Diagnostic Imaging and Newer Modalities for Thoracic Diseases

PET/Computed Tomographic Imaging and Endobronchial Ultrasound for Staging and Its Implication for Lung Cancer

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KEYWORDS

• Chest radiograph • Computed tomography • PET • MRI • Endobronchial ultrasound • Esophageal ultrasound • Navigational bronchoscopy

KEY POINTS

- Computed tomographic (CT) scanning is the test of choice to identify nodules (ie, low-dose CT scanning) and then to further delineate the abnormality (high-resolution CT scanning).
- Integrated PET/CT imaging is superior to either CT scan or PET imaging by itself in accurately characterizing lung cancers.
- Endobronchial ultrasound and esophageal ultrasound must be used in a strategically advantageous manner relying on their individual strengths to maximize their efficacy in the diagnosis and staging of lung cancer.

INTRODUCTION

Tailoring the optimal diagnostic approach for lung cancer requires that a defined goal be based on the results of any study that is planned. Modalities to detect and characterize lung cancer generally can be divided into those that are invasive versus those that are noninvasive. Aside from the standard chest radiograph (CXR), the noninvasive imaging techniques include computed tomography (CT), PET, and MRI. The invasive

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imaging modalities include endobronchial ultrasound (EBUS), esophageal ultrasound (EUS), and electromagnetic navigational bronchoscopy (ENB).

NONINVASIVE MODALITIES

Computed Tomographic Scans

- CT scanning is the test of choice to identify nodules (ie, low-dose CT [LDCT] scanning) and then to further delineate the abnormality (ie, high-resolution CT scanning)

The National Lung Screening Trial (NLST) was the landmark prospective randomized, controlled study that revealed a significant decrease in lung cancer–related mortality of 20% when LDCT scans were used (6.8%) compared with CXR alone (26.7%) in the 53,454 participants who were considered to be at "high risk." High risk was defined in this study as those patients who were current smokers or who were former smokers with a total of 30+ pack-years, aged 55 to 74 years old, as long as they had quit within the past 15 years[1] (**Box 1**). The results of this trial as well as others studies evaluating CXRs for lung cancer screening have led to guidelines recommending its avoidance as a lone screening test for lung cancer because it may miss detecting 4 times as many lung cancers compared with with scans.[2–4] Before the NLST, the International Early Lung Cancer Action Program (I-ELCAP) first demonstrated improvements in screening for smokers at high risk for lung cancer.[5] The I-ELCAP subsequently showed that CT imaging detected 4 times more lung cancers and 6 times more stage I lesions as compared with CXR alone when used in the context of screening a higher-risk population.[3–5] Cumulatively and particularly with the results of the NLST, the observed reduction in lung cancer–related mortality now serves as the backbone for the lung cancer screening recommendations from many organizations, including the US Preventive Services Task Force.[1,2,6–11]

From a technical standpoint, a lung cancer screening CT scan should involve low-dose helical (spiral) images from the thoracic inlet moving caudally to the inferior edge of the liver, ensuring that the adrenal glands are included. CT images must be viewed with less than or equal to 2.5-mm slice thickness and with reconstruction intervals less than or equal to slice thickness.[12,13] Additional imaging data may be acquired and reconstructed at less than or equal to 1.0-mm slice thickness and reconstruction intervals to allow for better characterization of small lung nodules.[12] Advanced technology in current iteration CT scanners allows for a high-resolution, comprehensive evaluation of the thorax in a single, several-second breath-hold.[14] Respiratory and cardiac motion artifacts are reduced with rapid acquisition, thereby allowing for more accurate lung nodule depiction, especially in areas that are harder to investigate such as in the bases of the lungs or in the lung parenchyma immediately adjacent to the mediastinum. Newer visualization techniques include maximum intensity projection, volume rendering, stereographic display, and computer-aided detection, which allow for enhanced lung cancer detection and enable the radiologist to better differentiate small lung nodules from other structures.[14] These technologies have also allowed for multiplanar reconstructions, which can then be used to generate 3-dimensional depictions of vascular and bronchial anatomy for potential future operative planning.

Computed tomographic scans in assessing pulmonary nodules

Pulmonary nodules are one of the most common findings on thoracic imaging, and therefore, it is imperative to make as accurate of a characterization as possible.[15] The size of a pulmonary nodule has been thought to correlate with the prevalence of malignancy: less than 5 mm, 0% to 1%; 5 to 10 mm, 6% to 28%; 10 to 20 mm,

Box 1
Key elements of annual lung screening guidelines endorsed by United States Preventative Services Task Force with further modifications endorsed by the other organizations (endorsing organizations in parentheses)

Inclusion Criteria

Age
55 to 80 years
55 to 79 years (AATS)
55 to 74 years (ACCP, ACS, ASCO, NLST, NCCN)

Tobacco History (ACCP, ACS, ASCO, NLST, NCCN)
Former smoker with a 30+ pack-year smoking
Former smoker quit within the past 15 years
Current smoker

