Chapter 2
Advances in Nonsurgical Sampling Techniques for the Diagnosis and Staging of Lung Cancer

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Introduction

Intrathoracic malignancy can present with symptoms, as an incidental finding on imaging performed for an unrelated reason or as a finding during lung cancer screening. Radiographic findings are judged in the context of clinical and historical features, allowing the clinician to characterize the overall picture as low, intermediate, or high suspicion for malignancy. Further radiology or laboratory testing provides clues as to the type and possible stage of malignancy. Ultimately the clinician must decide whether intervention or radiographic monitoring is indicated. In many patients, some form of pathologic sampling is required to determine the diagnosis and, if it is a malignancy, the stage of the malignancy. Depending on the tumor cell type, it may also be critically important to obtain the molecular profile, which has implications for prognosis or treatment.

There are multiple ways to sample lesions in the thorax. Suspected primary or metastatic parenchymal lesions may be amenable to percutaneous CT-guided needle biopsy. Primary and metastatic lesions can be accessed bronchoscopically with saline lavage or washing, cytologic brushing, forceps biopsy, or needle aspiration. Multiple surgical options are available, including mediastinoscopy, video-assisted thoracoscopic biopsy, and open thoracotomy. Selecting from among these options can be challenging, but the overriding goal should be to obtain all of the information

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Table 2.1 Nonsurgical sampling techniques employed for suspected intrathoracic malignancies

Sampling technique	Site(s) accessible	Staging procedure	Real-time imaging and sampling	Complication risk	Specimen(s) attainable
Wang	Central	Yes	No	+	FNA and biopsy
Radial EBUS	Central and peripheral	Yes[a]	No	+	FNA
Convex EBUS	Central	Yes	Yes	+	FNA
CT	Central and peripheral	No	+/–	++	FNA and biopsy
Navigational	Central and peripheral	No	+/–	+	FNA and biopsy

[a]Radial EBUS is now most commonly used for guidance of sampling peripheral nodules; its use in sampling mediastinal lymph nodes for diagnostic and staging purposes has largely been supplanted by Convex EBUS

needed for diagnosis and staging with the least risk to the patient. For a patient with suspected thoracic nodal metastasis, the ideal procedure is one in which diagnosis and staging are performed in a single step.

This chapter will address some of the more commonly used nonsurgical sampling techniques employed for suspected intrathoracic malignancies (Table 2.1). Selecting the sampling modality must take into account the current and future needs of the patient. The optimal paradigm for care of the patient with lung cancer involves multidisciplinary coordination, and the cytologist or pathologist should fully understand the rationale for and the limitations of each of these techniques in order to fully participate in this care. Although they may not be directly involved in the choice of a sampling modality or the performance of the actual procedure, pathologists play a critical role beyond simply providing a cytologic, histologic, or molecular diagnosis. It is essential that the pathologist provides regular feedback as to the quality and quantity of the specimen to the bronchoscopist, radiologist, or surgeon who is collecting tissue samples.

The sampling targets in the chest can be roughly divided into central lesions and peripheral lesions. Over 70 % of patients with non-small cell lung cancer (NSCLC) will have nodal involvement at the time of their initial presentation [1]; therefore, many patients will have both peripheral and central targets to choose from. The various nonsurgical techniques for sampling available can be broadly divided into bronchoscopic and radiologic techniques, although some modalities combine both bronchoscopic and radiologic approaches to obtain pathologic specimens. This chapter addresses three bronchoscopic techniques, including endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) using convex probe technology (CP-EBUS), endobronchial ultrasound-guided sampling of peripheral nodules using radial probe technology (RP-EBUS), and electromagnetic navigational bronchoscopy (ENB). It also discusses CT-guided techniques for the sampling of parenchymal lung nodules, including CT-guided needle aspiration (CTNA) and CT-guided biopsy (CTNB).

In this chapter, "sampling" refers to the group of procedures available to clinicians for tissue diagnosis in suspected thoracic malignancy. Physicians and patients alike use the word "biopsy" when referring to these procedures. While the latter term may be useful in discussing various options with patients, it is incorrectly applied to brushings and fine-needle aspirates which result in a cytologic sample and not a histologic one. The distinction is an important one for the clinician; it is important to understand the kind of information obtainable from the samples derived from the different procedures. An excellent example would be the case of pulmonary lymphoma. Cytologic sampling with EBUS-TBNA combined with flow cytometry may establish a diagnosis of lymphoma, but the added information obtained from histologic sample, which has greater preservation of nodal architecture than a cytologic sample, may be useful for guiding treatment decisions. Knowledge of these differences may guide procedural choices in certain clinical circumstances.

General Principles of Lung Cancer Management Pertaining to Pathologic Sampling

Multiple guidelines exist to aid in clinical decision-making for the care of a patient with suspected lung cancer. For instance, the American College of Radiology recently proposed the Lung Imaging Reporting and Data System to standardize management of lung nodules identified on screening based on the size of the nodule, presence of a solid component, and growth characteristics [2]. Once the decision to sample a target has been made, the optimal modality for sampling has to be determined. Characteristics of the lesion and clinical features of the case must be factored into an analysis of the risks and benefits of each potential approach. Some techniques are more suitable for lesions with particular characteristics, and many factors, including the location, size, and differential diagnosis, must be taken into account when choosing a sampling modality. It is important for the clinician to understand the sensitivity and the limitations of the available sampling techniques, particularly when choosing between them.

Multiple approaches may yield the correct pathologic diagnosis, but clinicians must look at the broad context of each individual's current and future care needs with respect to diagnosis, staging, and future treatment. The American College of Chest Physicians (ACCP) recently updated its guidelines for clinicians who deal with lung cancer (Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines). In the article entitled "Establishing the Diagnosis of Lung Cancer," Rivera and colleagues [3] outline the basic principles that should guide clinicians in their decision-making with respect to the selection of various diagnostic interventions. The clinician should strive to establish a pathologic diagnosis in the safest and least invasive way possible. Suspected solitary metastases should be confirmed pathologically. In patients with radiographic evidence for multiple metastatic foci in which

pathologic sampling of extrathoracic disease would be problematic or difficult, sampling of the primary focus of intrathoracic disease is appropriate. Suspected malignant effusions should be confirmed pathologically. For patients with suspected mediastinal involvement and no evidence on imaging for extrathoracic disease, the guideline emphasizes that the diagnosis should be established by the "least invasive and safest method," and bronchoscopy with TBNA, EBUS-TBNA, esophageal ultrasound-guided TBNA (EUS-TBNA), and transthoracic needle aspiration (TTNA) are listed as options.

