Bronchoscopic needle aspiration in the diagnosis of mediastinal lymphadenopathy and staging of lung cancer

ABSTRACT

Transbronchial needle aspiration (TBNA) has the potential to allow adequate mediastinal staging of non-small cell lung cancer with enlarged lymph nodes in most patients without the need for mediastinoscopy. Metastasis to the mediastinal lymph nodes is one of the most important factors in determining resectability and prognosis in non-small cell lung cancer. The importance of TBNA as a tool for diagnosing intrathoracic lymphadenopathy as well as in the staging of lung cancer has been reported in various studies. We performed a literature search in PubMed and Journal of Bronchology using the keyword transbronchial needle aspiration. TBNA is a safe and effective procedure to diagnose mediastinal lymphadenopathy. Real-time bronchoscopic ultrasound-guided TBNA is the new kid on the block, which can further enhance the sensitivity of bronchoscopy in the diagnosis of mediastinal lesions.

KEY WORDS: Bronchoscopy, lung cancer, mediastinoscopy, transbronchial needle aspiration

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INTRODUCTION

Differential diagnosis of mediastinal lymphadenopathy ranges from lymph node metastases, malignant lymphomas, infectious, immunologic, endocrine, and lipid storage diseases to disorders such as sarcoidosis, histiocytosis X, and Castleman's disease.[1] Treatment for this heterogeneous group of diseases is primarily nonsurgical, and exact histologic classification has great impact on the therapeutic approach.[2] It is therefore important to be able to differentiate between the various etiologies to be able to institute appropriate therapy and establish prognosis.

Non-small cell lung cancer (NSCLC) is the most common malignancy in the world and accounts for an estimated 1 million deaths each year.[3] The overall 5 year survival is approximately 15%.[4] However, the survival rate approaches 70% in some patients with resectable disease.[5] Metastasis to the mediastinal lymph nodes is one of the most important factors in determining resectability and prognosis.[6] From a practical standpoint, the involvement of disease in the mediastinum, which is reflected in the nodal designator in the system, is an important determinant of the appropriateness of the patient for surgical resection. Patients with stage IA, IB, IIA, and IIB disease can benefit from surgical resection. Patients with stage IIIA, IIIB, and IV almost never meet the criteria for surgery.

Transbronchial needle aspiration (TBNA) can be performed at bronchoscopy to sample mediastinal and hilar lymph nodes or mass lesions. We performed a literature search in PubMed using the keyword transbronchial needle aspiration. The importance of TBNA as a tool for diagnosing intrathoracic lymphadenopathy as well as in the staging of lung cancer has been validated in a number of studies.[7-10] Surgical methods for sampling mediastinal and hilar lymph nodes include mediastinoscopy, mediastinotomy, thoracotomy, and video-assisted thoracoscopy. Traditionally, mediastinoscopy has been recommended in patients with NSCLC in whom curative surgical resection is a possibility.[11] However, mediastinoscopy requires general anesthesia, and is a major procedure needing hospital stay.[12] The complication rate of mediastinoscopy is approximately 2-3%. In comparison, the complication rate of TBNA is <1%.[13] Furthermore, conventional mediastinoscopy cannot sample hilar tissue and is limited in the number of mediastinal lymph node (LN) stations that can be sampled. Advances in TBNA techniques, including rapid on-site cytologic evaluation, the use of 19-gauge needles for performing core biopsies, and, more recently, endoscopic and endobronchial ultrasound (EBUS) guidance have increased the diagnostic yield of this procedure considerably.[8,14-19] However, EBUS-guided TBNA requires sophisticated, costly equipment, and extensive operator training. As a result, the current application of EBUS-guided TBNA is limited to selected centers and does not

have extensive availability. In contrast, conventional TBNA is a technique that has the potential for widespread use since no sophisticated or costly equipment is necessary. The aim of the current review article is to summarize the various techniques available for the sampling of mediastinal lymph nodes with focus on the bronchoscopic approach. Conventional TBNA is also important as it can be combined with routine flexible bronchoscopy.