Additional (NCCN, AATS)
Age 50+ years *and* tobacco history of ≥20+ pack-year with at least one additional lung cancer risk factor:
- Major exposure to arsenic, beryllium, oadmium, chromium, nickel, asbestos, coal smoke, soot, silica, and diesel fumes
- Other cancers (small cell lung cancer, head cancers, neck cancers, Hodgkin lymphoma)
- Received radiation treatment to chest for other disease
- Family member with lung cancer (ie, parent, sibling, or child)
- History of COPD
- History of pulmonary fibrosis
- Second-hand smoke exposure

Exclusion Criteria

Age
Less than 55 years
Greater than 80 years

Tobacco History
Less than 30 pack-years
Quit greater than 15 years ago

Comorbidities (ASCO)
Severe comorbidities precluding potentially curative treatment and/or limit life expectancy (ASCO)

Discontinuation of Screening

Once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery

Abbreviations: AATS, American Association for Thoracic Surgery; ACCCP, American College of Chest Physicians; ACS, American Cancer Society; ASCO, American Society for Clinical Oncology; COPD, chronic obstructive pulmonary disease; NCCN, National Comprehensive Cancer Network.

33% to 60%; and greater than 20 mm, 64% to 82%.[16] Although there are variations, the more commonly accepted definition of a pulmonary nodule by CT imaging is a lesion with a diameter less than 30 mm. A pulmonary mass is considered to be a lesion greater than 30 mm.[17]

LDCT identifies small nodules in 10% to 50% of those screened with the vast majority of these being benign.[1–3,18] The wide range seen with nodule detection with CT scanning is not readily explained. Accurate staging for primary lung cancer requires precise demarcation of the tumor margin to assess the primary tumor (T) descriptor,

and this delineation is best accomplished with thin-slice high-resolution CT scanning.[13] Therefore, when an LDCT scan identifies a suspicious finding, a dedicated chest high-resolution CT (HRCT) scan should be pursued (**Fig. 1**). LDCT (20–50 mAs) has been shown to be comparable to conventional CT mode (140–300 mAs) in sensitivity and specificity for the detection of pulmonary nodules.[4] There is a significant difference in the radiation in LDCT scanning that ranges from 1.3 to 3.4 mSv, whereas in high-resolution CT imaging, it is 8.5 to 14.0 mSv.[19] In this context, a slice thickness, reconstruction interval of 1.5 to 2.5 mm provides a useful compromise between accurate demarcation of the tumor margin and image noise.[13,20] The noise that is identified typically is an irregular granular pattern in the images, which degrades image information.[21]

Lesions less than 3 mm are extremely difficult to identify on CT imaging because such small abnormalities are difficult to decipher from the lung's normal architecture, especially depending on the location of the presumed nodular finding.[22] The role of nodule location is particularly relevant with small lesions. These lesions are extremely difficult to identify when they are low apparent density or in a central location. Not surprisingly, peripheral lesions are identified more frequently (74%) compared with central (49%) and perihilar lesions (37%), owing to the absence of confounding structures that would be of similar size in the periphery.[22]

Computed tomographic scan in assessing regional lymph nodes

CT scanning has a sensitivity of 47% to 54% and a specificity of 84% to 88% in identifying abnormal hilar and mediastinal lymph nodes with roughly 40% of all nodes thought malignant (as defined by being >1 cm on short-axis diameter) actually being benign and 20% thought benign (as defined by being $\leq$1 cm on short axis) actually being malignant.[23] Volumetric CT histogram analysis is a relatively new means by which lymph nodes on CT can be evaluated.[24] Flechsig and colleagues[24] demonstrated a significant correlation between lymph node Hounsfield units and benign versus malignant disease with a median CT density being significantly higher for histologically positive lymph nodes (average: 33.2 HU) than for histologically negative lymph nodes (average: 10.1 HU). The incidence of malignancy was 88% above a cutoff value of 20 HU in the 10 fluorine-18 fluorodeoxyglucose (FDG) equivocal lymph nodes, and the incidence of benign findings was 100% in the interval between −20 and +20

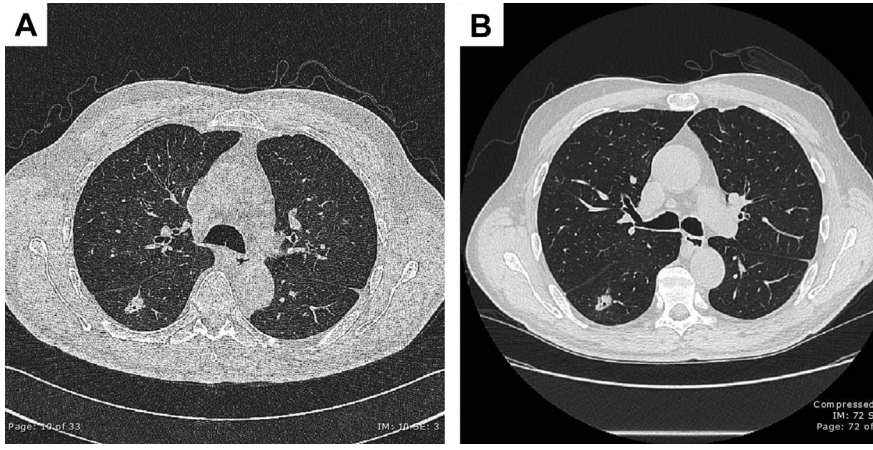

Fig. 1. Differences between low-resolution CT and HRCT scans. (*A*) LDCT scan of the chest with a grainier image and a (*B*) HRCT scan with a more refined image.