An important consideration in undiagnosed patients is minimizing the number of procedures they undergo during the course of their management, seeking wherever possible to perform staging and diagnosis in a single step. It may be tempting to perform a CT-guided biopsy of a large peripheral mass, but if this patient is later found to have suspicious N3 nodes on a subsequent PET and requires a subsequent EBUS-TBNA to pathologically establish nodal involvement, the patient may have undergone an unnecessary intervention. This principle requires that full radiographic staging be undertaken before deciding which intervention is optimal. Patients are often very anxious and want a definitive diagnosis as soon as possible, but in the majority of cases, it is far better to have the right information than to do something right away.

An important distinction between the diagnosis and staging of NSCLC and small cell lung cancer (SCLC) should be mentioned. In NSCLC, radiographic staging should guide pathologic sampling, so that the patient's true stage is established definitively to inform prognosis and guide therapy. In SCLC, which can often be suspected radiographically in a finding of bulky, central mediastinal tumor on imaging, the diagnosis can be established by sampling whichever site using whatever intervention is easiest and safest; staging of the disease is then determined radiographically [3]. In simplest terms, in NSCLC, radiology dictates pathologic sampling to establish a stage, whereas in SCLC, staging is usually radiographic.

Sampling Central Lesions

In patients with central targets, either masses or adenopathy in the mediastinum or parenchymal masses adjacent to the central airways from the trachea to the hila, bronchoscopic sampling is a consideration. "Blind" techniques for transbronchial needle aspiration (TBNA) of mediastinal lymph nodes were developed by Wang and colleagues [4, 5] at John Hopkins over 30 years ago. Yield and safety of this technique are limited by the blind nature of the procedure, but in expert hands, it is a safe and effective tool. Wang reported an overall diagnostic yield for malignancy of 85 %. Sensitivities for the procedure have been reported ranging from 39 to 89 % [6]. Prior to the development of EBUS-TBNA, the technique was usually employed only for large subcarinal (station 7) and precarinal (station 4R) lymph nodes and was, for the most part, performed routinely only by small percentage of pulmonologists [7]. Although newer technologies have largely supplanted blind TBNA,

Wang and others [4, 5] strongly advocate that this procedure still has a role to play in the diagnosis and staging of lung cancer, citing its benefits as minimal discomfort, decreased cost, reduced risk, and widespread availability.

Radial and Convex Probe EBUS

Radial ultrasound was first developed for the field of gastroenterology in the 1980s and was adapted to bronchoscopy as more miniaturized components were developed in the 1990s. Modern radial probe endobronchial ultrasound (RP-EBUS) (Olympus) utilizes an ultrasound processor and a reusable 20 MHz ultrasound probe that is inserted through the working channel of a standard bronchoscope with a minimum working channel diameter of 2.0 mm. The radial probe uses mechanical radial scanning from a rotating transducer which, when placed in contact with the airway wall, generates a 360° B-Mode Doppler image of the layers of the bronchial wall and deeper structures adjacent to the airway. The image produced is one perpendicular to the long axis of the probe. The 20 MHz frequency allows for high resolution of the separate layers of the airway wall while providing visualization to a depth of approximately 5 cm [8]. For larger, more central airways, the probe can be covered in a sheath which has water-filled balloon at the distal tip. This can be used to facilitate circumferential contact with the airway wall for 360° imaging, allowing for imaging of the central airways and airway wall as well as central peribronchial structures such as mediastinal lymph nodes and central parenchymal lesions. The probe's small diameter (1.4 mm at the distal tip) allows for probe access to areas of the lung periphery beyond the wedge position of the bronchoscope. It is this feature which allows it to be of use in localizing peripheral lung nodules for pathologic sampling, as will be discussed later.

Early reports of performance characteristics of this tool as a means of guiding conventional TBNA of mediastinal lymph nodes suggested that in expert hands, RP-EBUS guidance improved the overall yield of TBNA over the conventional techniques. Diagnostic yield for TBNA with RP-EBUS guidance has been shown to be superior to blind TBNA, although this comparison is colored by the fact that many studies of blind TBNA did not employ rapid on-site evaluation (ROSE) [6]. In a prospective randomized trial in 200 patients, Herth and colleagues [9] reported an overall yield of 80 % for RP-EBUS-guided TBNA versus 71 % with standard TBNA ($p < 0.05$). The superiority of RP-EBUS was derived from improved yield in nodal stations other than the subcarinal station 7; at station 7, no significant difference was seen [9]. The main disadvantage of the radial probe EBUS is that real-time pathologic sampling is not possible. The probe must be withdrawn from the working channel of the bronchoscope in order to allow for the insertion of a brush, needle, or forceps. This technique has the same final limitation of blind TBNA: after identification of a target lesion, the probe is removed, and the subsequent needle stick remains a blind procedure. The probe can be deployed inside a 2.0 mm diameter guide sheath, which can be left in place after ultrasound localization of a target,

facilitating placement of a sampling tool and allowing for multiple passes at an identified target. Other disadvantages of the radial probe EBUS are its lack of color Doppler visualization of blood flow for the identification of vessels, as is possible with convex probe technology, and mechanical frailty of the probes. Although reusable, the delicate radial EBUS probes have a limited lifetime of up to 75 uses when handled with care [10].

Convex Probe EBUS

Despite its demonstrated superiority over conventional, blind TBNA for sampling central targets, RP-EBUS did not gain widespread use because of the development and introduction of curvilinear or convex probe ultrasound (CP-EBUS) technology. CP-EBUS represents an advance over radial probe technology in that it permits real-time pathologic sampling during ultrasound imaging. The convex probe technology uses a series of ultrasound transducers arranged in a curvilinear pattern at the distal end of a dedicated CP-EBUS bronchoscope. Multiple manufacturers of bronchoscopic systems currently offer a CP-EBUS platform. On the Olympus EBUS bronchoscope, the most widely used system, the curvilinear array provides a 60° field of view which is parallel to the long axis of the bronchoscope. The convex EBUS probe uses multiple quad-frequencies of 5, 7.5, 10, and 12 MHz, allowing for a depth of penetration of the ultrasound image to 5 cm, although the resolution is insufficient to differentiate the layers of the airway wall. The EBUS convex probe scope has a working channel with a diameter of 2.2 mm which terminates just proximal to the ultrasound probe head and which is angulated distally 35°, allowing the TBNA needle to pass over the probe in the plane of the ultrasound image. This permits real-time TBNA, with visualization of the needle in the target structure, representing a significant advantage over RP-EBUS. Other advantages include the optional color Doppler visualization of blood flow for the identification of vessels.

