

REVIEW ARTICLE:

MINIMALLY INVASIVE DIAGNOSIS AND MEDIASTINAL STAGING OF LUNG CANCER: ENDOBRONCHIAL ULTRASOUND GUIDED TRANSBRONCHIAL NEEDLE ASPIRATION

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ABSTRACT

Mediastinal involvement by lung cancer is a common finding, which presents a challenge to physicians. Obtaining specimens for cytologic and histologic evaluation is crucial for both diagnosis and staging of lung cancer. Surgical biopsy methods are effective, but invasive and expensive. They commonly require hospitalization, general anesthesia and mechanical ventilation. Minimally invasive modalities are now at the disposal of physicians and surgeons that provide highly effective means of obtaining tissue specimens. Conventional transbronchial needle aspiration can be used with traditional diagnostic flexible bronchoscopes available in most hospitals. Endobronchial ultrasound and endoscopic ultrasound are complimentary imaging modalities that permit real-time guidance and verification of successful lymph node biopsy. They are highly sensitive and specific diagnostic tests and enable physicians to access a wide range of lymph node locations within the mediastinum.

ARTICLE

INTRODUCTION:

Mediastinal lymph node tissue sampling plays a critical role in the diagnosis and staging of patients with lung cancer. The seventh edition revisions to Tumor, Node, Metastasis (TNM) lung cancer staging have recently been published by the International Association for the Study of Lung Cancer (IASLC) staging project¹ with demonstration of prognostic implications based on nodal staging². Treatment options also vary greatly by stage, necessitating the accurate staging of patients.

Surgical staging, typically by mediastinoscopy, is considered the gold standard and has a high sensitivity and specificity³. Mediastinoscopy or other surgical staging methods, however, usually require general anesthesia, hospital admission, and have higher associated morbidity and expense. In contrast, transthoracic needle aspiration is suboptimal as it can only be used to target enlarged lymph nodes (>1.5 cm diameter) in select locations with a high risk of complications, including a significant rate of pneumothorax.³ Radiographic imaging techniques, such as computed tomography (CT), positron-emission tomography (PET), and magnetic resonance imaging (MRI), have improved greatly but these modalities still lack the sensitivity and specificity required for accurate staging of mediastinal lymph nodes⁴. Recent advances in endoscopic sampling of mediastinal lymph nodes have granted physicians minimally invasive means to diagnose and determine appropriate treatment options for their patients.

Mediastinal Lymph Node Stations:

Until recently, there has been disparity in the definition of mediastinal lymph node locations. The first map of mediastinal lymph node stations was developed by Naruke⁵ in 1967 and has been endorsed by the Japan Lung Cancer Society. While the Mountain and Dresler revision of the American Thoracic Society (ATS) map has been widely used in North America⁶, it has not been routinely used in Europe; furthermore, European surgeons have proposed additional variations of their own⁷. Current TNM lung cancer staging uses a new lymph node map with the intention of unifying discrepancies between prior mediastinal lymph node maps⁸. An outline of the new IASLC lymph node station definitions is summarized in Table 1. Figure 1 depicts CT images of several lymph node stations frequently biopsied by minimally invasive methods.

Several important discrepancies between prior lymph node maps have been clarified by the new IASLC lymph node staging project. Since lymphatic drainage in the superior mediastinum is predominantly towards the right, the division of the right and left paratracheal lymph nodes (stations 2 and 4) are now designated at the left lateral border of the trachea rather than at the midline. (Figure 1) Definitions for prevascular lymph nodes (station 3a) have been further defined to involve nodes anterior to the superior vena cava and the left carotid artery, on the right and left respectively. Nodes previously defined as prevascular lying directly anterior to the trachea have now

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been included in the station 4R designation. New definitions have also clarified discrepancies between the Mountain and Dresler and the Naruke classification systems for subcarinal (station 7) lymph nodes. The prognostic value of this new lymph node classification system has been recently demonstrated with a retrospective 5-year survival of 84% for patients with N0, 52% with N1, 36% with N2, and 20% with N3 disease.²