MEDIASTINAL LYMPH NODE ANATOMY

The lymph node anatomy in the revised TNM classification for lung cancer based on the N1, N2 mediastinal lymph nodes is given in Table 1 reproduced as per International Staging committee (ISC) of the International Association for the Study of Lung Cancer (IASLC) regional nodal stations for lung cancer staging.[20]

ETIOLOGY OF MEDIASTINAL LYMPHADENOPATHY

There are many causes of mediastinal and hilar lymphadenopathy, including infection, neoplasm, granulomatous disease, and reactive hyperplasia.[1] Infections consist predominantly of tuberculosis, fungal infection (pulmonary histoplasmosis and coccidioidomycosis), viral pneumonia, and mycoplasma pneumonia. The neoplastic causes include lymphoma, leukemia, metastatic carcinoma from lung cancer, cancer of the esophagus and breast cancer, and extrathoracic primary tumors (kidney, testis, head and neck neoplasms). Hilar and mediastinal lymphadenopathy may also be observed in Castleman's disease, thoracic amyloidosis, angioimmunoblastic lymphadenopathy, chronic berylliosis, Wegener's granulomatosis, cystic fibrosis, and chronic mediastinitis. Sarcoidosis is a highly frequent cause of intrathoracic lymphadenopathy, particularly in young adults.

DIAGNOSTIC MODALITIES

The diagnostic modalities available currently are bronchoscopicTBNA, mediastinoscopy, thoracoscopy, and image-guided procedures.

Transbronchial needle aspiration

Technique[21]

Anesthesia and perioperative care

Moderate sedation using benzodiazepines and opiates has been shown to reduce cough and improve patient comfort. Particular benefit was also noted in patients undergoing transbronchial lung biopsy or TBNA. Upper airway obstruction following sedation may lead to hypoxemia during the procedure and this is effectively treated with insertion of nasopharyngeal tube and/or jaw support.[22] Sedation reversal with flumazenil and/or naloxone is required in a minority of patients. Pre-procedure, nebulized bronchodilators should be administered to patients with asthma. Patients with COPD may not benefit with pre-procedure administration of bronchodilators.[23]

Techniques and instrumentation

TBNA is performed via bronchoscopy. TBNA of mediastinal lymph node should be performed before complete examination of the airway or any other diagnostic bronchoscopic procedure to avoid contamination. For the same reasons, suction should be minimized during scope insertion. A needle catheter is passed through the working channel of the bronchoscope and guided to the area of the tracheobronchial tree overlying the mediastinal lymph node of interest. The needle catheter using a 22 gauge cytology needle or a 19 gauge histology needle is then advanced through the tracheal or carinal wall into the mediastinal lymph node, and an aspiration biopsy obtained. [Figures 1 and 2] Either one of the three techniques of TBNA can be applied.[24]

a) **Jabbing Technique:** The needle catheter is passed through the working channel of the bronchoscope. The needle is brought out, scope being held firmly at the mouth or nostril, and the needle pushed through the tissues.
b) **Piggyback Technique:** The needle catheter is passed through the working channel of the bronchoscope. The needle is brought out, holding the catheter against the insertion channel using fingers. Advance the scope and catheter together in order to penetrate the airway wall with needle.
c) **Hub against Wall Technique:** The needle catheter is passed through the working channel of the bronchoscope. The needle is kept in. Push the catheter hub against the airway wall. Hold the catheter against the airway wall. Needle is then brought out so that it penetrates into the target.

Cytology

For specimen acquisition, a smear is prepared by placing the needle aspirate on to the slide and the specimen is placed in alcohol immediately. At least two adequate samples are obtained, using the smear method for cytology and analyzing all flush solution and cell block sample. After TBNA, cooperate and review pathology slides with an experienced

Table 1: Proposed nodal zones with their nodal stations[19]

Nodal zones	Nodal stations
	N2 nodes
Upper zone	Highest Mediastinal (#1)
	Upper Paratracheal (#2)
	Prevascular & retrotracheal (#3a,#3p)
	Lower paratracheal (#4)
Aortopulmonary zone	Subaortic (#5)
	Paraaortic (#6)
Subcarinal zone	Subcarinal (#7)
Lower zone	Paraesophageal (#8)
	Pulmonary ligament (#9)
	N1 nodes
Hilar zone	Hilar (#10)
	Interlobar (#11)
Peripheral zone	Lobar (#12)
	Segmental (#13)
	Subsegmental (#14)

Figure 1: Transbronchial needle aspiration of the subcarinal lymph node

Figure 2: Transbronchial needle aspiration of the right paratracheal lymph node

cytopathologist, and review your TBNA procedure by video.[25] Rapid on-site examination by cyto-pathologist has been shown to improve diagnostic yield.