There are several disadvantages of the EBUS convex probe bronchoscope. The ultrasound transducer in the tip of the bronchoscope is distal to the light source and viewing port, and the direction of view is angulated 35° forward, parallel to the vector of the needle as it exits the scope, in contrast to the head-on field of view of standard bronchoscopy. This obliquely angulated view, which does not include the ultrasound transducer in the field, can make learning to use the EBUS convex probe scope difficult and perhaps raises the risks of traumatic injury to airway structures during bronchoscopy. Passage of the scope through the vocal cords can be particularly difficult and should be done with extreme care, as vocal cord injuries have been reported [11].

The EBUS convex probe bronchoscope is also larger than standard bronchoscopes, with an outer diameter of 6.9 mm. For this reason, EBUS convex probe bronchoscopy is done via the oral route, and airways smaller than 6.9 mm cannot be accessed. The size of the scope typically permits EBUS-TBNA of hilar nodal stations 11 and 12, however, as noted below [8]. The scope has a maximum flexion

range (angulation up) of 120° and a maximum extension range (angulation down) of 90°. With the needle in the working channel, some degree of flexion is lost, and directing the scope into apically directed segments can be challenging. Airway wall contact can be facilitated by using a water-fillable disposable balloon which fits over the transducer head. This can be particularly useful in the trachea and the mainstem bronchi, where contact with the wall can be made difficult by limits in scope flexion, particularly with the needle and sheath in place, and by the irregular contours of the tracheal rings.

Another disadvantage of the EBUS convex probe bronchoscope is its lack of a video processor. The apparatus of the ultrasound transducer occupies space in the distal end of the bronchoscope which normally houses the video processor in a modern video bronchoscope. An EBUS scope utilizes older fiberoptic technology which has lesser image quality. The size of the scope, which limits access to more distal airways, along with the fact that the field of view is both obliquely angled and of lesser quality than a standard scope, mandates the need for a full inspection with a standard scope, before or after the EBUS bronchoscopy, in those patients with suspected NSCLC who are yet unstaged, to look for endobronchial disease or other foci of neoplasm. With the convex probe EBUS bronchoscope, sampling can be done of airway-adjacent parenchymal lesions and upper paratracheal (2 L and 2R), lower paratracheal (4 L and 4R), subcarinal (7), hilar (10 L and 10R), interlobar (11 L and 11R), and lobar (12 L and 12R) nodal stations. The prevascular/retrotracheal (3), subaortic (5), para-aortic (6), paraesophageal (8), and pulmonary ligament (9) nodal stations are not accessible via the tracheobronchial tree with the CP-EBUS [8]. Studies have shown that EBUS-TBNA using convex probe technology can be used in combination with endoscopic esophageal ultrasonography (EUS) to access the additional stations at 8 and 9, and some authors have used the CP-EBUS itself in the esophagus for this purpose [12].

The convex probe EBUS bronchoscope uses disposable needles available from multiple manufacturers. The needles are designed to be anchored to the bronchoscope and have an inner stylet, a movable sheath, and a stopping mechanism that limits needle travel to a fixed distance. The inner stylet serves to minimize the chances that a plug of bronchial wall will occlude the distal lumen of the needle. The needles have a movable sheath which can be deployed into the visual field of view prior to needle deployment to ensure that the needle leaves the working channel at the 35° angulation which will allow it to clear the ultrasound transducer and minimize the chance of a costly deployment into the transducer itself. The needles have a dimpled tip that serves to make them more echogenic, enhancing visualization in the ultrasound image. 21- and 22-gauge needles are now available. The larger inner diameter of the 21-gauge needle can provide larger samples at the expense of increased stiffness; this may allow for easier needle penetration but can limit scope mobility. Studies comparing the yield and complication rates of the 21- and 22-gauge needles have shown similar yields with slightly bloodier specimens obtained with the larger gauge [13, 14]. Use of the 21-gauge needle has been shown to result in fewer needle passes per aspirated node, and some have suggested that it may be superior with regard to better preservation of histologic architecture as well as

quantity of tissue obtained [14]. The latter may have important ramifications when it comes to having adequate tissue for molecular testing in NSCLC, although data on this point is lacking.

A thorough ultrasonographic survey of the mediastinum at the time of CP-EBUS-TBNA is essential. Multiple studies of the performance characteristics of CP-EBUS-TBNA have identified PET-negative lymph nodes which were found to have malignant invasion on TBNA. Herth and colleagues showed that CP-EBUS can identify micrometastasis in patients with lung cancer and a radiographically normal mediastinum [15]. Although the percentage of cases in which CP-EBUS-TBNA upstages patients from their radiographic staging is small, they do occur, and these cases highlight the need for a full ultrasound assessment of accessible nodes and a full sampling from N3 to N2 to N1 nodes, irrespective of PET status, whenever possible in unstaged patients. In certain circumstances, however, targeted sampling is sufficient. In patients with radiographic stage 4 disease and difficult to access metastases, for example, a targeted EBUS-TBNA to establish a diagnosis may be wholly appropriate [3].

Target identification should begin before the procedure, with a careful analysis of the imaging. During the actual procedure, target identification with ultrasound should be done before the needle is inserted into the bronchoscope. The needle/sheath apparatus is then inserted and locked into place, and the sheath is deployed into the field of view and locked into place, ensuring that the needle will leave the bronchoscope at the proper angle, missing the transducer. After re-identifying the target lesion, the distance to the target (i.e., the distance of desired needle deployment) must be estimated or calculated using x and y axis centimeter markings on the view screen and the Pythagorean theorem. The stop mechanism on the needle handle is then set to this distance. Color Doppler visualization can be used to determine if blood vessels lie in the needle path. A variety of needle deployment techniques and sample collection techniques have been described. Firm deployment of the needle with the inner stylet in place can facilitate smooth needle penetration through the bronchial wall. Pitfalls at this stage often involve obstructing tracheal or bronchial rings, which can necessitate scope repositioning. After needle deployment, agitation of the stylet, ensuring that it is pushed as far distally as possible, can help to discharge a bronchial plug if one has been collected. Some operators use a suction technique, with suction ranging up to negative 20 cc, while others use no suction. A locking suction syringe is included with the Olympus EBUS needle package. The needle is then pushed in and pulled out across the span of the target, with care taken not to pull the tip of the needle out of the tissue, which could result in aspiration of the specimen into the suction syringe. Some operators use as many as 10–15 passes across a target lesion. Suction, if used, is then turned off, the needle is pulled fully into the sheath, the sheath is retracted, and the needle is removed from the bronchoscope.

It is important for the bronchoscopist to spend a moment to focus on the patient immediately after the TBNA. The puncture site should be visually observed for hemostasis. The puncture site should also be inspected for its location with respect to the desired target determined by careful examination of the imaging; was the intended target truly sampled? Precision in this regard is critical to prevent inadvertent upstaging or downstaging, as could be the case if a 10R hilar node was sampled instead of an intended nearby mediastinal 4R lymph node.