HU. Others have noted that there is an increased likelihood of lymph node metastasis if the primary lesion: (1) is solid or spiculated, (2) has a peak enhancement greater than 110 HU, (3) has a net enhancement of greater than 60 to 70 HU on CT scan, (4) is centrally located, or (5) is associated with a pleural effusion.[25,26] Cumulatively, these studies demonstrate promise with respect to the ability of CT scans to distinguish benign from malignant disease, but have not allowed CT scanning to definitively determine if a lymph node harbors metastatic disease.

Integrated PET with Computed Tomography

- Integrated PET/CT imaging is superior to either CT scan or PET imaging by itself in accurately characterizing lung cancers

Integrated PET/CT is the most accurate noninvasive imaging modality for the staging of primary lung cancers.[27,28] Integrated PET/CT refers to when PET is fused with CT scanning and is proven to be a superior imaging modality to either obtained as a sole modality (Fig. 2). Current recommendations for PET/CT imaging include obtaining

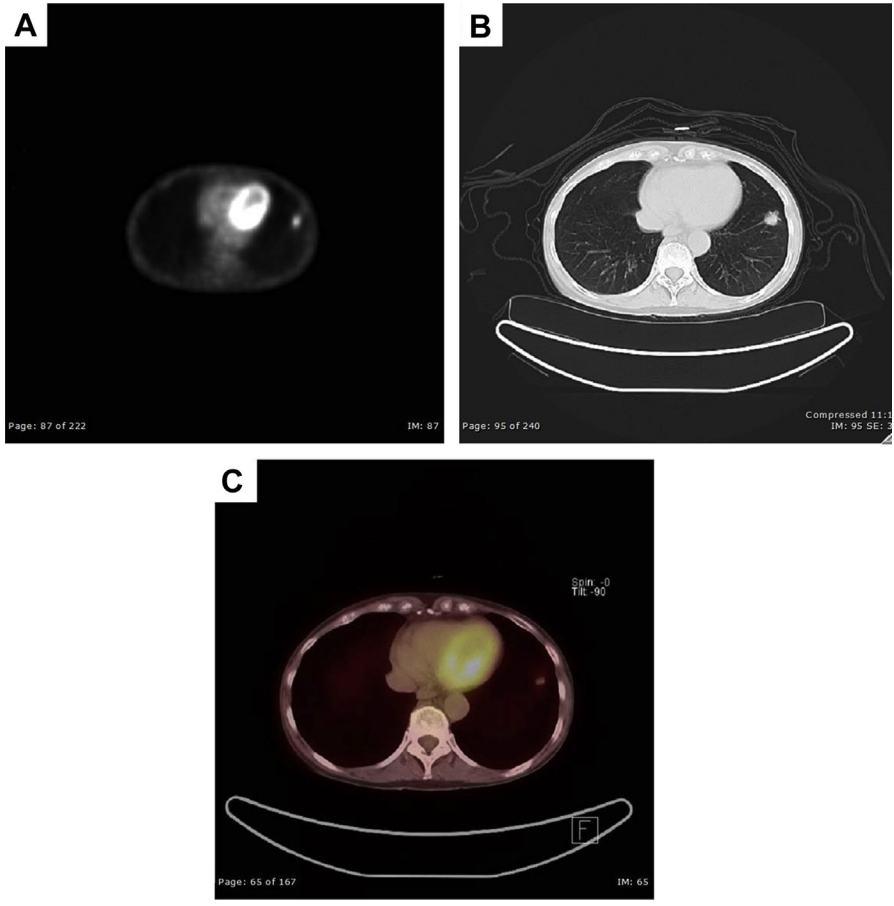

Fig. 2. Differences between a PET scan, CT scan, and integrated PET/CT imaging. (*A*) Attenuation-corrected PET scan, (*B*) CT scan of nodule, (*C*) integrated PET/CT scan of the same nodule.

images from the skull base to the thigh with a slice thickness of 2.5 mm to gain the most accurate demarcation of the tumor margin while maximizing the signal-to-noise ratio.[13] PET imaging alone without CT scan fusion is not adequate as a sole modality because it lacks the spatial resolution to accurately and definitely characterize areas of interest.[18,29,30] The paucity of anatomic landmarks on PET imaging is made up for when the images are fused with that of the anatomic cross-sectional data from CT imaging.[31]

The PET component uses an FDG tracer to depict abnormal metabolic uptake with a sensitivity of 79% to 85% and a specificity of 87% to 92% for identifying malignancy.[32] In order to have the PET component have the highest true yield, patients must fast for 4 to 6 hours before the test as well as avoid strenuous activity for 24 to 48 hours before the examination.[13] The FDG tracer is dosed based on the patient's height and weight. Patients with elevated hemoglobin A1c may not be candidates for PET because this can affect the FDG tracer metabolism, with the upper cutoff number varying by institution.