Mediastinoscopy

Mediastinoscopy is performed in the operating room.[26-28] The procedure involves an incision just above the suprasternal notch, insertion of a mediastinoscope alongside the trachea, and biopsy of the mediastinal nodes.[11] Right and left high and low paratracheal nodes (stations 2R, 2L, 4R, and 4L), pretracheal nodes (stations 1 and 3), and anterior subcarinal nodes (station 7) are accessible via this approach. Node groups that cannot be biopsied with this technique include posterior subcarinal nodes (station 7), inferior mediastinal nodes (stations 8 and 9), aortopulmonary window (APW) nodes (station 5), and anterior mediastinal nodes (station 6). Rates of morbidity and mortality as a result of this procedure are 2% and 0.08%, respectively.[29] This procedure does require general anesthesia and carries risks of bleeding and left laryngeal nerve injury.[30]

Video-assisted thoracoscopy

Video-assisted thoracoscopic surgery, also known as VATS, can be used to access mediastinal nodes. This is done under general anesthesia and in general is limited to an assessment of only one side of the mediastinum. Access to the R-sided nodes is straightforward, but access to the L paratracheal nodes is more difficult.[31]

CT fluoroscopy-guided TBNA

Computed tomography (CT) fluoroscopy-guided imaging has been assessed in certain centers to improve the yield and safety of TBNA.[32,33] CT fluoroscopy enables rapid localization of the position of the bronchoscopic tip after each movement on the in-room monitor. The needle can be observed as it is planted in the airway to assure that it is directed toward the intended biopsy site. Once the needle has been advanced, CT fluoroscopic images provide assurance that the needle is in

the target lesion. Although both the 21-gauge and 19-gauge aspiration needles are readily visualized, the latter is more easily identified. The bronchoscope causes a substantial artifact but does not interfere with identification of the needle position. The feedback provided by CT fluoroscopy allows a rapid documentation of needle malposition, enabling immediate adjustment. A CT fluoroscopic sequence on completion of the procedure permits immediate detection of and intervention for pneumothorax or hemorrhage. A potential concern with this technique is the use of several minutes of fluoroscopy. Conventional fluoroscopy dose factors are approximately 70 kVp and 2 to 10 mA. By comparison, CT fluoroscopy dose factors are approximately 120 kVp and 30 to 50 mA. Thus, the dose from CT fluoroscopy is at least five times greater than that from conventional fluoroscopy. The other issues involved with this procedure are the requirement for a radiologist during the procedure and the CT scan slot for the procedure, contributing to increased additional cost. According to Goldberg *et al*,[34] with CT fluoroscopy guidance, the rate of successful passes was 62%. Also, 5.2% penetrations punctured great vessels with CT fluoroscopy guidance.

CT-guided TTNA

The ability to carry out CT-guided transthoracic needle aspiration for the diagnosis and staging of cancer in the mediastinum has generally been reported to be high. In a study by Bilaceroglu *et al*,[35] they reported a sensitivity of 82%, although approximately 12% of patients required the placement of a catheter for the evacuation of a pneumothorax.

NEWER MODALITIES

Endobronchial ultrasound-guided TBNA
EBUS currently exists in two forms.[36]

Radial probe EBUS
Radial probe (RP) EBUS utilizes a rotating transducer at the end of a probe, which produces a 360° image to the long axis of

the bronchoscope; the probe is placed through a guide sheath in the working channel of the bronchoscope to visualize the lesion but is then withdrawn. The selected biopsy instrument (needle, forceps, brush) is placed through the sheath and remains in place to stabilize the lesion during the biopsy. Unless one uses a two-channel bronchoscope with RP EBUS, a real-time image-guided biopsy is unavailable.