Although institutional protocol or physician preference may drive decisions regarding the type of sedation used for EBUS-TBNA, the procedure can be performed with either general anesthesia (GA), anesthesia-monitored deep sedation, or with topical anesthetic agents and moderate sedation. Results from the American College of Chest Physicians Quality Improvement Registry, Education, and Evaluation (AQuIRE) Registry, a 6-center, prospective study involving over 1,200 patients published in 2013, showed that using GA or deep sedation for EBUS-TBNA has the potential to improve patient comfort and results in the sampling of a greater number of nodal stations, possibly allowing for (or reflective of) a more systematic or thorough sampling of thoracic nodes [16, 17]. Some studies have shown that use of moderate sedation resulted in lower overall procedural yield [16]. In the AQuIRE Registry data set, the use of GA did not affect complication rates for the procedure, but it increased procedure time and the likelihood of a need for escalation of care post procedure [18]. EBUS-TBNA done with moderate sedation has the advantages of not requiring an operating room or anesthesiologist, which could lower overall procedural cost.

Performance Characteristics of EBUS-TBNA

Until CP-EBUS-TBNA became widely available, surgical mediastinoscopy was the procedure of choice for the sampling of mediastinal lymph nodes to establish a diagnosis and/or to stage the disease in patients with suspected stage II or stage III NSCLC. Multiple studies throughout the early years of EBUS-TBNA have reported similar or superior sensitivity and specificity to surgical mediastinoscopy. Adams and colleagues performed a meta-analysis of the CP-EBUS-TBNA studies published through 2008, finding a pooled specificity of 1.00 (95 % CI 0.92 to 1.00) and a pooled sensitivity of 0.88 (95 % CI 0.79 to 0.94) [19]. Gu and colleagues performed a meta-analysis which included a total of 11 studies with 1,299 patients, finding that EBUS-TBNA had a pooled sensitivity of 0.93 (95 % CI, 0.91–0.94) and a pooled specificity of 1.00 (95 % CI, 0.99–1.00) [20]. Yasufuku and colleagues published results of a prospective trial in which 159 patients underwent CP-EBUS-TBNA followed by mediastinoscopy under GA. They showed CP-EBUS-TBNA to have a sensitivity, negative predictive value, and accuracy of 81 %, 91 %, and 93 % respectively, compared to 79 %, 90 %, and 93 % for surgical mediastinoscopy [21]. The potential advantages of CP-EBUS over mediastinoscopy go beyond issues of sensitivity and negative predictive value. Whereas mediastinoscopy requires general anesthesia, EBUS can be performed with either general anesthesia, anesthesia-monitored deep sedation, or with topical anesthetic agents and moderate sedation. Lung cancer staging and diagnosis using EBUS-TBNA results in lower overall procedural risk compared to mediastinoscopy [22] and can result in lower overall healthcare costs [23, 24]. As noted above, EBUS-TBNA has a greater range of nodal stations that can be sampled compared to mediastinoscopy.

Expert interventional pulmonologists and thoracic surgeons performed the majority of published studies on the sensitivity of EBUS-TBNA for lung cancer, and the

majority of the studies were conducted exclusively in patients under GA. Even in expert hands, procedural yield can vary greatly from center to center. In the AQuIRE registry, which included 6 hospitals, diagnostic yield (with yield defined as TBNA providing a specific diagnosis) ranged from 37 % to 54 % [17]. The performance characteristics of EBUS as a tool in widespread clinical use are not well known, and some operators may struggle to replicate the results seen in clinical trials.

Complications can occur with CP-EBUS-TBNA as with any bronchoscopy. As noted, there are multiple features of the CP-EBUS bronchoscope and the CP-EBUS-TBNA technique which make it more challenging to master than standard bronchoscopy. A significant majority of the published studies examining the performance characteristics of CP-EBUS-TBNA report no complications with the procedure. However, vocal cord injury [25], pneumothorax [26], pneumomediastinum [6], mediastinitis [27, 28], empyema [29], nonfatal hemorrhage [30], and fatal hemorrhage [31] have been published or presented. Despite these, the overall complication rate for CP-EBUS-TBNA is indeed low. The AQuIRE Registry examined complication rates in 1,317 cases performed in 6 centers by 12 clinicians over a 19-month period. They found an overall complication rate of 1.44 % (95 % confidence interval, 0.87–2.24 %). Sustained hypoxia (0.3 %), pneumothorax (0.2 % if no concurrent transbronchial biopsy was performed), bleeding (0.2 %), and respiratory failure (0.2 %) were all seen. One death occurred in the cohort, resulting from bleeding following an endobronchial biopsy done during the procedure and not from the TBNA [18].

The complication rates for EBUS-TBNA in widespread clinical use are not well known but are also likely low. Asano and colleagues published the results of a nationwide survey of EBUS-TBNA in Japan, where the procedure is widely available, pooling data from 210 centers that did 7,345 cases over an 18-month period. They reported a complication rate of 1.23 % (95 % confidence interval, 0.97–1.48 %), one procedure-related death (from a cerebrovascular hemorrhage), and procedure-related infection rate of 0.19 %, including cases of mediastinitis, pneumonia, pericarditis, cyst infection, and sepsis [32]. The reported procedure-related infection in the Japanese study, which was not seen in the AQuIRE Registry data, was likely a result of the fact that the latter study limited complications to events occurring within 24 h of the procedure.

The possibility of inappropriate or inadequate staging by CP-EBUS when done by an inexperienced operator is another concern, however. The potential for erroneously upstaging or downstaging a patient with NSCLC has been cited by some as a reason to recommend that a minimum of 50 cases be proctored before a bronchoscopist is considered to have reached an appropriate level of competency with the procedure [33].

There are several major limitations to EBUS-TBNA which have critical clinical implications and important implications for the cytopathologist. Nondiagnostic aspirations are common and can occur for multiple reasons. Most studies of EBUS-TBNA classify a lymph node aspirate as nondiagnostic if it contains neither malignant cells nor lymphocytes. Rates of nondiagnostic EBUS-TBNA range from 4 % to 23 % across published series. These rates describe the final result of a patient's

complete procedure, which most often involves multiple aspirations of a target lesion. When rapid on-site evaluation (ROSE) is employed, multiple aspirations of a target are often necessary before a diagnostic specimen is obtained; therefore, the nondiagnostic rate of individual aspiration attempts is lower. For this reason, when ROSE is not available, it is suggested that 3 aspirations be performed at each target to optimize yield [34, 35].

