Role of EUS in Mediastinal Nodes, Masses, Cysts, and Lung Cancer

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Abstract

Full minimally invasive evaluation of all lymph node stations (with the exception of station 6) is now possible with the advent of endobronchial and trans-esophageal endoscopic ultrasound. Endoscopic ultrasound fine-needle aspiration (EUS-FNA) allows sampling of mediastinal lymph nodes relevant to lung cancer staging, particularly in the subcarinal area (station 7), lower para-esophageal lymph nodes (station 8), inferior pulmonary ligament lymph nodes (station 9), and celiac lymph nodes. EUS-FNA is an extremely powerful nonsurgical option for sampling metastatic nodes, sarcoidosis, and lymphoma. Both adrenal glands can be sampled by EUS-FNA through the transgastric approach or the trans-duodenal approach. EUS-FNA is also able to sample central primary lung masses abutting the esophagus, particularly when other techniques fail. EBUS-FNA has the distinct advantage to reach areas that have proven inaccessible to EUS. These stations include the right and left upper and lower para-tracheal areas (4R and 4L; 2R and 2L), right and left hilar areas (station 10) and the right and left interlobar stations (station 11). It is best to work in a multidisciplinary fashion with colleagues in thoracic surgery, pulmonary, radiology, and oncology to individualize the best staging approach for the patient.

Key Words: Lung cancer, Lung cancer staging, Mediastinal lymph node, Endoscopic ultrasound, Endobronchial ultrasound, Fine needle aspiration, Adrenal gland, Lymphoma, Sarcoidosis, Mediastinal cyst, Duplication cyst

INTRODUCTION

Trans-esophageal endoscopic ultrasound (EUS) is the most accurate, efficient, and safe tool for evaluating the posterior mediastinum. The surging interest in mediastinal EUS is fueled by the rising demand for precise staging of nonsmall cell lung carcinoma (NSCLC), as well as uninvestigated mediastinal adenopathy and centrally located chest masses.

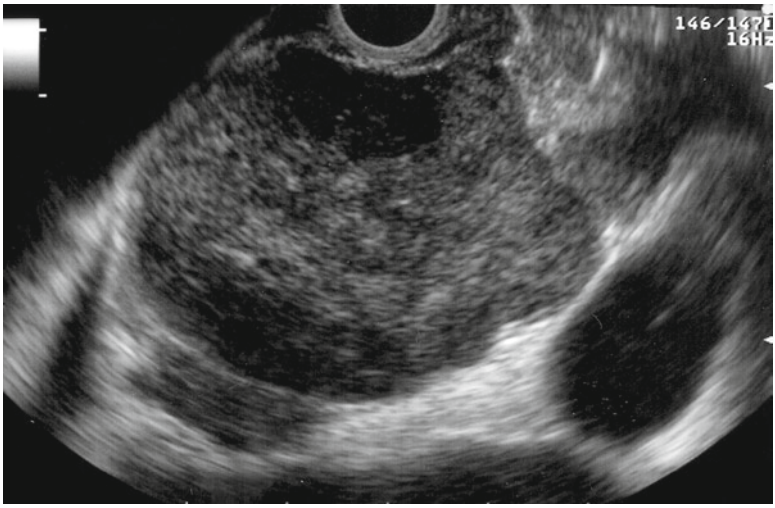

Fig. 1. Melanoma. EUS-FNA along with immunostains confirmed recurrent metastatic melanoma to the mediastinum.

Since the differential diagnosis of posterior mediastinal abnormalities includes benign and malignant etiologies, tissue acquisition by fine-needle aspiration (EUS-FNA) is essential. Benign entities include tuberculosis, granulomatous disease, sarcoidosis, histoplasmosis, and lymphoma (1). Metastases include primary carcinoma of the lung and esophagus, as well as extrathoracic sites such as the head and neck, breast, melanoma (Fig. 1) and subdiaphragmatic sites such as renal (Fig. 2) (2), gastric and pancreatic cancer (3). This chapter reviews the role of EUS in the mediastinum and in evaluating patients with known or suspected lung cancer.

Mediastinal Cysts

EUS can distinguish cystic lesions (bronchogenic or duplication cysts) from solid mediastinal masses seen on cross-sectional imaging. Foregut duplication cysts account for up to 15% of primary mediastinal masses. Bronchogenic cysts usually reveal one of two echogenic patterns: anechoic and simple (the majority are filled with a clear liquid) or anechoic pattern admixed with solid debris (4).