MINIMALLY INVASIVE BIOPSY METHODS

Conventional Transbronchial Needle Aspiration

Methods of sampling mediastinal lymph nodes via transbronchial needle aspiration (TBNA) were first described with rigid bronchoscope with subsequent adaptation to flexible bronchoscopy by Wang and colleagues⁹. TBNA can be used for both the diagnosis and staging of malignancy involving the mediastinum. Conventional TBNA requires careful examination of the patient's CT scan and intimate knowledge of mediastinal anatomy in order to locate target lymph nodes and avoid other mediastinal structures, such as blood vessels, based primarily on bronchoscopic airway landmarks. Despite its clinical usefulness, however, surveys have shown that conventional TBNA remains an underutilized technique performed by only 10-30% of pulmonologists.^{10,11} Primary concerns limiting the use of TBNA have included lack of training, low yields, and fear of damage to the bronchoscope. However, bronchoscopist training and improvements in cytologic specimen handling can redress many of these issues that have previously limited the use of TBNA.¹²

A variety of commercially available flexible needles and catheter systems can be deployed via the working channel of a flexible bronchoscope. The needle is kept sheathed within the catheter during insertion through the bronchoscope to prevent equipment damage. For the same reason, it is advised to keep the bronchoscope straight during catheter insertion. Advancing a sheathed needle through an angled bronchoscope, such as when the distal tip is flexed, can still result in damage to the working channel from puncture of the needle through the catheter sheath. To this end, the catheter and sheathed needle are often introduced with the bronchoscope in the neutral position within a large airway such as the trachea. The needle can be safely deployed once the metal hub of the catheter can be visualized extending outside the bronchoscope.

Ideally, the needle should penetrate the intercartilaginous space as perpendicular as possible to the airway wall. (Figure II) There are four commonly used methods of needle insertion. For the "jabbing method", the deployed needle is inserted into the airway wall by holding the bronchoscope stable while the catheter is advanced in a jabbing motion. In the "piggyback method", the deployed needle is inserted by advancing the bronchoscope and catheter together as a unit by holding the catheter position stable relative to the bronchoscope at the proximal end of the working channel and advancing the bronchoscope. The "hub against the wall method" keeps the needle sheathed while the bronchoscope is positioned with the distal end of the catheter fixed against the airway wall; the action of unsheathing the needle from the catheter advances the needle into the airway wall. The "cough method" is performed simultaneously with any of the other methods by having the patient forcefully cough to assist the penetration of the needle through the airway wall.¹³

Once the needle has been inserted through the airway wall, suction is applied to the catheter by a syringe. The needle is then agitated within the lymph node by manually advancing and retracting the catheter. Aspiration of blood into the catheter suggests the possibility of unintentional insertion into a mediastinal blood vessel; in this case, suction should be removed, the needle and catheter should be flushed with saline, and the needle should be reinserted into a different location. After successful lymph node aspiration, the needle is then retracted back into the catheter sheath and the catheter is removed from the bronchoscope after visual confirmation of successful needle retraction. Similar to insertion of the TBNA catheter into the bronchoscope, the bronchoscope should be kept straight during removal to prevent damage to the working channel. Slides can then be made from the aspirate for cytologic examination. Samples are removed from the needle by gently forcing air with a syringe through the catheter and needle, expelling the sample onto a cytology specimen slide.

Diagnostic yield with conventional TBNA is quite variable with reported sensitivities ranging from 15-85%.^{14,15} Review of the literature has demonstrated multiple factors that increase the diagnostic yield of conventional TBNA.¹⁶ The presence of enlarged lymph nodes on CT imaging is associated with improved diagnostic yield compared to cases without radiographic enlargement. Furthermore, diagnostic yield has been shown to increase linearly with increasing lymph node diameter from <1 cm to 2.5 cm.¹⁷ Lymph nodes >2.5 cm did not result in further increases in yield. Conventional TBNA for malignancies originating in the right lung are associated with higher yields than those from the left lung. The subcarinal (station 7) and right lower paratracheal (station 4R) are also associated with higher diagnostic yields than the left lower paratracheal region (station 4L).¹⁸ Larger 19-gauge needles can provide core histology samples and can produce higher diagnostic rates versus 21 and 22 gauge cytology needle samples. Regarding the question of how many aspirates are required to maximize sensitivity, Chin et al demonstrated that TBNA yield improved from 42% on the initial pass to 57% after the seventh pass without significant improvement

in yield with subsequent aspiration attempts.¹⁹ In fact, no new cancer diagnoses were made after the seventh TBNA pass. Diagnostic yields are higher in malignant than in non-malignant diseases, with small cell lung cancer having a higher sensitivity compared to non-small cell lung cancer (NSCLC) and lymphoma having a relatively lower sensitivity. Availability of rapid on-site cytopathologic examination (ROSE) and increased experience of the bronchoscopist have also been shown to positively impact yield.