The transbronchial approach results in contamination of the cytologic specimen with bronchial cells; in one study of CP-EBUS-TBNA, bronchial cells were seen in up to 80 % of specimens [36]. A finding of only bronchial cells in the aspirated specimen is not uncommon with EBUS-TBNA. This occurs when the hollow bore needle picks up a bronchial plug as it passes through the airway wall, despite the presence of the stylet. The bronchial plug can occlude the needle tip, preventing successful aspiration of the target. Even if it is discharged by pushing out the stylet, it can be aspirated back into the needle after suction is applied. Certain characteristics of the tumor itself can contribute to a nondiagnostic finding. Necrotic tumors may contain few cells, for example.

One key to optimizing yield and to optimizing the efficiency of EBUS-TBNA lies with ROSE of the aspirated specimens. In a large meta-analysis, ROSE was shown to increase the sensitivity of EBUS-TBNA from 80 % to 88 % while decreasing procedure times [37]. Most (but not all) studies showing improved sensitivity and negative predictive values for EBUS-TBNA over mediastinoscopy used ROSE. Resource limitations are a reality in clinical medicine, and ROSE is not available in every institution, but the bronchoscopist who performs EBUS-TBNA should strongly advocate for it in order to optimize the benefits to patients.

CP-EBUS-TBNA as Part of a Multidisciplinary, Multimodality Approach to Lung Cancer

With or without ROSE, the cytopathologist plays a critical role in the performance of the operator, providing feedback on the quality and quantity of samples obtained. Whether done by the bronchoscopist, bronchoscopy nurse, or cytopathologist on site, proper handling, triage, and processing of the aspirated sample is crucial to optimize the yield for immunohistochemical staining and full molecular analysis in the case of adenocarcinoma.

The negative predictive value of EBUS-TBNA is not 100 %, and false negatives do occur [38, 39]. Most studies classify EBUS-TBNA samples as negative or benign if they contain lymphocytes but no malignant cells. False negatives in nodal aspirates can occur due to true nodal sampling error, resulting from a needle pass missing microscopic lymph node invasion or due to limited sampling of a station with multiple nodes in which tumor invasion is present in only some. Nondiagnostic findings and false negatives present less of a clinical problem if EBUS-TBNA is employed as part of a sequential strategy. In patients where the suspicion of nodal involvement is high based on imaging, an EBUS-TBNA with a negative or nondiagnostic result

should undergo confirmatory mediastinoscopy or other surgical sampling [36]. Confirmatory surgical sampling can be done as a separate procedure or as part of a combined procedure; at some institutions, EBUS-TBNA is performed immediately preceding a planned resection, with surgical intervention aborted if a patient is found to have mediastinal lymph node involvement. Most studies report a positive predictive value of 100 % for EBUS-TBNA, and therefore, confirmatory mediastinoscopy in patients with a positive EBUS-TBNA is not needed. In certain cases, a nonmalignant positive finding which drastically changes the level of clinical suspicion for malignancy, such as a finding of fungal infection, might lead to a reassessment of the likelihood of malignancy and therefore lead to an alternate approach. For patients in whom cancer remains a concern, however, the use of confirmatory surgical sampling after a negative or nondiagnostic EBUS-TBNA avoids a missed diagnosis.

Perhaps the most useful role for EBUS-TBNA is in patients with suspected N2 disease who will be receiving neoadjuvant chemotherapy in anticipation of later surgical resection. Such patients need diagnosis and pathological staging prior to therapy, following which they may require repeat pathological staging after chemotherapy. If mediastinoscopy were the only modality for staging available, the second mediastinoscopy would be complicated by the presence of scarring from the first. With EBUS-TBNA, initial confirmation of N2 disease can be done without surgery. If there is radiographic evidence of residual nodal disease after chemotherapy, then EBUS-TBNA can be performed a second time to confirm this. If there is radiographic evidence of a good response and surgery is planned, a mediastinoscopy can be done immediately prior to resection to confirm the clearance of nodal disease. This algorithm is shown in Fig. 2.1 [40].

It should be noted that the idea that EBUS-TBNA is superior to mediastinoscopy is not shared by all. In a recent review in the Annals of Thoracic Surgery, Shrager points out that in many of the studies comparing EBUS-TBNA to mediastinoscopy, EBUS was performed under general anesthesia, eliminating the theoretical benefits of a procedure performed under moderate sedation [41]. EBUS-TBNA has the potential for false negatives due to sampling error, and without confirmatory mediastinoscopy,

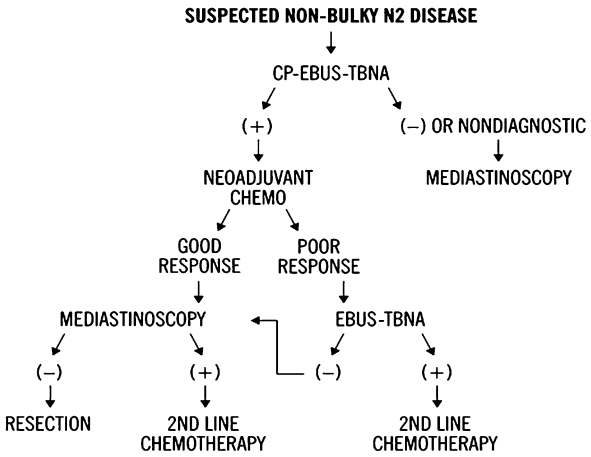

Fig. 2.1 Treatment algorithm for suspected non-bulky N2 disease

the potential downside is great: missed N3 disease could lead to unnecessary surgery, whereas missed N2 disease could lead to a failure to prescribe beneficial neoadjuvant chemotherapy. When EBUS-TBNA is followed by confirmatory mediastinoscopy, the costs are additive. Shrager therefore advocates strongly for mediastinoscopy, not EBUS, as the procedure of choice in patients who have a low suspicion of mediastinal disease [41].

Quite rapidly, use of the convex probe for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has become the procedure of choice for sampling of mediastinal and airway-accessible central targets in patients with suspected lung cancer and other intrathoracic pathologies. Use of this technique has gained favor among both pulmonologists and surgeons. Unlike the blind Wang technique, the technique of EBUS-TBNA has not been confined to interventional pulmonologists, and many general pulmonogists who do few other interventional procedures have begun to perform the procedure. Given the importance of accurate staging in lung cancer, it is critical that this modality for sampling be handled with expert care.