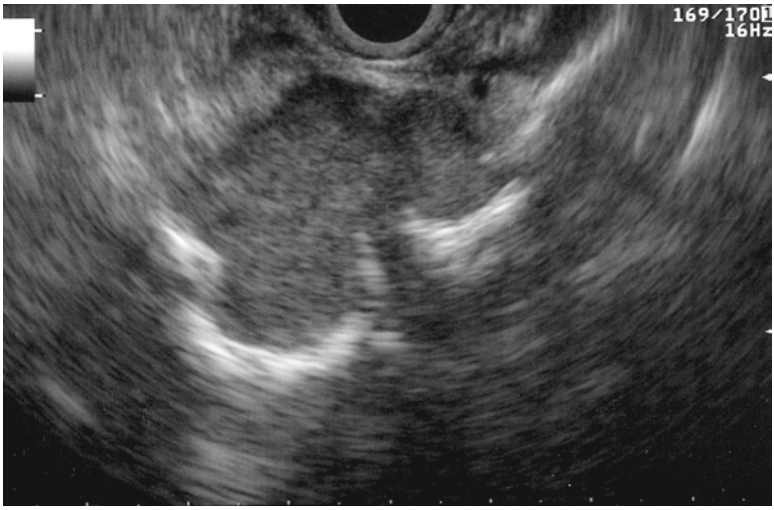

Fig. 2. RCC metastasis. EUS-FNA (with immunostains) diagnosed renal cell carcinoma metastatic to the spine.

ROLE OF FNA

We do not advocate aspirating simple cysts since they have a classic appearance by EUS and can be accurately identified by CT (4). Unlike trans-gastric aspiration, the relatively higher pH in the esophagus and the high oral bacterial load may promote infection of the mediastinal cyst. The approach to heterogeneous cysts is not, however, as straightforward since these cysts are often incorrectly interpreted as solid masses by cross-sectional imaging (CT or MRI). Such cysts are usually filled with thick echogenic and tenacious debris seen as hyperechoic reflectors. Aspiration usually results in a frothy, brownish fluid. The high viscosity can limit the yield to just a few drops for interpretation. The rationale to aspirate such lesions is to rule out a cystic metastasis. Prophylactic antibiotics should be given (5–7) as there have been case reports of infection without antibiotic coverage.

THE LUNG MASS

Another important indication for EUS is sampling primary lung masses, particularly when the lesion is close to the esophagus or for those not otherwise amenable to percutaneous or surgical approaches (8). This approach has been shown to provide tissue diagnosis of primary lung masses when other modalities have failed and when neoadjuvant therapy

is planned for borderline or unresectable masses. It can be especially helpful in obviating surgery in small cell lung carcinoma (Figs. 3 and 4). Surprisingly, we have not encountered complications of pneumothorax in sampling primary lung masses (9).

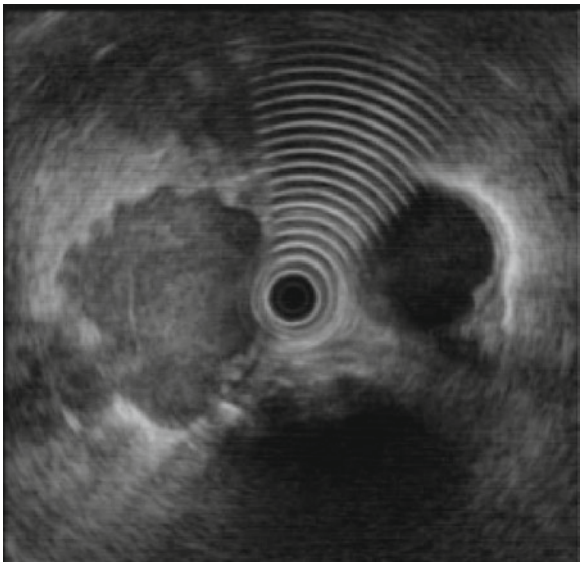

Fig. 3. Subcarinal mass invading the mediastinum.

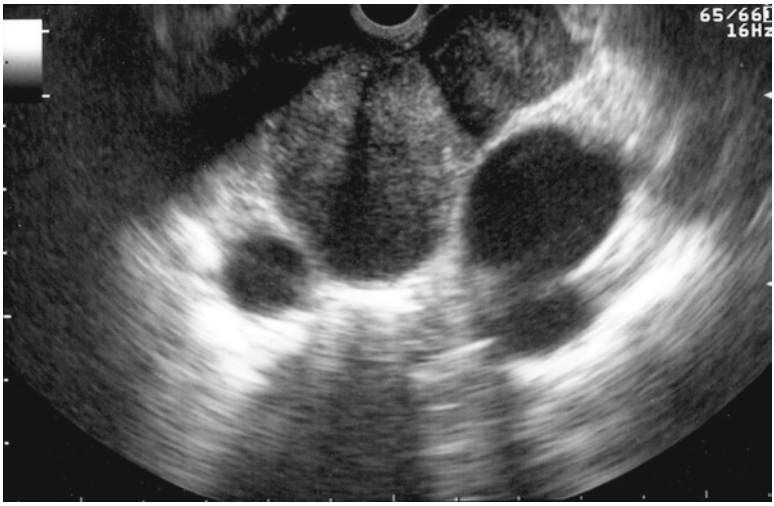

Fig. 4. Bulky N2 disease. EUS-FNA confirmed N2 disease in a patient with NSCLC.