There are areas of the body that have increased uptake of the FDG tracer that are not pathologic, and these must be known so as to not create undue alarm. The most concentrated areas of normal FDG uptake at 1 hour after injection are the brain, heart, and urinary tract. Low-level activity may be seen normally in the thyroid gland, breast, and mediastinal blood pool. Laryngeal uptake can be identified after talking. Physical activity and anxiety can increase uptake within muscle groups in what should be in a symmetric, and if applicable, bilateral fashion.[18] Therefore, a sound grasp of the context in which a PET/CT scan is performed must be understood.

Integrated PET/computed tomography to evaluate the primary lesion

The standardized uptake value (SUV), defined as the activity per milliliter within the region of interest divided by the injected dose in megabec-querels per kilogram of body weight, of a lesion greater than 2.5 originally was deemed concerning for malignancy.[30] Since then, the maximum SUV (SUVmax) of greater than 2.5 has been used widely as the cutoff value suggestive of malignancy. This threshold, however, is associated with a wide range of sensitivity (40%–97%) and specificity (60%–96%).[33] This observation may be linked, in part, to false negative results in small nodules (<1 cm) because they may not have the necessary critical mass of metabolically active malignant cells for accurate detection.[34] False negatives occur in small early stage adenocarcinoma, small early squamous cell carcinomas, bronchoalveolar cell carcinoma, and some carcinoid tumors.[35] False positives (nonmalignant lesions with a high SUVmax) also can occur in disease states such as tuberculosis, aspergillomas, rheumatoid nodules, Wegener granulomatosis, and amyloidosis.[35] Cerfolio and colleagues[36] showed that patients with a high SUVmax ($\geq$10) were more likely to have poorly differentiated tumors, more likely to have an advanced stage, and less likely to undergo complete resection of their disease. Patients with squamous cell carcinoma also were found to have a higher SUVmax (13.2) than those with other types of non–small cell lung cancer (NSCLC 8.9).[36] Despite the potential ominous findings associated with elevated SUVmax, some investigators have shown no difference in overall survival or progression-free survival between high and low SUVmax groups.[37] This finding may be reflective of the heterogeneity in treatment rather than a direct effect of the SUV value, per se. Outside of a quantitative assessment, qualitatively, a nodule or mass with increased uptake of ^{18}FDG in 3 planes as compared with the background on a PET scan is also concerning for malignancy.[30]

Integrated PET/computed tomographic scans to evaluate lymph node involvement

Similar to the data for primary lung nodules, an SUVmax of 2.5 or greater has been used to differentiate benign from malignant lymph nodes.[38,39] One prospective,

multicenter comparison of CT alone to integrated PET/CT allowed for an 11% increase in accuracy in detecting lymph node metastasis on a per-patient basis.[40] Integrated PET/CT appears to be a better predictor than PET alone for N status.[40] The metabolic characteristics obtained from PET imaging combined with the information regarding lymph node size from CT imaging allows for improved staging accuracy.[41] The risk of mediastinal disease is increased if the SUVmax of the primary lesion is greater than 4.[38]

Integrated PET/CT detects unexpected mediastinal lymph node FDG avidity in 10% of patients originally thought not to have mediastinal disease on other imaging.[41] As with other modalities, there is a risk of false positive findings in mediastinal and hilar lymph nodes. This risk is higher in larger lymph nodes, in those with a higher volume of lymphocytes and macrophages, in reactive lymph nodes, and in those with lymphoid follicular hyperplasia.[40] When the area of concern is small (5–7 mm), the sensitivity of PET drops significantly to only 40% as compared with when investigating larger lymph node stations of concern (8–10 mm) at 78%.[42] Lee and colleagues[43] described lymph node density as an adjunct to FDG avidity in those nodes deemed to have "mild FDG uptake" (SUVmax 2–4), where using density criteria (median HU 25–45) increased the sensitivity (88.3%) and specificity (82.6%) in this subgroup. There are no trials showing a difference in PET/CT imaging between different lung cancer subtypes. A retrospective review by Wang and colleagues[44] found no significant difference in SUVmax on preoperative PET/CT in patients with what was later pathologically proven to be positive lymph node disease between squamous cell carcinoma and other forms of NSCLC.