Pathologic Sampling of Peripheral Lesions

General Principles

Peripheral lung nodules present different challenges for clinical decision-making and for pathologic sampling. Once a lung lesion is identified, multiple features are assessed to determine the likelihood of malignancy, including patient age, size of the nodule, smoking history, evidence of adenopathy, increasing nodule size on serial studies, and irregular lesion borders [42]. For solitary, peripheral nodules (SPN) for which there is a high suspicion of malignancy (estimated to be >60 %) [43], the option of primary resection should be considered. Although the ACCP Guidelines refer to this as a "diagnostic dilemma," this is not the case for some patients, where primary resection fulfills the criteria for "least" and "safest." A patient with suspected early-stage disease by PET-CT imaging who is a good candidate for surgical resection (calculated to have sufficient lung function to tolerate lobectomy or pneumonectomy, as dictated by the location of the primary tumor) should undergo VATS wedge resection of the tumor with frozen section analysis to definitively establish the diagnosis of malignancy, followed immediately by nodal staging and definitive resection if occult N2 or bulky N1 nodal disease is absent. In these patients, a biopsy of the primary tumor would be an unnecessary step in the majority of cases. In a high suspicion lesion, only a benign biopsy finding that led a very high degree of confidence that a false negative was unlikely should avert definitive resection. A finding of environmental fungal disease, such as histoplasmosis, coccidioidomycosis, or cryptococcosis, or a finding of tuberculosis, might satisfy these criteria, although the incidence of these findings in SPN is rare [42]. Rolston and colleagues [44], in a 3-year analysis of all of the patients referred to the University of Texas for suspected lung cancer, found that the diagnostic workup for suspected malignancy led to a finding of benign disease in only 6.7 % and a finding of infection mimicking lung

cancer in only 1.3 %. The majority of the patients had an SPN on imaging, and they found no radiographic features which were necessarily predictive of either infection or neoplasm [44]. The possibility of a false-negative biopsy finding in a high suspicion patient should strongly favor an approach of definitive resection in these patients, contingent on having established good lung function [3, 43].

In other cases, uncertainty as to the nature of solitary peripheral nodule (SPN) or mass drives the need for pathologic sampling. Many pulmonary nodules are discovered incidentally on imaging done for other reasons. With the findings of the National Lung Screening Trial (NLST) showing a 20 % reduction in deaths from lung cancer among current or former heavy smokers who were screened with low-dose helical computed tomography (CT) versus those screened by chest X-ray, more individuals at risk for lung cancer will undergo CT imaging in the near future, and more pulmonary nodules of unclear clinical significance will be identified [45]. Given that the observed reduction in lung cancer mortality was invariably due to early accurate identification of malignant disease and subsequent early intervention, the diagnosis of the cancerous peripheral lung nodule is critical.

A total of 96.4 % of the positive screening results in the low-dose CT group in the NLST were *false positives*, however [45]. In the management of a patient with an uncharacterized SPN of unknown clinical significance, the clinician must determine based on the clinical context whether intervention is needed and, if so, what type. Some nodules, by virtue of their radiologic characteristics or stability over time, can be assumed to be benign, whereas some warrant immediate surgical resection. In between these extremes of inaction and complete surgical removal fall many pulmonary nodules and masses which require either radiologic monitoring or a biopsy to determine pathology, which in turn dictates the need for further intervention.

Clinical context is unique for every patient, however, and patient participation in the discussions related to these decisions is important. There are some patients for whom the idea of contemplating surgical resection without an established diagnosis is overwhelming, and pathologic sampling may be necessary to get them to the place where they can accept the imperative for potentially curative resection. In patients with an SPN where the suspicion of malignancy is low or intermediate, or in patients for whom surgical resection is not or may not be an option, or in patients with clear radiographic evidence of stage 4 disease where the primary lesion is the easiest and safest site to sample, multiple modalities are available. Bronchoscopic sampling (lavage, cytologic brushing, TBNA, and forceps biopsy), CT-guided needle sampling, bronchoscopic sampling with RP-EBUS guidance, and EMN bronchoscopy are options to be considered. The last three modalities will be discussed in detail.

Radiographically Guided Needle Sampling of an SPN

Image-guided sampling of a thoracic target can be done with plain fluoroscopy, or with transthoracic ultrasound imaging if the lesion is near the pleural surface, or with CT guidance. CT-guided sampling allows for precise needle positioning,

resulting in high yields and low morbidity, and is typically done by an experienced interventional radiologist. This procedure can be performed as an transthoracic fine-needle aspiration (TTNA), which is done with a smaller gauge needle (typically 20–22 g) and which yields a cytologic sample, or as a transthoracic needle biopsy (TTNB), most often done with a hollow larger-bore needle with a cutting mechanism following CT-guided insertion of a thinner localizing needle. TTNB is intended to yield a core histologic specimen which can demonstrate tissue architecture. Both can be done with or without ROSE, and the two procedures can be done in combination, usually TTNA followed by a TTNB. ROSE can be effectively used in a combination procedure to provide additional information beyond confirmation of a diagnosis. ROSE of an aspirate cytology specimen can confirm lesional tissue to guide the subsequent core biopsy, which can be sent in its entirety for pathologic processing, without "wasting" additional tissue for on-site fixation.

CT-guided sampling can be done with intermittent imaging with interval needle repositioning or with CT fluoroscopy with the radiologist tableside. Real-time CT fluoroscopic sampling is possible, with needle positioning done with active fluoroscopic imaging, although this can be technically difficult. Needle insertion is typically done with a breath hold, with cessation of tidal respiration rather than at deep inspiration. The challenges of CT-guided intrathoracic sampling include difficulties that arise as a result of a target size and location and accommodating respiratory motion. Although it would seem reasonable that a lesion adjacent to the pleura would be easier to access than a deeper, intraparenchymal lesion of the same size, this is often not the case. A needle passing through some lung tissue will result in an anchoring of the needle in place, and a deeper lesion can allow for more subtle directional changes on the way to the target that may not be possible with a lesion against the pleura as repositioning might necessitate repuncturing the pleura multiple times, thereby increasing the chance for complications.

If given a choice, needle insertion from the back with the patient prone is preferred over needle insertion with the patient supine for several reasons. First, patient anxiety is typically less if they are unable to see the long sampling needle. Second, it is generally recommended that patients recover post procedure with the biopsy site down, so that the weight of the lung rest on the puncture site, and it is easier for a patient to recover supine than prone.