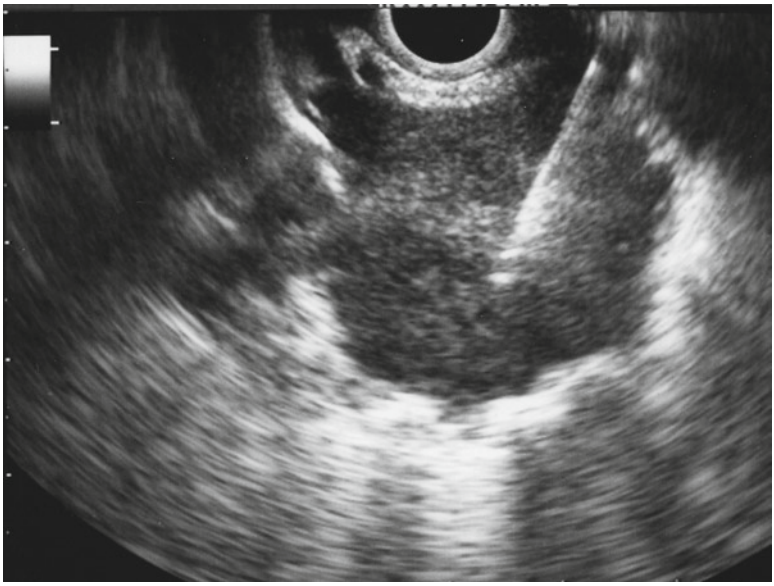

Fig. 5. Primary lung mass: EUS-FNA of a centrally located mass confirmed primary NSCLC.

LUNG CANCER

NSCLC (Fig. 5) is the number one cause of cancer death worldwide. Despite improvements in cross-sectional and functional imaging and attempts to screen those at high risk, the incidence and mortality rate of NSLC are unchanged. For the vast majority of patients, surgery with or without neoadjuvant therapy is the only hope for cure. For most, with the exception of the earliest stage tumors, the likelihood of cure after surgery remains poor (10).

The frequently inexorable progression of disease across all stages is driven by unrecognized metastases. Node positive NSCLC confirmed by EUS-FNA is more likely to receive neoadjuvant chemotherapy versus surgery compared to node negative lung cancer. Early, routine EUS-FNA provides important prognostic information and determines the most effective management (11).

RATIONALE FOR EUS

Mediastinal lymph node metastases are common (up to one third of patients) and generally indicate unresectable disease. Ipsilateral or subcarinal mediastinal nodal metastases (N2) or contralateral mediastinal

lymph node involvement (N3, stage IIIB) generally obviates surgical resection (12). Primary surgery is reserved for the minority of patients without nodal and/or distant metastases (stage I–II) (10).

Accurate staging minimizes unnecessary surgery, provides prognosis, and determines eligibility for clinical trials. Despite the increasing variety of competitive and complementary staging techniques, there is no broadly accepted consensus on how best to stage patients with the greatest accuracy and least morbidity. Reliance on chest computed tomography (CT) and integrated positron emission tomography (PET) scanning alone to stage and evaluate surgical candidacy is plagued by false positive results and potentially over-treatment or delayed surgery. Pathologic confirmation of enlarged or PET positive lymph node findings should be systematically pursued prior to surgical resection.

BEFORE YOU START

EUS for lung cancer staging requires a thorough understanding of the tumor, node, and metastasis (TNM) classification which has been revised in 2010 (Table 1) (13). Endosonographers should be especially familiar with the nodal staging. Additionally, familiarity with the Mountain–Dressler regional lymph node classification system (Fig. 6) (14, 15) as well as a new international lymph node map defining the anatomical boundaries for lymph node stations is necessary (13). Whenever possible, radiographs must be reviewed prior to embarking upon EUS and target "the worst first" – those metastases which impart the most advanced stage.

In general, the lower posterior mediastinum is ideally suited to EUS. EUS can access the lower para-tracheal space (station 4R and L), the subcarina (station 7), distal para-esophageal nodes (station 8), the pulmonary ligament (station 9), and varyingly the AP window (station 5). An "unsung" advantage of EUS is its ability to detect and sample celiac, left and right adrenal glands, hepatic, and ascitic or pleural fluid metastases otherwise (16) missed by cross-sectional imaging (17). These areas are uniquely in the domain of EUS and have significant impact in the treatment decision and prognosis in patients with NSCLC.