Integrated PET/computed tomographic scans to delineate metastases

Integrated PET/CT detects unexpected metastases in 10% to 15% of patients with NSCLC.[41] A review of all randomized control trials using PET or PET/CT in the evaluation of patients with lung cancer showed that its greatest benefit was in identifying metastatic disease in patients with a high chance of such involvement.[45] Preoperatively, integrated PET/CT has reduced the total number of thoracotomies including those thoracotomies used for staging in those NSCLC patients presumed to have advanced disease.[30] Integrated PET/CT scans are replacing bone scintigraphy in most cases because it has been shown to be a very sensitive imaging modality to detect osseous disease. One meta-analysis described a higher sensitivity (92%) and specificity (98%) with integrated PET/CT scanning as compared with bone scintigraphy (sensitivity 86%, specificity 87%) in correctly identifying metastatic disease to bone.[46]

Future advances in integrated PET/computed tomographic imaging

Alternative methods to improve upon current integrated PET/CT imaging are on the horizon. One such approach uses respiratory gating of PET/CT scans, whereby data acquisition corresponds to a specific part of the respiratory cycle phase. This unique approach is different than standard PET/CT techniques, whereby patients are allowed to breathe freely during the examination. Respiratory-gated PET/CT scan use has not been proven to be superior at this time, but has the potential to play a role in the management of patients with early stage disease because it shows slightly improved clinical staging accuracy and higher interobserver agreement between nuclear medicine physicians.[47]

PET imaging using other tracer materials to achieve more sensitive and specific imaging than presently available with ^{18}FDG is under investigation at this time. A fluorine-18-A-methyltyrosine tracer is currently in clinical trial phases.[48] Other tracers such as 11C-methionine (protein metabolism marker), 11C-choline (a marker of the cell

membrane component phosphatidylcholine), and 18F-fluorothymidine (a marker of cell proliferation) have also been studied, but the experience is limited, with no clear clinical advantage identified yet.[49]

INVASIVE EVALUATION

Invasive studies allow the clinician to obtain tissue for both diagnosis and staging. Before using an invasive option for either of these purposes, it is recommended that imaging will have afforded the clinician the knowledge of selecting the target that would provide a diagnosis and the highest possible stage in a safe manner.[50] In certain circumstances, such as in those patients who are suggested to have a peripheral stage IA tumor, invasive preoperative evaluation of mediastinal nodes may not be required.[2,51] However, in general, most abnormal imaging should be confirmed by tissue biopsy using the method that will best ensure accurate staging because evidence shows that more complete staging workups improve patient outcomes.[52–54] In fact, most practice guidelines recommend that patients with a peripheral lesion, defined as being in the outer third of the lung parenchyma, concerning for cancer, require tissue diagnosis before further management can be planned.[55] It is recommended that patients with peripheral pulmonary nodules be considered for a CT-guided transthoracic needle aspiration (TTNA) as an initial diagnostic option.[26,56,57]

Computed Tomographic Imaging to Guide Percutaneous Biopsies

Although CT scans are not used to biopsy lesions, per se, CT still allows for real-time guidance in assessing nodules to allow for percutaneous sampling in the same way an endoscope is used.[58] The indication for biopsy put forth by the I-ELCAP protocol was when a solitary nodule measured 15 mm or more in size, was a solid nodule that had grown on follow-up scans, or was a nonsolid or part-solid nodule that persisted in size and did not resolve on 1- or 3-month follow-up scans.[2,59] More recent guidelines are more stringent and recommend that nodules greater than 8 mm in diameter that have either a pretest probability of malignancy $\geq$10%, PET avidity, or when a fully informed patient desires a definitive diagnostic procedure, should have a biopsy performed.[2] Additional guidelines for nodules greater than 8 mm also include undergoing a biopsy if there are any data to support a substantial suspicion of lung cancer.[8,10,60]

Transthoracic needle biopsy (TTNB) may provide more information over only the cellular material obtained by TTNA alone because the core needle provides more material by which information regarding cellular architecture and degree of invasiveness can be obtained. The sensitivity of CT-guided TTNB for malignancy ranges from 74% to 97%, and its specificity ranges from 95% to 100%.[58,61–64] A recent review found that CT-guided TTNB was a reliable procedure associated with an 88% to 91% sensitivity for the diagnosis of lung cancer, specifically with the yield being enhanced to 97% when larger core needles ($\geq$18 gauge) were used.[65] If the sample or results of a biopsy are inadequate or inconclusive, respectively, and the suspicion of malignancy remains high, additional biopsy tests should be attempted.[66] Unfortunately, percutaneous procedures also are associated with a significantly higher pneumothorax rate because the needle traverses the pleura and lung.[40,55] These CT-guided transthoracic lung biopsies are associated with an overall incidence of complications that vary greatly (1.7%–45%).[55]

Endoscopically Directed Biopsies

- EBUS and EUS must be used in a strategically advantageous manner relying on their individual strengths to maximize their efficacy in the diagnosis and staging of lung cancer