Procedural complications are rare, but include risk of bleeding, pneumothorax, pneumomediastinum, hemomediastinum, bacteremia, and pericarditis.¹³ Other potential risks include damage to the bronchoscope by the TBNA needle which require costly repairs.

Endobronchial Ultrasound Transbronchial Needle Aspiration

When performing conventional TBNA, the bronchoscopist relies upon careful evaluation of the patient's CT scan and correlation between the anatomical landmarks within the tracheobronchial tree relative to mediastinal structures. Despite this, there is no direct confirmation of successful sampling of the lymph node, though ROSE is useful to corroborate cytologic findings during the procedure. Aside from difficulty correlating mediastinal anatomy to airway findings, another source of difficulty in successful lymph node sampling is that lymph node location has been shown to vary as much as 6.2 ± 2.9 mm with respiration²⁰. Real-time visual confirmation of needle penetration into the target node ensures proper biopsy location even for very experienced proceduralists.

Miniaturization of ultrasound transducers has allowed the use of endobronchial ultrasound (EBUS) guidance in diagnostic flexible bronchoscopy. Initially performed with a 360° radial ultrasound probe, current dedicated EBUS bronchoscopes use a linear (convex) transducer which produces an image along a 50° arc when placed in contact with the airway wall. A saline-filled balloon can then be used to improve the contact of the bronchoscope transducer and the airway wall, thereby improving transduction of sound waves and image acquisition. Use of these specialized EBUS bronchoscopes allows the bronchoscopist to image mediastinal structures, including real-time confirmation of biopsy needle insertion into the lymph node. Doppler ultrasonography further enables the bronchoscopist to differentiate between lymph nodes and mediastinal blood vessels. (Figure III)

The bronchoscopist must take into consideration several distinct differences between linear EBUS bronchoscopes and traditional diagnostic bronchoscopes. Commercially available EBUS bronchoscopes have a larger outer diameter (6.2-6.9 mm), which necessitates oral introduction of the bronchoscope. Optical image resolution is generally inferior and oriented at an angle due to the presence of the ultrasound transducer making airway evaluation more difficult. The angulation range of the flexible bronchoscope tip is also reduced; angulation range for an EBUS bronchoscope is typically 120° flexion and 90° extension, compared to diagnostic bronchoscopes with 180° flexion and extension maneuverability. As a result, most bronchoscopists will opt to do their initial airway evaluation with a diagnostic bronchoscope before switching to the EBUS bronchoscope to survey the mediastinal lymph nodes and perform EBUS-guided TBNA.

Compared to conventional TBNA, EBUS-guided TBNA has a substantially improved yield with reported sensitivity greater than 95%, specificity of 100%, and accuracy of 90%.²¹ The higher sensitivity of EBUS-guided TBNA allows for fewer aspirates to be performed. Lee and colleagues demonstrated 69.8% sensitivity for NSCLC after the first EBUS-guided TBNA aspirate, 83.7% after the second aspirate, and 95.3% after the third aspirate.²² A prospective, randomized comparison between conventional TBNA and EBUS-guided TBNA demonstrated no significant difference in sensitivity for subcarinal lymph nodes, but a significant increase in EBUS-guided yield for all other nodal stations (58 vs. 84%, $p < 0.001$).²³ The lack of difference in subcarinal lymph nodes between the two methods, however, may reflect the higher yields associated with biopsy of the subcarinal lymph node region and the degree of expertise of the bronchoscopists.