Evaluation of the anterior and right-sided mediastinum is limited by intervening tracheal and proximal bronchial air (stations 2 and 4R). These locations should be considered for bronchoscopic sampling, particularly with endobronchial ultrasound (EBUS) as discussed below. A recent summary of 13 prospective studies underscores the high accuracy of EUS (18).

Table 1
TNM classification of lung cancer

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastatic in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Anatomic stage/prognostic groups

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIb	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

A recent case series suggested a single trans-aortic EUS-FNA for intrapulmonary tumors, and enlarged lymph nodes lateral to the aorta (station 6) was feasible. Malignancy was confirmed in 64% of patients, who otherwise would have undergone mediastinotomy or an open procedure (19).

WHICH TEST IS BEST?

Patients with newly diagnosed NSCLC face a dizzying array of invasive staging options and no modality is perfect or universally available. Mediastinoscopy (MS) and trans-bronchial fine-needle aspiration (TBNA) are widely established but are primarily limited respectively by increased invasiveness and a modest negative predictive value (NPV). EUS-FNA has emerged as a diagnostic and staging tool because

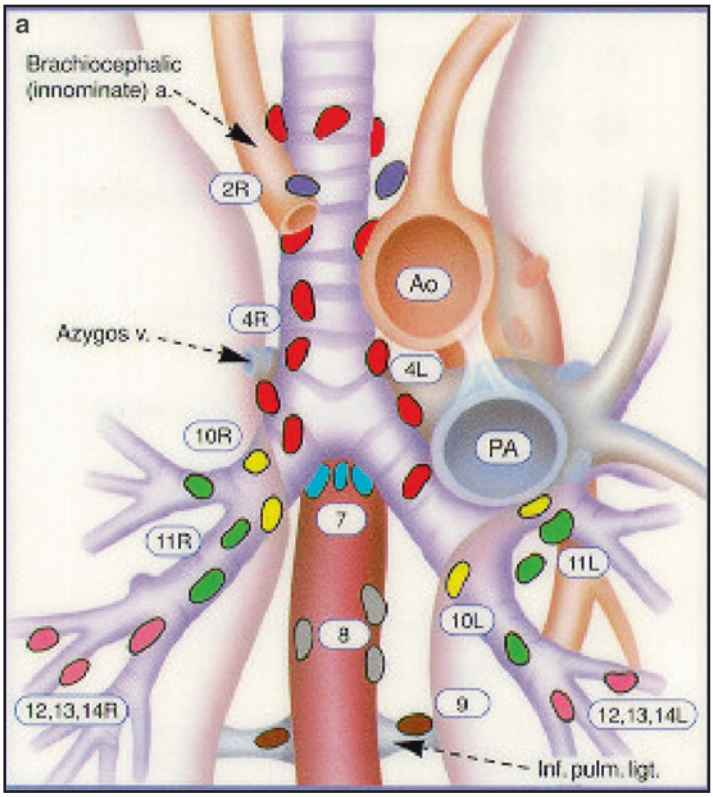

Fig. 6. The Mountain and Dressler regional lymph node classification (**a**) anterior view, (**b**) posterior view.

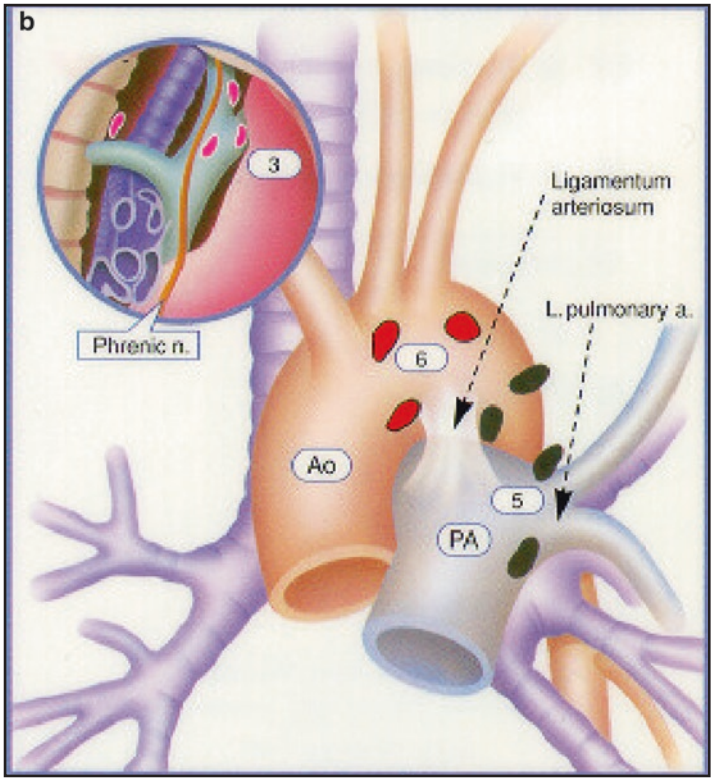

Fig. 6. (continued)

of its safety, accuracy, and patient convenience. For those endosonographers embarking a new programmatic application, integration of EUS into institutional clinical pathways is best achieved by participation in a multidisciplinary thoracic tumor board.