The pleura is a fibrous membrane which, unlike the lung parenchyma, is innervated; crossing the pleura can cause pain. If the clinician does not cross the pleura in a rapid fashion but instead hesitates with the needle tenting the membrane, the resulting patient response can result in a laceration of the lung rather than a puncture, possibly resulting in pneumothorax. Emphysematous areas of lung adjacent to the entry site may also increase the risk of pneumothorax and should be avoided if possible. If a needle is inserted into the lung but misses the target lesion necessitating a second needlestick, it may be preferable to leave the first needle in place. This is because the first needle will tend to stabilize motion of the lung, aiding in the positioning of the second needle, and because of the possibility of pneumothorax following removal of the first needle. The patient will have this pneumothorax regardless with removal of the first needle, but better to have this complication after second

(hopefully successful) sampling rather than before. One advantage of CT-guided biopsy performed by interventional radiology is that a chest tube, if needed, can be placed with imaging guidance by the radiologist obtaining the biopsy or aspiration. Sampling using a needle mechanism that employs a coaxial technique in which a single needle puncture is followed by multiple samplings over the finder needle has been thought to mitigate pneumothorax risk, although this potential benefit has not been seen in all studies [46].

Performance Characteristics

TTNA has been shown to have good sensitivity for identifying malignancy in SPN. The 2007 ACCP Guidelines present an excellent review of the literature on the performance characteristics of transthoracic sampling for suspected lung cancer. No new relevant literature was identified in the 2013 ACCP Guidelines, which again presented the 2007 findings. In a meta-analysis of 46 studies, with nondiagnostic, nonspecific, and benign findings all considered to be negative, the pooled sensitivity of TTNA was 90 % (95 % CI, 88–91 %) with a range of 62–99 % [3]. These studies included TTNA performed under fluoroscopic guidance and CT guidance. In the presence of a nonspecific benign diagnosis following multiple passes and documented needle tip in the target, pathology follow-up demonstrated that approximately 90 % of lesions are benign [47]. False negatives do occur, however, therefore a nondiagnostic, nonspecific, or benign finding should prompt consideration of additional investigation, if the initial suspicion of cancer is high, as previously discussed. This could include re-sampling, resection, or close radiographic monitoring with careful attention to growth.

The performance characteristics of TTNA and TTNB have been compared in case series with variable results. Tuna and colleagues [48] retrospectively compared the yield in 105 patients who underwent CT-guided transthoracic lung biopsy, 83 by TTNB and 22 by TTNA. They reported finding a definitive diagnosis in 87 of 105 patients (83 %) overall, with 94 % of the diagnoses showing a malignancy. The sensitivity of TTNB was significantly higher, with a sensitivity of 92 % compared to a sensitivity of only 78 % for TTNA [49]. Ten percent of patients overall had a pneumothorax, and only 2 % had hemorrhage, with no significant difference in complications between TTNA and TTNB. Klein and colleagues [49] published a retrospective review of CT-guiding sampling performed on 127 lesions in 122 patients, with 87 samplings done as a TTNA and 99 sampling done as a cutting needle TTNB. Both procedures were performed using a coaxial technique with sampling needles placed through a 19-gauge needle placed in the lesion. TTNA was done with a 20-gauge Westcott needle (Becton Dickinson, Franklin Lakes, NJ) or a 22-gauge Chiba needle (Cook). TTNB was done with a 20-gauge ASAP automated cutting needle (Medi-Tech/Boston Scientific, Watertown, MA) or a 20-gauge Temno automated cutting needle (Bauer Medical, Clearwater, FL). The overall diagnostic yield for the study was 88 %. The sensitivity was 95 % for malignancy and 91 % for benign disease.

Although no significant difference was found for sensitivity between fine-needle aspiration and core biopsy of malignant lesions (92 % vs. 86 %), a statistically significant difference was found for benign lesions (44 % vs. 100 %). Pneumothorax rate in this study was high, occurring in 54 % of patients [49].

Complications

Pneumothorax and hemorrhage are the most common complications of TTNA and TTNB. Richardson and colleagues [50] recently searched retrospectively over 5,000 cases of CT-guided thoracic samplings in the UK, reporting a pneumothorax rate of 20.5 %, with 3.1 % requiring chest drainage (3.1 %). Pneumothorax was similar in procedures done with a core cutting biopsy needle and those done as a FNA. Hemoptysis occurred in 5.3 % and death in 0.15 % of cases. Hiraki and colleagues [51] reported a much higher rate of pneumothorax in over 1,000 cases performed over a 9-year period in Japan using a 20-gauge coaxial cutting needle. They found an overall incidence of pneumothorax of 42.3 %, with 11.9 % needing a chest tube. In one of the largest series to date, Wiener and colleagues [52] reviewed over 15,000 CT-guided biopsies of pulmonary nodules identified in the 2006 State Ambulatory Surgery Databases and State Inpatient Databases for California, Florida, Michigan, and New York. 15.0 % of procedures (CI, 14.0 % to 16.0 %) were complicated by pneumothorax, and 6.6 % (CI, 6.0 % to 7.2 %) of patients required a chest tube. Bleeding was uncommon, with only 1.0 % (95 % CI, 0.9 % to 1.2 %) of procedures complicated by hemorrhage. Smokers and patients with chronic obstructive pulmonary disease were at higher risk for complications [52].

The risk factors predisposing to pneumothorax are variable across different studies. Some studies have shown pneumothorax rate to be independent of the size of the lesion and the size of the needle, whereas others have shown the opposite. Needle dwell time (the amount of time spent with the needle in the lung parenchyma), the need to cross a fissure, and the number of total punctures have been thought to correlate with the chance of pneumothorax. In the Japanese series, depth of the lesion, a lower lobe lesion, and needle trajectory <45° were associated with pneumothorax risk, and emphysema increased the risk of needing chest tube placement. Clinical features like prior lung or pleural surgery and the presence of pleural adhesions might be of some protective benefit [53].

RP-EBUS

Convex probe EBUS evolved from radial probe EBUS, but they each now have a separate potential role to play in the management of patients with suspected thoracic malignancy. As noted above, the size of the CP-EBUS scope limits its reach in the segmental airways, so it plays little role in the diagnosis of most peripheral

nodules. RP-EBUS has retained a useful role in the diagnosis and sampling of peripheral nodules, at least in the hands of experienced practitioners. The probe's small diameter (1.4 mm at the distal tip) allows for access to areas of the lung periphery beyond the wedge position of the bronchoscope. The high resolution with ability to delineate the layers of the bronchial wall allows for direct observation of bronchial wall invasion which could inform staging. Use of RP-EBUS to guide bronchoscopic sampling of peripheral lesions has been shown to improve the yield over standard bronchoscopy. Steinfort and colleagues published a meta-analysis of 16 studies with 1,420 patients. They found a specificity of 100 % (95 % CI 99–100) and a sensitivity of 73 % (95 % CI 70–76) for the detection of lung cancer. Yield was significantly better for lesions greater than 2 cm in size [54]. The rate of pneumothorax was very low, ranging from 0 % to 5.1 %, and the risk of bleeding was extremely low, with no patients experiencing bleeding which required an intervention. The 2013 ACCP Guidelines recommend consideration of RP-EBUS as an adjunct imaging tool for the bronchoscopic sampling of a suspicious SPN in patients where pathologic diagnosis is desired [3].