Interestingly, aspiration may not be required during EBUS-guided biopsy of lymph nodes. A recent trial demonstrated no significant difference in the adequacy of cytologic specimens obtained with EBUS-guided TBNA when comparing samples obtained with suction versus samples obtained just from needle penetration of the lymph node. Avoiding use of suction theoretically decreases the likelihood of traumatic bleeding, which makes cytologic interpretation difficult; conversely, however, there was no significant benefit from avoiding suction either. Another area under investigation involves the use of ROSE for EBUS-guided TBNA. While demonstrated to be beneficial in conventional TBNA, its use in EBUS-guided TBNA may not be as clinically significant.²⁵

There are several other important considerations when evaluating the addition of EBUS-guided TBNA at an institution. EBUS-guided TBNA has been shown to increase procedure time by an additional 6.3 to 30 minutes.²⁶ Bronchoscopists require additional training with the equipment and yield with this technique has been suggested to improve with increased experience.²⁷ The American College of Chest Physicians recommends that a bronchoscopist

perform 50 supervised procedures to gain competency with the specialized equipment and ultrasound image interpretation.²⁸ Equipment costs are another important consideration, as the EBUS bronchoscope requires a separate ultrasound processor and specialized biopsy catheters. Capital equipment costs were estimated to be over \$72,000 (U.S.) in 2007 and have increased with the release of newer generations of equipment. As a result, EBUS is a valuable tool when used by a trained and experienced pulmonologist or thoracic surgeon who frequently perform the procedure, such as at an academic or cancer center with a large referral base.

Endoscopic Ultrasound Fine Needle Aspiration

Transesophageal endoscopic ultrasound (EUS) has been used by gastroenterologists for biopsy and staging of subcarinal and paraesophageal lesions. A specialized EUS endoscope with a radial ultrasound transducer is used to perform fine needle aspiration (FNA) of mediastinal lymph nodes within reach of the esophagus, which is positioned posterior and slightly to the left of the trachea. Numerous studies have demonstrated the utility of EUS-guided FNA, with a pooled sensitivity of 83% and specificity of 97% from a meta-analysis of 18 studies.²⁹ Primary use of EUS-guided FNA is for subcarinal and paraesophageal lymph node (stations 7 and 8, respectively), and therefore EUS-guided FNA should be considered as a complimentary modality to EBUS-guided TBNA. EUS can also be used to biopsy metastatic disease in subdiaphragmatic sites such as the left adrenal gland, celiac lymph nodes, and liver. Specialized centers have demonstrated the ability to perform both transesophageal and transbronchial lymph node sampling with the same EBUS bronchoscope during one extended procedure. , Given the unique training required for each procedure, however, most centers will opt to have a separate bronchoscopist and endoscopist perform their respective procedure, but potentially timed back-to-back to utilize the same procedural sedation.

Surgical Methods

In contrast to minimally invasive methods of mediastinal tissue sampling, surgical biopsy is considered the gold standard but has higher associated risk, require operating room and equipment availability, commonly require hospitalization, and is more expensive. Knowledge of surgical alternatives is important, however, when determining the best diagnostic approach for a patient. Furthermore, surgical methods are sometimes required when non-invasive methods are not feasible or unrevealing.

Cervical mediastinoscopy utilizes a rigid mediastinoscope which is inserted in an incision above the suprasternal notch and used to biopsy and/or resect lymph nodes adjacent to the trachea. The procedure allows access to the bilateral upper and lower paratracheal nodes (stations 2R, 2L, 4R, and 4L), pretracheal nodes (stations 1 and 3), and anterior subcarinal nodes (station 7). The procedure is performed in an operating room under general anesthesia, though patients can often be discharged on the same day. Sensitivity is approximately 80% with a 10% false negative rate³. Sensitivity with videomediastinoscopy may be higher (90%). As many as half of the false negative cases, however, may be due to nodal involvement in stations not accessible to mediastinoscopy.

Anterior mediastinotomy (Chamberlain procedure) can be used to access to lymph nodes in the aortopulmonary (AP) window (station 5). It uses an incision in the 2nd or 3rd intercostal space to the left of the sternum. An extended cervical mediastinoscopy can also be used for these lymph nodes with the mediastinoscope inserted at the suprasternal notch and positioned lateral to the aortic arch.