CROSS-SECTIONAL IMAGING

CT is the most common initial staging modality due to its widespread availability and ease of interpretation. While excellent for distant metastatic staging, the performance of CT in evaluating the mediastinum is not optimal (20). A meta-analysis, including 3,829 patients across 20 studies, revealed a NPV of 82% (18% were found to have advanced disease at surgical staging) (21). The sensitivity and specificity of CT for mediastinal nodes ranges from 57 to 82% (22).

CT and EUS should be considered complementary approaches. CT is most useful for primary tumor imaging and for a "lay of the land" while EUS provides a focused exam of select metastatic sites. Direct comparisons between EUS and CT in detecting mediastinal adenopathy have been performed (23–25) and the sensitivity of EUS for mediastinal lymph node detection was consistently above 90%. It is crucial to note that in patients with an unremarkable chest CT, EUS-FNA detected advanced disease and obviated the need for more invasive staging in a significant portion of patients (17, 26). In the absence of extrathoracic metastases, EUS-FNA is useful regardless of CT findings.

FUNCTIONAL IMAGING

CT with integrated 18F-fluorodeoxyglucose positron emission tomography (PET–CT) has become the noninvasive gold standard. Despite initial enthusiasm that functional imaging might obviate the need for tissue sampling or FNA, PET–CT findings are not recognized as definitive proof of N2-N3 disease (27). PET is widely thought to be more accurate than CT, but false positives are common (up to 39%) (28).

Despite these shortcomings, PET–CT remains an excellent and irreplaceable part of the metastatic evaluation. A meta-analysis of 18 studies with 1,045 patients reported a pooled sensitivity, specificity, positive predictive value (PPV), and NPV of PET for staging mediastinal lymph nodes in NSCLC patients of 84, 89, 79, and 93%, respectively (29).

EUS-FNA can be used to document suspicious findings on PET–CT with great accuracy (97% accuracy (28), 93% sensitivity, and 100% specificity) (14). In that study, EUS confirmed N2/N3 disease in 69% of patients who were PET avid in the mediastinum. Importantly, one third of these lesions were outside the reach of surgical MS. More than a quarter of PET avid patients were found to have no nodal metastases after EUS-FNA, and 70% of "PET suspicious" patients had no mediastinal spread at surgery. These results underscore the point that functional imaging cannot replace tissue confirmation.

Furthermore, in unexplained mediastinal lymphadenopathy, EUS-FNA complemented PET findings by improving specificity and thus accuracy of diagnosis. The PPV approached 100% with overall accuracy 97% in lymph node pathology. Equivocal PET findings are particularly suited for minimally invasive EUS-FNA in which tissue diagnosis is invaluable (30).

FAILED BRONCHOSCOPY AND EUS RESCUE

TBNA is a widely employed blind technique with a poorly defined diagnostic yield (31, 32). It is associated with complications such as bleeding and pneumothorax (31). EUS-FNA "rescue" can be done immediately after an unrevealing TBNA if on-site cytology demonstrates a nondiagnostic specimen.

EUS AND MEDIASTINOSCOPY

Mediastinoscopy long considered the gold standard, is the most invasive staging technique. It is relatively costly, requires general anesthesia, and may require hospital admission. While safe, it carries the greatest procedural risk (33, 34). In a sense, EUS-FNA and MS are both competing and complementary techniques, although the future of lung cancer staging is likely to exclude surgical staging altogether. Two prospective studies directly compared EUS-FNA to MS (22, 25) in one the combination of EUS-FNA and MS increased the sensitivity to 86% compared to EUS-FNA alone (61%) or MS alone (53%) (25). Compared to MS, EUS-FNA offers wider access to the posterior mediastinum, including the subcarina, the inferior mediastinum, and the aortopulmonary window (APW).

MEDICAL MEDIASTINOSCOPY

Combined with EBUS (Fig. 7) for interrogation of the anterior mediastinum, the concept of complete "medical mediastinoscopy" is likely to largely replace surgical staging (35). Up to 10% of thoracotomies with intent to resect result in "open and shut" without resection; an additional 25–35% are ultimately futile on the basis of postoperative recurrence. In a recent study, the sensitivity and specificity approached 100% when EUS-FNA was combined with EBUS-TBNA (Table 2) (17, 36).