The primary advantage of EBUS or EUS over surgical cervical mediastinoscopy is that it can be performed with sedation and rarely requires general anesthesia in skilled hands. Another advantage is that in addition to accessing the mediastinal lymph nodes for sampling, EBUS more so than EUS provides the added advantage of being able to biopsy the hilar lymph nodes and the lung parenchymal lesion itself. EBUS and EUS allow complementary evaluation of almost all mediastinal lymph node levels when combined (**Box 2**).[67]

EUS and EBUS have been shown to be safe techniques with low morbidities and mortalities. Studies of patients undergoing EBUS for peripheral lung nodules have reported an overall low incidence of complication ranging from well under 1%–5%. Specific complications have included pneumothorax (0.8%–2.1%), pulmonary infections (0.5%), and bleeding (1%–5%).[68–72] Deaths due to complications from these procedures are extremely rare (0.04%), with those mortalities occurring in patients with poor preoperative performance status defined by their American Society of Anesthesiologists Physical Status Classification of III or IV.[40]

Advances in on-site tissue sample investigation, referred to as ROSE (ie, Rapid Onsite Evaluation), have also allowed for another advantage with EBUS and EUS in that the biopsies are examined while the patient is undergoing the procedure itself. ROSE of cytology when used with EBUS or EUS sampling has been shown to correlate with 94.8% of lymph nodes having a clear diagnosis on the first pass biopsy as compared with subsequent passes.[73] Therefore, with the addition of

Box 2
Indications for endoscopic biopsies

EBUS

1. Sampling tissue from lung nodule or mass
   - R-EBUS if peripheral (outer 1/3)
   - L-EBUS if central
   - Tissue sampling for biomarker testing (use ROSE if possible)
   - Peripheral nodule/mass of any size in a patient with poor surgical candidacy and/or if other techniques are higher risk for that particular patient (ie, CT-guided TTNA in severe bullous chronic obstructive pulmonary disease)
2. Staging patients with lung cancer with mediastinal or hilar lymph node involvement
   - Clinical hilar (N1) and/or mediastinal (N2 or N3) disease by CT and/or PET/CT scan
   - Central tumor
   - Peripheral tumor and >3 cm
3. Confirming pathologic diagnosis of enlarged lymph nodes in suspected or confirmed lymphoproliferative or infectious diseases
4. Evaluating tracheobronchial tree
   - Biopsy abnormal tissue
   - Assess depth of invasion
5. Sampling tissue from mediastinal nodule or mass
6. Sampling abnormal-appearing tissue concerning for malignant infiltration of the mediastinum

EUS

1. Biopsying left adrenal lesion when concerned for metastasis
2. Biopsying levels 5, 8, and 9 lymph nodes
3. Biopsying of celiac and infradiaphragmatic retroperitoneal lymph nodes

ROSE, the need for more than 3 biopsy passes may be unnecessary. The true benefit of ROSE is that the sampled tissue is evaluated in real time to reduce the rate of nondiagnostic sampling. Furthermore, ROSE has been shown to correlate very well with final pathology and may guide the proceduralist in the order and way the tissues are sampled.[74] If no onsite assessment is available, it is recommended that the needles be changed between sampling of N3, N2, and N1 nodes rather than simply flushing the needles in between sampling of different nodal stations to avoid cross-contamination.[32]

Endobronchial Ultrasound

EBUS was introduced in 1990 and has the advantage of being able to obtain sufficient tissue samples for histologic diagnosis, including immunohistochemistry, which is important in many diseases.[74] Masses adjacent to the airway, intrapulmonary nodules, and mediastinal tumors of unknown cause often times require advanced pathologic diagnosis for definitive diagnosis, and EBUS is able to accomplish this.[40,74]

EBUS uses a radial (R-EBUS) or linear (L-EBUS) probe with a bronchoscope and uses frequencies between 5 and 10 MHz with a penetration at 5 MHz to about 6 to 8 cm (**Fig. 3**).[40,74] The current EBUS iteration includes a dedicated biopsy needle (typically 22 gauge) allowing EBUS-TBNA of levels 2R, 2L, 4R, 4L, 7, 10R, 10L, 11R, and