Video assisted thoracoscopy (VATS) can be used to biopsy unilateral paratracheal nodes. Reported sensitivity varies widely, ranging from 50-100%³. The variability largely stems from the lone prospective multicenter trial in which VATS staging was only feasible in 75% of patients³². VATS also has potential use in evaluating for non-resectable T4 tumors which would preclude surgical resection as well as involvement of the pleura, pleural fluid, or diaphragm. VATS requires general anesthesia and patients must be able to tolerate double lumen intubation with single-lung ventilation during the procedure.

Clinical Considerations

As with any other diagnostic scenario, clinicians must choose the best biopsy method for their patient depending on a multitude of factors, including the sensitivity of the test, risk of the procedure, expense, and alternative methods. Lymph node location and patient comorbidities will obviously play a significant role in this decision-making process. Radiographic imaging including CT, PET, and/or combined PET/CT are useful tools to help the physician identify lesions to target when diagnosing and staging a patient, but tissue biopsy is still required. Positron emission tomography (PET) has a higher sensitivity and similar specificity (74% and 85%, respectively) for identifying mediastinal metastasis compared to CT (51% and 85%)³³.

In addition to identifying lesions that can be biopsied with high sensitivity and low risk procedures, it is also important to consider the radiographic stage of the patient. Targeting the highest stage lesion first can provide simultaneous diagnostic and staging information and prevent subjecting the patient to unnecessary separate procedures. For

example, EBUS-guided biopsy of an N3 lymph node can obtain tissue for diagnostic identification for a malignancy cell type as well as characterize the patient at a minimum of TNM Stage IIIB. Thus, a single procedure can provide both a diagnosis and dictate further therapeutic options.

Utilization of complimentary methods of minimally invasive mediastinal staging also allows non-surgical staging of a significant portion of the mediastinum. Wallace and colleagues demonstrated a significant increase in diagnostic sensitivity when using combined EBUS and EUS (93%) compared to either modality alone (69% for either modality alone).³⁴ However, surgical biopsy should be considered if minimally invasive methods are non-diagnostic for lesions that are high risk to change the TNM stage of a patient or alter the treatment approach. Table II highlights the lymph node stations accessible by commonly used mediastinal biopsy methods.

CONCLUSIONS

Diagnosis and staging of lung cancer involving the mediastinum is an important, but often challenging task. Minimally invasive methods of obtaining mediastinal tissue samples are highly sensitive, first-line options which also minimize patient risk and cost of care.

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Table I: Summary of IASLC Lymph Node Stations⁸

<i>Description</i>	<i>Station</i>	<i>Location</i>
Low Cervical, Supraclavicular, and Sternal Notch	1 (R+L)	Between the lower margin of cricoid cartilage and the clavicles, divided bilaterally by the midline of the trachea
Upper Paratracheal	2R	Between the apex of right lung and pleural space to the caudal margin of the intersection of innominate vein with trachea and extending to the left lateral border of the trachea
	2L	Between the apex of left lung and pleural space to upper border of aortic arch, and to the left of the left lateral border of the trachea
Prevascular	3a	Anterior to the superior vena cava (on the right) and left carotid artery (on the left), posterior to the sternum, and extending from the apex of the chest to the level of the carina
Retrotracheal	3p	Posterior to the trachea extending from the apex of the chest to the level of the carina
Lower Paratracheal	4R	Between the caudal margin of the intersection of the innominate vein with the trachea to the lower border of the azygos vein and extending to the left lateral border of the trachea
	4L	Between the upper border of the aortic arch to the upper border of the left main pulmonary artery, and to the left of the left lateral border of the trachea
Subaortic	5	Lateral to the ligamentum arteriosum and between the lower border of the aortic arch and the upper border of the left main pulmonary artery
Paraaortic	6	Anterior and lateral to the ascending aorta and aortic arch lying between the upper and lower borders of the aortic arch
Subcarinal	7	Between the tracheal carina and the superior border of the left mainstem bronchus on the left, and the inferior border of the bronchus intermedius on the right
Paraesophageal	8 (R+L)	Adjacent to the esophagus extending from the upper border of the lower lobe bronchus on the left, and the lower border of the bronchus intermedius on the right
Pulmonary Ligament	9 (R+L)	Nodes within the pulmonary ligament between the inferior pulmonary vein and the diaphragm
Hilar	10 (R+L)	Immediately adjacent to the mainstem bronchus and hilar vessels between the lower rim of the azygos vein on the right, and the upper rim of the pulmonary artery on the left, and the bilateral interlobar region
Interlobar	11 (R+L)	Between the origin of the lobar bronchi; 11R can be further subdivided into 11s (between the upper lobe bronchus and bronchus intermedius) and 11i (between the middle and lower lobe bronchi)
Lobar	12 (R+L)	Adjacent to the lobar bronchi
Segmental	13 (R+L)	Adjacent to the segmental bronchi
Subsegmental	14 (R+L)	Adjacent to the subsegmental bronchi