ENDOBRONCHIAL ULTRASOUND

EBUS is a novel diagnostic tool for mediastinal staging. Two prospective studies combined EUS-FNA with endobronchial ultrasound guided trans-bronchial needle biopsy (EBUS-TBNA) (37). The difference in sensitivity between the two procedures was not statistically

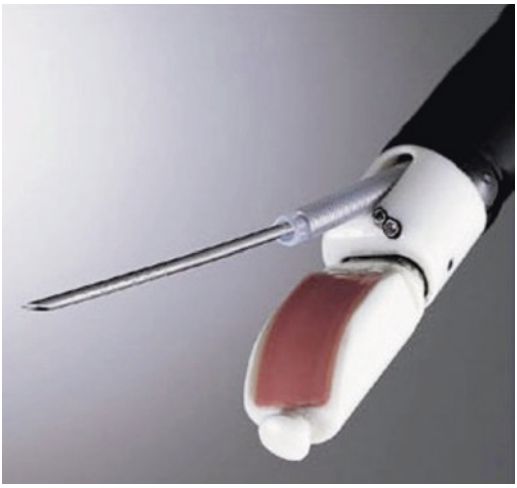

Fig. 7. Tip of endobronchial echoendoscope (EBUS) with FNA needle.

Table 2
Comparison of EUS-FNA, EBUS-FNA and combined approaches (medical mediastinoscopy) in the evaluation of mediastinal lesions

	Sensitivity (%)	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
EUS-FNA	80	100	100	66	86
EBUS-TBNA	85	100	100	72	89
Combined	100	100	100	100	100

significant and the combined approach had higher sensitivity and accuracy than either modality alone.

Additional larger trials are necessary to evaluate the utility of combined approach in unselected populations. We suspect combined EUS-FNA and EBUS-TBNA will be shown to provide total "medical mediastinoscopy" and in most cases obviate the need for surgical exploration.

Addition of EUS to a routine work-up in a small study which included chest CT, TBNA and, in some circumstances PET, reduced the need for surgical staging by an estimated 78% in patients with enlarged posterior mediastinal nodes (35).

SHOULD EUS BE EMPLOYED IN SUSPECTED EARLY LUNG CANCER?

The role of EUS-FNA after a high quality, negative PET–CT remains controversial in the patient with a small peripheral carcinoma. EUS-FNA has been reported to upstage an otherwise resectable patient (29). Such cases suggest the utility of EUS-FNA even in patients with no significant mediastinal lymph node metastases on PET. However, the yield of EUS-FNA and MS in a negative integrated PET–CT may be low (37).

EUS can be used, however, in a subgroup of patients that might harbor undetected N2 disease such as those whose tumor have high SUV >10 and those with poorly differentiated tumors (37).

THE LINEAR EXAM

A linear mediastinal exam typically begins 30 cm from the incisors. At this level, one should appreciate the cardiac motion from the left atrium and ventricle. Pulling back slightly will bring in to view the subcarinal space where the left atrium drains into the pulmonary artery. Remember that clockwise rotation of the scope along its axis brings left-sided structures into view. Gentle pullback will then reveal the APW, the space defined by its two named great vessels. The aorta can be seen to round off into its oblong appearing arch by turning clockwise about 90° and pulling back about 2 cm from the APW.

The descending aorta is identified with the CLA echoendoscope at about 35 cm from the incisor. A continuous and steady push of the CLA endoscope to about 45 cm – while the aorta is maintained in view – leads to the identification of the celiac axis bifurcation. A gentle clockwise maneuver will lead to the “seagull” shaped organ, the left adrenal gland. In patients with metastasis to the adrenal, the gland loses its normal shape and takes the form of a mass (Figs. 8 and 9). Occasionally, one limb of the adrenal is slightly enlarged; commonly this is a benign adenoma.

Recent reports suggest that those nodes lacking a central Doppler signal (intranodal blood vessel) are much more likely to be malignant (38, 39).

THE FNA TECHNIQUE

The sensitivity and specificity of EUS without FNA for diagnosing mediastinal lymph node metastases ranges between 54–75% and 71–98%, respectively (6, 7). The introduction of FNA for tissue confirmation

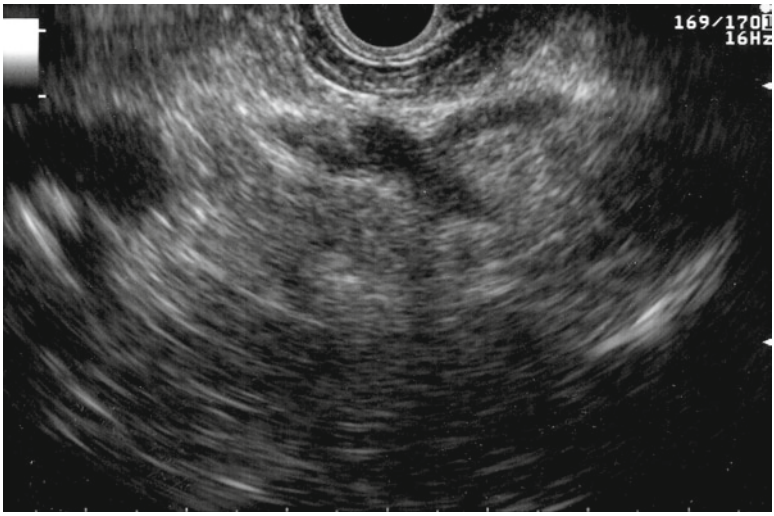

Fig. 8. Normal appearing "seagull" adrenal gland (curvilinear echoendoscope).