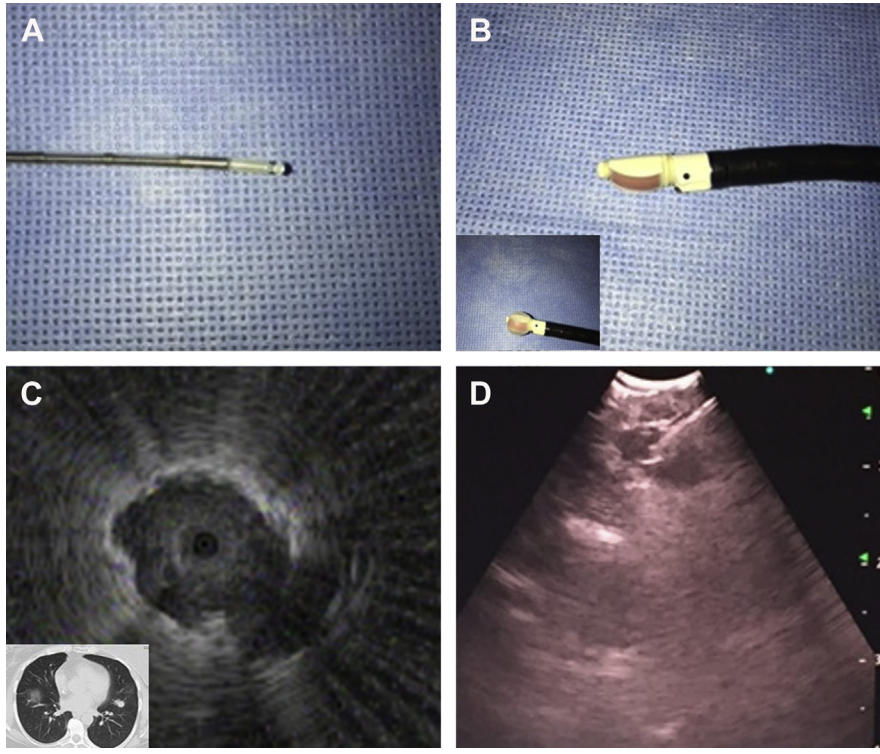

Fig. 3. EBUS. (*A*) Radial probe, (*B*) linear probe with inset image showing balloon expansion, (*C*) ultrasound image of pathologic pulmonary nodule using radial probe with inset showing lesion on CT scan, (*D*) ultrasound image showing needle within a pathologic lymph node using linear probe.

11L.[40,67,74,75] L-EBUS facilitates TBNA of mediastinal lymph nodes, hilar lymph nodes, intrapulmonary lymph nodes, and central lesions under real-time ultrasound guidance.[76,77] The L-EBUS probe typically is larger than a standard flexible bronchoscope and requires oral intubation.[78] R-EBUS allows for evaluation of central airways and their wall structure (ie, defining airway invasion), hilar lymph nodes, mediastinal lymph nodes, intrapulmonary lymph nodes, and peripheral lung lesions.[33,76,77] The more peripheral intrapulmonary lymph node levels 12 to 14 are also accessible if a miniature R-EBUS probe is used.[67] Small R-EBUS probes (miniprobes) allow for the biopsy of peripheral nodules independent of lesion size with sensitivities ranging from 61% to 80%.[26,77] The further development of even smaller probes with guiding catheters and more advanced miniprobes will solve the navigation issue to move farther into the periphery.[77]

The prevalence of positive mediastinal lymph node disease following a negative EBUS-TBNA is reported to be low at 4.9%.[79] On the other hand, one retrospective study using EBUS sampling for negative CT and PET imaging (ie, unsuspected N2 disease) found that there was an incidence of malignancy in 17.6% of the EBUS samples obtained.[80] Generally, EBUS-TBNA is useful in biopsying centrally located, paratracheal and peribronchial tumors with a diagnostic sensitivity of 82% to 94%.[78]

There are no consistent characteristics on EBUS to predict malignancy. One study suggested that a round or oval shape was correlated with malignancy[73]; however, this has not been universally accepted criteria. Consequently, no particular ultrasound shape characteristic should deter the proceduralist from proceeding with a biopsy. Nevertheless, 3 variables have been correlated strongly with false negative EBUS outcomes: (1) central location of the lung tumor, (2) nodal enlargement on CT, and (3) FDG-avidity for mediastinal lymph nodes on PET imaging.[81]

Endoscopic Ultrasound

EUS-guided biopsy gives the proceduralist the ability to sample lymph nodes that are not accessible via an EBUS approach (levels 5, 8, and 9 lymph nodes and the infradiaphragmatic and retroperitoneal lymph nodes).[67] EUS-guided fine-needle aspiration (FNA) uses a curved linear array ultrasound transducer, which allows for real-time ultrasound-guided needle sampling of the lymph node stations accessible from the esophagus as well as lung and pleural lesions.[82,83] The location of the esophagus, which is posterior and to the left of the trachea, makes right-sided visualization and sampling more of a challenge even when the lymph nodes are grossly enlarged.[67] The lymph nodes that can be sampled include some of the paratracheal lymph nodes (levels 2R 2L, 4R, and 4L), although anatomic constraints make it challenging to reliably access these levels especially anterior to and to the right of the trachea. Not surprisingly, EUS is associated with an incidence of false negative biopsies in these areas of 19%.[67,82] EUS is better suited for reaching the lymph nodes in the subcarinal (level 7), aortopulmonary window (level 5), periesophageal (level 8), and inferior pulmonary ligament (level 9) stations as well as the infradiaphragmatic retroperitoneal lymph nodes close to the aorta and celiac trunk.[52,67,75,82] EUS-FNA can use a transgastric approach to biopsy abnormalities of the left adrenal glan.[83,84] It is noted that EUS is inferior to transcutaneous ultrasound in the evaluation of the right adrenal gland due to the esophagus's left-sided location.[67]