Abbreviations: IASLC = International Association for the Study of Lung Cancer; L = left; R = right

Table II: Accessibility of Lymph Node Stations by Different Modalities

Modality	Accessible Lymph Node Stations
Standard mediastinoscopy	Superior mediastinal, subcarinal Stations 1, 2, 3, 4, and 7
Extended mediastinoscopy	Aortic nodes Stations 5 and 6
Anterior mediastinoscopy (Chamberlain Procedure)	Aortic nodes Stations 5 and 6
VATS	Superior mediastinal (right), subcarinal, and aortic nodes Stations 1, 2R, 3, 4R, 5, 6, and 7
TBNA	Superior mediastinal, subcarinal, N1 nodes Stations 1, 2, 3, 4, 7, 10, 11, and 12
TTNA	Superior mediastinal (anterior) Stations 1, 2, 3, and 4
EUS-FNA	Left lower paratracheal, subaortic, inferior mediastinal Stations 4L, 7, 8, and 9
EBUS-TBNA	Superior mediastinal, subcarinal and N1 nodes Stations 1, 2, 3, 4, 7, 10, 11, and 12

Adapted from: Mountain and Dresler⁶

Figure I: Examples of IASLC Lymph Node Stations

Horizontal computerized tomography images descending through the thorax from Panels A to D. A) Right lower paratracheal lymph node (station 4R). B) Right and left lower paratracheal lymph nodes (stations 4R and 4L). 4L lies below the aortic arch and between the aorta and pulmonary artery to the left of an imaginary line tangential to the left border of the trachea (white dotted line). The inferior border of the 4R station is defined by the azygous vein (white dotted arrow). C) Right hilar lymph node (station 10R) lies inferior to the azygous vein within the interlobar region, as demonstrated by the origin of the right upper lobe bronchus. D) The subcarinal lymph node (station 7) is located inferior to the carina and between the mainstem bronchi.

Abbreviations: Ao = aorta; BI = bronchus intermedius; IASLC = International Association for the Study of Lung Cancer; LB = left mainstem bronchus; PA = pulmonary artery; RB = right mainstem bronchus; SVC = superior vena cava; Tr = trachea