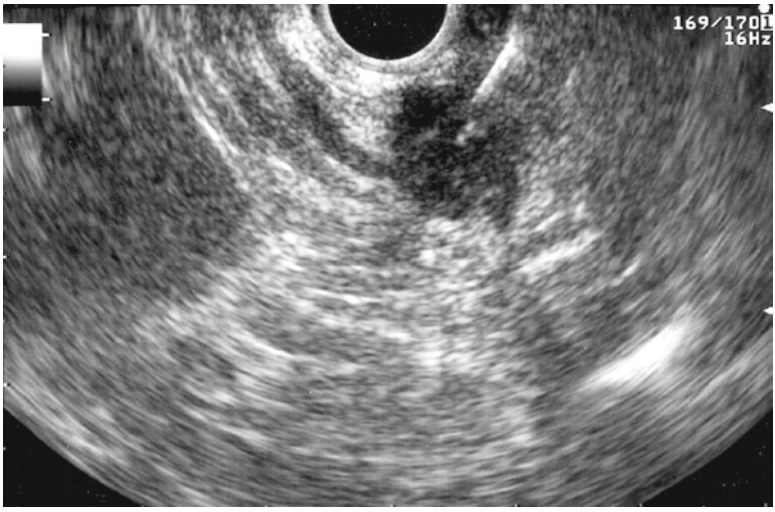

Fig. 9. Adrenal metastasis. An 11 mm nodule in the left wing of the left adrenal gland.

markedly improved the accuracy to 94–95% (Fig. 10) (9, 10, 12). Typically, 3–4 passes is sufficient for lymph nodes, a primary mass may require additional sampling. We use the smallest gauge needle possible (25-ga)

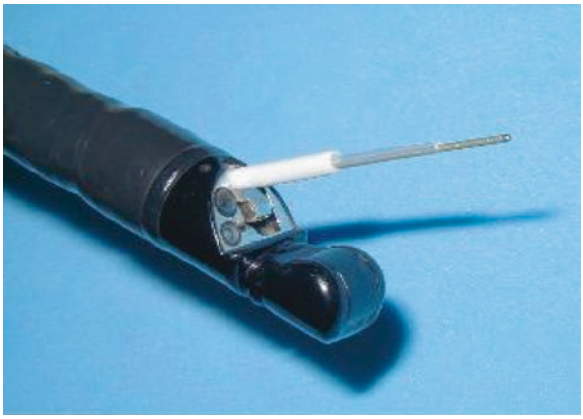

Fig. 10. Tip of linear echoendoscope with FNA needle.

to minimize hemorrhagic contamination yet still provide sufficient material. Adjunctive use of negative suction through the supplied syringe can increase overall cytologic yield but may also draw in more contaminating blood. In cases when EUS-FNA is nondiagnostic, a 19-gauge Trucut biopsy needle designed for use in conjunction with an echo endoscope may be useful to procure larger specimens for histopathological analysis. This approach is particularly useful in evaluating patients with Hodgkin's lymphoma (40).

SELECTIVE NODAL TARGETING

There has been a great deal of interest in defining nodal echo qualities that best predict the likelihood of harboring metastatic disease. In general, suspicious features include sharp borders, a uniformly hypoechoic appearance, rounded shape, and a short axis diameter of >1 cm (Fig. 11). EUS-FNA sampling of smaller suspicious lymph nodes undetected by CT imaging offers equivalent diagnostic sensitivity to larger malignant lymph nodes. This has great impact, particularly in unexpected locally advanced disease (41). The PPV for lymph nodes that meet all criteria is quite good (80%), but sensitivity is imperfect. Only about 25% of lymph nodes in one study exhibited all of these features (40). It is important to remember small triangular lymph nodes in the subaortic space (station 5) are relatively common and usually benign, especially in smokers, urban dwellers, and those with chronic lung disease.