EUS-guided FNA has been reported to decrease the need for surgical mediastinoscopy by 68% when used as the initial staging tool.[41,83,85] EUS-guided FNA has a sensitivity of 84% to 92.5%, specificity of 89% to 100%, and positive predictive value of 79% to 100% in confirming suspicious mediastinal lymph nodes for malignancy that are detected by FDG-PET in patients with suspected or proven NSCLC.[86] In patients

with negative lymph nodes on CT scan (ie, <1 cm), EUS has been shown to identify malignant mediastinal involvement in 25% of those patients as well as identify invasion or left adrenal involvement in 18.75%.[87] Surgical mediastinoscopy continues to have an important role in working up patients with concern for mediastinal lymph node involvement when EBUS/EUS sampling is negative.[2]

Endobronchial Ultrasound Combined with Esophageal Ultrasound

Accurate staging of the disease may be enhanced through combining the EBUS and EUS (EBUS + EUS) techniques. This approach is supported by the results of the Assessment of Surgical Staging versus Endobronchial and Endoscopic Ultrasound in Lung Cancer prospective randomized trial. This study showed a sensitivity of 79% for detecting mediastinal lymph node metastasis with immediate surgical staging alone versus 85% for EUS + EBUS only.[88] The same study showed that when EUS + EBUS was negative followed by immediate surgical mediastinoscopy to confirm this finding, the sensitivity was 94%.[88] Ultimately, this approach resulted in fewer thoracotomies. It was determined that 11 patients needed to undergo mediastinoscopy in order to detect one single patient with N2 disease missed by combined EBUS + EUS.[88] These findings may represent a point in the evolution of a possible enhanced role in combined endoscopic modalities that may challenge surgical staging in the future.

Electromagnetic Navigational Bronchoscopy

ENB was approved for use in 2004 and is used to evaluate lesions that are peripherally located beyond the depth that a traditional bronchoscope can reach.[89] This technique uses an electromagnetic array to create an electromagnetic field around the patient with a computer system that then uses a preoperative CT scan to provide the bronchoscopic probe location on a screen in 3 dimensions.[90] It combines conventional and virtual bronchoscopy to enable the guidance of bronchoscopic instruments to target areas within the peripheral lung parenchyma.[91] This system is analogous to a Global Positioning System that is used to guide an automobile's navigation. The navigation system shows a "road map" of the bronchial tree on the display screen that the proceduralist can follow. The diagnostic yield of this technique for biopsying these peripheral lesions varies widely and is reported to range from 55.7% to 94%.[91–93]

Other uses for ENB have also included marking peripheral lesions with dye, placing fiducials for nonpalpable lesions before planned thoracoscopic resections, and placing brachytherapy catheters.[91,92] Relatively small series have demonstrated complete success when using ENB for localizing and resecting lung parenchymal lesions.[92] Although promising, refinements to ENB are needed to fully define the scope of its applicability.

DISCUSSION

In terms of noninvasive studies, although CXRs have been the historical workhorse in evaluating patients with lung cancer, CT scanning has become the diagnostic imaging study that has allowed for the greatest anatomic detail. Integrated PET/CT scanning has now emerged as an important adjunct to imaging for lung cancer because of its sensitivity in detecting metabolic activity that would be suggestive of malignancy. Other modalities and advances in imaging either have been shown to be inferior to these 2 imaging modalities or have yet to supplant these 2 modalities as the mainstays in the workup of patients with lung cancer. Nevertheless, more data regarding the refinements in these modalities surely will hone their utility in the diagnosis and staging

of lung cancer. With respect to invasive studies, EBUS and EUS techniques are evolving modalities that are approaching the effectiveness, particularly when used in conjunction, that is rivaling more traditional surgical diagnostic and staging procedures. Furthermore, advances such as ENB have the potential to steer innovation down new exciting avenues.

SUMMARY

In summary, CXR, although useful in detecting some thoracic abnormalities, should not be part of a formal screening or staging protocol exclusively. Rather, LDCT scanning should be used to screen for lung cancer in high-risk patients as defined by national and international guidelines. Once an abnormality is identified by screening LDCT, additional imaging should be performed with HRCT scanning to characterize the abnormality in greater detail. If concern for a malignancy remains, a follow-up PET/CT scan should be used to further delineate the lesion as well as complete noninvasive staging through the assessment of the mediastinum and the identification of, or lack thereof, possible metastatic disease. Mediastinal involvement of disease then can be confirmed by minimally invasive techniques such as EBUS and EUS. In experienced hands, these techniques are approaching an efficacy similar to that of cervical mediastinoscopy in being the definitive invasive staging procedure. EBUS may provide the additional benefit over cervical mediastinoscopy of allowing the clinician to achieve a tissue diagnosis of the pulmonary lesion during the same setting of mediastinal staging.

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