Navigational Bronchoscopy

The search to improve diagnostic yield in the bronchoscopic sampling of SPNs has led to efforts to guide the bronchoscope and sampling tools through the tracheobronchial tree to the target lesion. These "navigational" systems employ 3-D reconstructions of the tracheobronchial tree from CT imaging, often with a virtual endobronchial view akin to the view seen through the bronchoscope, to produce a virtual roadmap to the lesion. One commercially available system, iLogic System (superDimension, Inc., Herzliya, Israel and Minnesota, MN), combines elements of virtual bronchoscopic reconstruction with real-time 3-D directional and positional mapping. Termed electromagnetic navigational bronchoscopy (ENB), this guidance system has been shown to improve the yield of diagnostic sampling over conventional bronchoscopy.

The technique of ENB was first reported in animal experiments in 2003 [55] and later described in humans in 2006 by the same researchers [56]. Leong and colleagues [57] have recently published an excellent review of ENB which describes both the iLogic System and the ENB procedure in detail. The system utilizes a software program and several pieces of novel hardware, including an extended working channel which functions as a guide sheath, an 8-way steerable probe with a miniaturized EM sensor at the distal tip, and a low frequency electromagnetic field generator and emitter.

A patient's CT imaging, which must be in the appropriate, standardized DICOM format (Digital Imaging and Communications in Medicine, Rosslyn, VA), is uploaded into the ENB software planning program prior to the procedure. The planning software converts the CT images into a multi-planar 3-D reconstruction and displays axial, coronal, sagittal, and 3-D views, and both the target lesion and a bronchial pathway to the lesion are plotted. At the time of the procedure, the patient

is placed supine on the bronchoscopy table with an EM emitter, or location board, placed under the mattress. Additional location pads are placed on the patient's chest, and an EM field is generated which encompasses the patient's thorax.

An inspection bronchoscopy is performed with the EWC extending 8 mm from the distal end of the scope and the sensor probe, or location guide, deployed in the EWC. The location guide collects data on its position and orientation in the tracheobronchial tree 166 times per second to the ENB software program, and this information is superimposed on the virtual 3-D map (provided by the CT images) in real time. In the course of a full inspection bronchoscopy, the data collected automatically "registers" the patient's anatomy with the virtual 3-D reconstruction of the CT images. The two data sets are then aligned and presented as an overlay on the procedure screen. The highest allowable divergence between the two 3-D images is 5 mm; greater divergence should prompt re-registration. The aligned overlay of these two data sets is presented on the software's procedure display for real-time guidance through the tracheobronchial tree to the lesion. The display shows multiple views of the overlaid imaging, including the previously mapped route to the lesion and a head-on "tip view" showing the target as well as distance and direction to the target. Arrows in the tip view direct the operator to manipulate the steerable probe in the direction of the target as the probe is advanced. After reaching the target lesion with the probe and extended working channel, the location guide is removed and the working channel is left in place to allow introduction of tools for sampling. Fluoroscopy can be used to confirm positioning, as can RP-EBUS, deployed through the working channel after the LG is removed. ENB can also be used for the placement fiducial markers for subsequent interventions, including surgical resection or radiation.

Performance Characteristics of ENB

ENB has been extensively studied since its development and has been consistently shown to improve the diagnostic yield of bronchoscopic sampling. Leong and colleagues [57] examined data from 12 studies of the performance of ENB, reporting diagnostic yields ranging from 59 to 77 %. Rates for pneumothorax were low, ranging from 0 to 10 %. There are multiple studies comparing the sensitivity and yield of ENB over conventional bronchoscopic biopsy techniques. In one of the larger single center series of 92 biopsies in 89 patients, Eberhardt and colleagues [58] reported an overall diagnostic yield of 67 %, with only 2 cases leading to pneumothorax. ENB has been used to guide SPN biopsy as well as lymph node biopsy. Gildea and colleagues prospectively studied 60 subjects undergoing ENB; they reported a navigational success rate (reaching the target lesion) of 100 %, with a yield of 74 % for SPN and 100 % for lymph nodes [59].

Multiple factors have been shown to affect yield. The procedure is technically challenging, and experience helps. Lamprecht and colleagues [60] looked at 112 cases comparing yield in the first 30 cases to the last 30, showing yields of 80 % and 87 % respectively. Larger lesions had a higher yield, with diagnoses obtained in 89 % of lesions greater than 2 cm compared to 75 % in lesions less than 2 cm. Location of

the lesion did not appear to affect yield [60]. In one study, the presence of a "bronchus sign," an area of hypoattenuation on CT leading to or into an SPN, was the only variable on multivariate analysis which appeared to affect diagnostic yield of ENB [61].

Comparison and Combination of Sampling Techniques

ENB is a newer technology than RP-EBUS, and its role in the management of SPNs is still being elucidated. Studies have shown that in expert hands, ENB increases the diagnostic sensitivity of bronchoscopic sampling over standard bronchoscopy. ENB requires equipment and software that represents a capital expense for the institution or operator; it requires time for data entry; and it requires expertise with the software and the hardware. As with all technological advances, it is remains to be seen whether the yield and complication rate seen in clinical studies can be duplicated in wider clinical use.

It is also obvious that all nodules are unique and each will have features that will alter the balance of risks and benefits in a way that may favor one diagnostic approach over another. Location with respect to the pleura, relationship to the airways and blood vessels, and relationship to emphysematous lung all will affect the expected sensitivity of a procedure and the potential for complications in an individual patient.

Comparing TTNA or TTNB with ENB, studies suggest that an ENB approach may offer the advantage of a lower complication rate at the expense of decreased sensitivity; an ENB approach would therefore increase the likelihood of requiring a second, alternate diagnostic intervention (subsequent CT-guided biopsy or VATS), increasing overall risk and increasing overall costs, in the subset of patients with nondiagnostic results on ENB. Researchers have used modeling to compare serial testing with ENB followed by CTGB or CTGB followed by ENB. The approach utilizing ENB as an initial modality could be more than twice as expensive, although the risk of complications would likely be lower than with the reverse serial strategy. Combining the two procedures in serial testing would have a combined sensitivity of 97 % [62].

Real-world utilization is likely to be dictated by clinical considerations, however not modeling. As noted, there are certainly features of individual tumors and individual patients which make one approach favorable over another and each case must be evaluated with an eye toward yield and risk specific to the clinical circumstances.

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