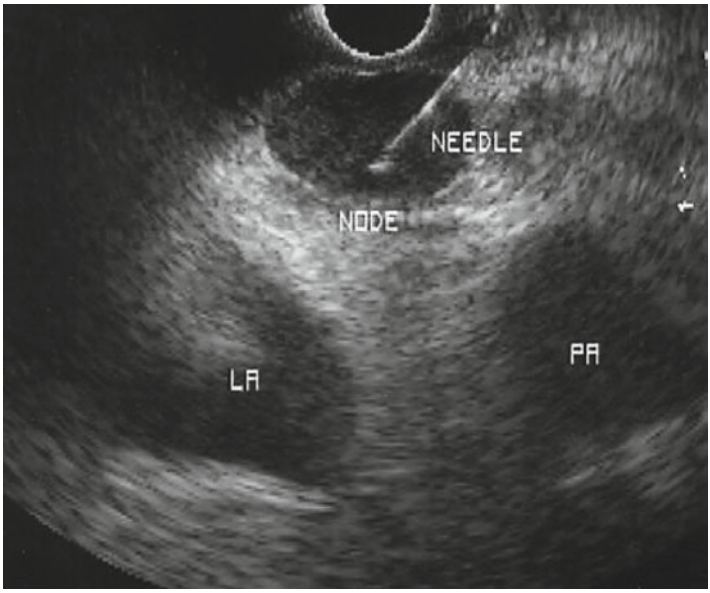

Fig. 11. EUS-FNA of lymph node.

DOES EUS PREDICT T4 DISEASE?

Studies have also demonstrated high sensitivity and specificity of EUS-FNA for advanced tumors (T4 by direct invasion of the mediastinum, heart, great vessels, trachea, esophagus, vertebral body, or carina) or malignant pleural effusion retrospectively (42) and prospectively (25). Surgery is generally contraindicated in T4 disease. The role of EUS in defining T4 disease, however, remains unclear. One retrospective study assessed the accuracy of EUS in discriminating T4 disease. Among 175 patients, 8 were diagnosed at surgery as T4, including 2 with malignant pleural effusions by EUS-FNA. The sensitivity, specificity, PPV, and NPV of EUS for T4 extent were 87.5, 98, 70, and 99%, respectively. Three of five patients, thought to have mediastinal invasion at EUS, were surgically staged as T2, highlighting the risk of over-staging. Caution should be excercised when staging primary lung or mediastinal masses by EUS since over-staging may occur particularly for mediastinal invasion.

EUS AFTER INDUCTION THERAPY

Patients who have completed induction therapy, in anticipation of surgery with intent to cure, present a unique challenge. The problem of "restaging" after therapy relates to scarring and inflammatory change.

CT is particularly inaccurate (58%). Such scarring limits subsequent surgical staging such as MS with an incompletion rate as high as 40% (17, 43). A few studies have examined the role of EUS-FNA to evaluate the mediastinal response to neoadjuvant chemotherapy (17, 36). A recent study of 28 patients demonstrated that postinduction EUS-FNA had a high NPV with 93% accuracy. Although concordant with PET–CT restaging findings, invaluable pathological confirmation with this minimally invasive procedure (avoiding MS) establishes its superiority and confidence in selecting the most appropriate preoperative "intent to cure" surgical candidates (33).

NEW APPLICATIONS

EUS-guided fiducial placement of CyberKnife radiotherapy of mediastinal and abdominal malignancies is a newer application which further expands the role of EUS. Eleven of thirteen patients underwent successful placement of three to six fiducials through a 19-gauge fine needle for directed radiation therapy. One infectious complication was reported (34). Further studies are forthcoming in defining this EUS application.

COST EFFECTIVENESS OF EUS IN LUNG CANCER

Cost-efficacy has been evaluated prospectively (17) and in decision analysis modeling (31). The studies demonstrated a cost benefit with EUS-FNA compared to MS and concluded EUS-FNA could reduce the cost of staging by 16–40%. The cost of MS in these studies was, however, quite conservative, as calculations were based on the assumption that patients would stay in a hospital for a total of 3 days (15, 17).

TRAINING

Performing EUS at a high level requires the completion of a dedicated fourth year fellowship. Among the various indications for EUS, mediastinal exams are among the most readily learned. In one study, the learning curve of EUS-FNA was assessed using two residents (17). Two residents each performed 29 and 25 procedures and, not surprisingly, failed to reach the ability of experienced operators. The American Society for Gastrointestinal Endoscopy (ASGE) recommends a minimum of 150 cases of supervised EUS, 50 of which should include FNA (32). Equally controversial is defining who should be performing

trans-esophageal lung cancer staging. Since lung cancer is not in the clinical domain of most gastroenterologists, other specialists are pursuing training in trans-esophageal EUS. Short courses in mediastinal EUS are increasingly available to both pulmonologists and thoracic surgeons.

CONCLUSION

EUS has redefined the way we evaluate patients with posterior mediastinal lesions and especially those with NSCLC. Despite the broad evidence base supporting its utility, the integration of routine EUS in patients with NSCLC outside of tertiary care centers has not been rapidly adopted. In time more data will better define the role of EUS in the diagnosis of mediastinal masses as well as the diagnosis and staging of lung cancer.

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