes would be N3 in a given patient and sample that first, preferably with onsite cytology examination. Demonstrating negative N3, the next nodes to be sampled are N2 followed last by N1 if N2 is negative. It is not sufficient to flush needles with saline between stations, as some cells from the first aspirate may contaminate subsequent samples. If no onsite assessment is possible, it may be necessary to change needles, therefore, between sampling of N3 and N2 and N1 nodes, depending on the situation.

Lymph nodes being sampled in staging procedures are often small and can be difficult to access. An understanding of the way metastatic cells occupy nodes is important to maximize the chance of obtaining true positive aspirates. Furthermore, where aspirated material is equivocal on cytology, it may be possible to use the features of the actual EBUS image to support a benign tissue diagnosis, which includes both the vascular patterns and the grayscale pattern of the nodes.

The flow of lymph into lymph nodes occurs via channels that drain predominantly into the subcapsular sinusoids and then to the parenchymal sinusoids. This flow pattern is responsible for the observation that small metastases of breast cancer identified on hematoxylin & eosin sections are usually located in the subcapsular sinusoids. Viale and colleagues reported that metastases were largely found in the subcapsular zone where afferent lymphatics enter lymph nodes. Cserni studied the localization of metastases in the sentinel lymph nodes of patients with breast cancer. In 23 (72%) of sentinel nodes of 32 node-positive patients, metastases were more likely to be localized or more voluminous on the inflow side of the lymphatics draining from the tumor.

While puncturing the lymph node using EBUS, it is easier to puncture the center area than the marginal area (Fig. 1). Kurimoto and colleagues histopathologically investigated 124 resected metastatic lymph nodes in patients with lung cancer. In 20% to 25% of lymph nodes, metastases were only detected in the marginal area of the lymph node. Therefore, if the onsite cytologic evaluation by EBUS-TBNA is negative after puncturing into the center of the lymph node, it is recommended to puncture the needle into the marginal area of the lymph node.

For obtaining sufficient specimens, the authors usually perform the “outer sheath method.” This outer sheath method comprises pressing the outer sheath of the puncture needle against the
bronchial wall immediately before puncture, then moving the entire bronchoscope back up the wall and performing the puncture after the tip of the outer sheath is caught in a concavity between 2 rings of cartilage, which can be observed on the monitor, watching the top right of the image for the sheath to “drop” between 2 cartilages.

During aspiration biopsy, it is important to avoid necrotic areas in lymph nodes—this can be achieved by targeting areas of the node with maintained blood supply as demonstrated by power Doppler.\textsuperscript{42,43} Use of power Doppler imaging to detect nodal vessels and biopsy of perivascular tissue may possibly increase the rate of diagnosis, particularly when metastasis of squamous cell carcinoma or small cell carcinoma is suspected. In the authors’ experiences, vessels in metastatic lymph nodes wind irregularly, and vessels in sarcoidosis run straight inside lymph nodes. Also, in sarcoidosis, the hyperechoic interface echo between clumped lymph nodes is always found (Fig. 2). The surface of these nodes is relatively flat. Diagnostic accuracy of 92\% is obtained using the presence of this flat interface for ruling in sarcoid (plus absence of the interface indicating malignancy).

Patterns of intranodal vessels with power Doppler are classified as (1) straight vessels from the hilum (Fig. 3), (2) aberrant vessels (Fig. 4), (3) subcapsular vessels, and (4) decreased perfusion. Three patterns (aberrant vessels, subcapsular vessels, decreased perfusion of intranodal vessels) in metastatic nodes were found in metastatic lymph nodes, diagnostic accuracy also 92\%. Combining the appropriate vascular and interface echo patterns gives diagnostic accuracies of 95\% and 94\% for sarcoi’d and malignancy, respectively.

**ASSESSMENT OF EBUS IMAGES USING COMPUTER ANALYSIS**

There is a long history of attempting to use aspects of B-mode images to “support” a tissue diagnosis. Adibelli and colleagues\textsuperscript{44} investigated cervical lymph node echogenicity, contour, longitudinal-to-transverse diameter ratio, and the presence of the hilus and identified only the presence of the hilus as a significant discriminator. Cole and colleagues\textsuperscript{45} documented that, in node metastases with maximum diameter \( \geq 15 \) mm, sensitivity and specificity of ultrasonography were 81.3\% and 81.6\%, respectively. Kebudi and colleagues\textsuperscript{46} diagnosed axillary lymph node metastasis of breast cancer using B-mode ultrasound based on centric echogenicity, cortical thickening, length/width ratio, and lymph node diameter and reported a sensitivity of 79.1\%, specificity of 77.7\%, positive predictive value of 82.6\%, and negative predictive value of 73.6\%.

**Fig. 1.** A representative metastatic lymph node (squamous cell carcinoma). Metastasis (arrow) was largely found in the subcapsular zone.

**Fig. 2.** The interface echo. The hyperechoic interface echo between lymph nodes means that the surface of the lymph nodes is relatively flat and the space between lymph nodes exists.

**Fig. 3.** Straight vessels from the hilum (sarcoidosis). Straight Intra-nodal vessels branching from hilum.
Starting around 1986, research began on computer-assisted support systems known as artificial neural networks (ANN).47 ANN has been studied as a system mimicking the biologic nervous system48 and is currently used in pattern recognition. The diagnostic sensitivity, specificity, and accuracy of ANN using ultrasound of cervical lymph node metastasis from oral cancer have been reported at 80.6%, 94.6%, and 93.6%, respectively,49 and these figures are comparable to CT and magnetic resonance imaging. Tagaya and colleagues50 reported that the diagnostic accuracy of ANN for peribronchial lymph node malignancy was 91.2%, significantly higher than that for the surgeon with 5 years of experience at 78%.

Automated grayscale analysis of EBUS images has shown correct classification of benign versus malignant in 44 of 51 lymph nodes (86.3%).51 Other new technologies in computer-aided diagnosis will appear in the near future.

MICROMETASTATIC DISEASE AND ISOLATED TUMOR CELLS

The clinical significance of occult disease in N2 nodes is relevant to this review because numerous studies now report positive aspirates in normalized and PET-negative nodes.15 The term micrometastatic disease refers to lymph nodes, which have been surgically resected and undergone immunohistochemistry to detect malignant cells that were not seen on standard hematoxylin & eosin sections. Several studies have in fact documented life expectancy in cohorts of patients with such nodes compared with those with no micrometastatic disease in surgically resected nodes; 3 groups found a significant survival reduction.52–54 More relevant to the present discussion are nodes with isolated tumor cells (ITC), defined as single tumor cells or small clusters of cells, smaller than 0.2 mm in greatest diameter, whereas micrometastases are clusters of tumor cells measuring between 0.2 and 2 mm in greatest diameter.55 Rena and colleagues55 reported a series of 87 patients resected for T1 carcinoma, of whom 19 nodes in 14 patients had either micrometastases or ITC. Two-year and 5-year recurrence-free survival was similar for patients with either micrometastases or ITC, and these authors concluded that the significance of the detection of this remained controversial.

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