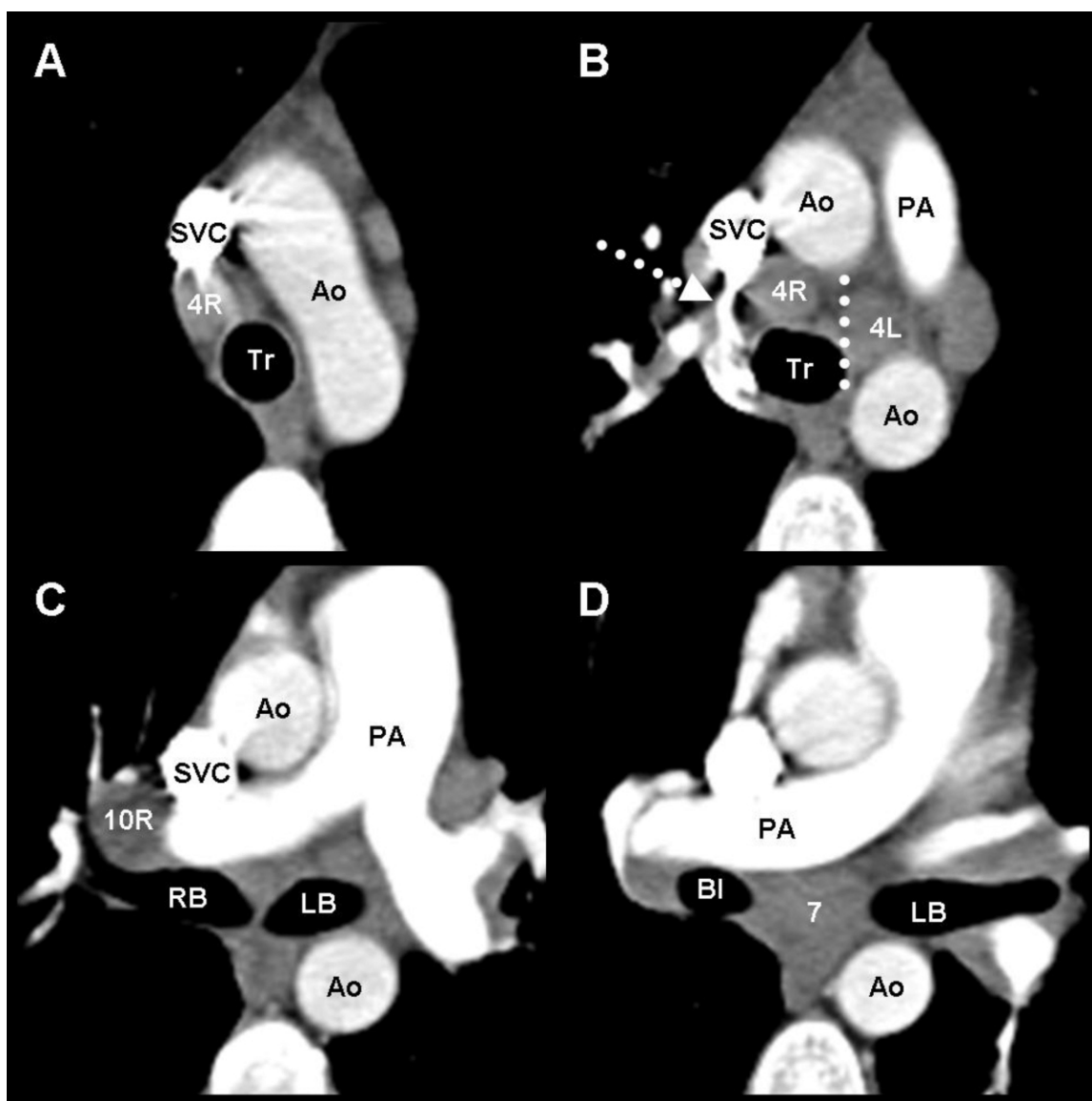
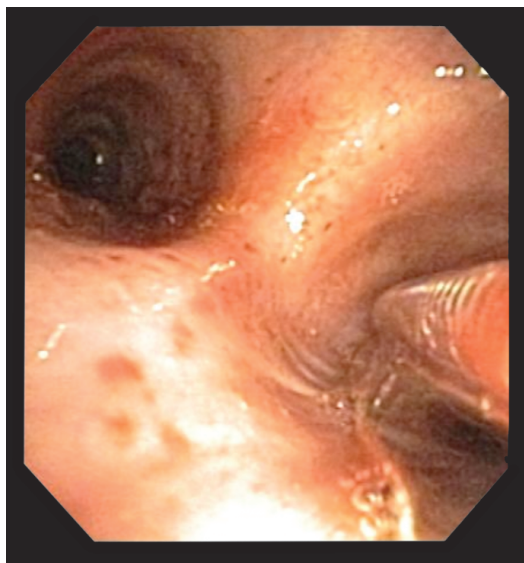


Figure II: Conventional TBNA

Example of a TBNA catheter deployed through a flexible bronchoscope with the needle successfully inserted through the bronchial wall and into the underlying subcarinal lymph node (station 7).

**Figure III: Linear EBUS-Guided TBNA**

A)EBUS bronchoscope. The linear transducer is located in the distal portion of the bronchoscope. Visual optics are oriented at 35° (not shown).B)EBUS bronchoscope with saline-filled balloon and TBNA needle deployed.C)Ultrasound image of a lymph node (superior) and mediastinal blood vessel (inferior) confirmed with doppler imaging (white box). Presence of blood flow is indicated by color display (yellow).D)Real-time imaging of lymph node needle aspiration.