Linear/Convex EBUS

The linear EBUS bronchoscope, which incorporates the ultrasound transducer at its distal end, utilizes a fixed array of transducers aligned in a curvilinear pattern. This generates a 50° image parallel to the long axis of the bronchoscope. Doppler capability differentiates tissue from vascular structure. Ultrasound and the white-light bronchoscopic images can be viewed simultaneously. The use of "other" TBNA needles with the linear EBUS bronchoscope has led to its damage, so specially designed TBNA needle-within-a-catheter device, which is passed through the 2.0 mm working channel, must be used. Biopsy is performed under real-time imaging. Due to the diameter of the linear EBUS (approximately 7mm), a 30° view, and a suboptimal-quality white-light image that limits its use in general inspection of the airways, complete inspection of the airways may require performing standard FB leading to additional time, labor, and thus cost.

In the case of mediastinal or hilar adenopathy and peritracheal lung mass, RP or linear EBUS improves the yield, eliminating the need for additional procedures. Time for accomplishing EBUS with TBNA has been reported from 6.3 min to 30 min (compared to standard FB with TBNA, 3.8 min).[14,17,37,38]

Endoscopic ultrasound-guided TNA (EUS-TNA)

Needle aspiration of mediastinal lymph nodes through the wall of the esophagus has been performed with esophageal ultrasound guidance.[39] This technique is particularly useful for inferior pulmonary ligament, esophageal, subcarinal, and APW nodes (stations 9, 8, 7, and 5). Nodes that are anterolateral to the trachea (stations 2R, 2L, 4R, and 4L) are difficult to sample reliably (but are more commonly involved with lung cancer). If TBNA is combined with first routine diagnostic bronchoscopy then the need for such additional procedures can be significantly reduced.

Electromagnetic navigation bronchoscopy

The introduction of electromagnetic navigation bronchoscopy (EMNB)[40] with a steerable instrument is an image-guided localization system, which is designed to guide bronchoscopic tools to predetermined points within the bronchial tree. The device uses three separate technologies that are combined to enable navigation of dedicated tools within the lung in real time. The first component is the planning software, which converts digital imaging and communications in medicine standards (DICOM) images from a CT scan into multiplanar images with three-dimensional reconstruction and virtual bronchoscopy of the airways. The second component is a

steerable probe that contains a position sensor attached to an eight-way steerable instrument that has the ability to navigate turns in the endobronchial tree. The third component is an EM board, which is a field generator connected to a computer containing the planning data. The exact position of the steerable probe when placed within the EM field is depicted on the system monitor. Thus, ENB has the ability to guide bronchoscopy instruments to reach lung targets for transbronchial biopsy (TBBX), brushing, or TBNA procedures.[41-44] EMNB is a safe procedure that, with some training, is associated with high diagnostic success, higher than those reported for routine diagnostic bronchoscopy and perhaps similar or superior to some other advanced techniques such as EBUS independent of size and location. Yield may be further increased with more flexible dedicated peripheral instruments. In future applications, EMNB may be used with fusion computed tomography/positron emission tomography (CT/PET) for procedure planning; in addition, guided instruments may further extend the utility of this new technology.

COMPLIMENTARY ROLE OF PET SCAN WITH TBNA

PET scanning has been reported to significantly improve the rate of detection of mediastinal lymph node involvement in patients with NSCLC and also has a high negative predictive value.[45] PET scan, in itself, is incomplete in the mediastinal lymph node staging of NSCLC and needs to be supplemented by pathological confirmation of PET-positive lymph nodes or PET-negative enlarged lymph nodes. TBNA is a minimally invasive staging procedure, which is able to preclude the need for additional staging for the mediastinum,[46] and is cost-effective if performed during the first diagnostic bronchoscopy in all patients with suspected lung cancer.[47]

According to the study by Bernasconi *et al*,[48] both these diagnostic tools are complementary and are able to enhance the diagnostic value of the individual modality for a specific lymph node station. In particular, the negative predictive value of a specific enlarged lymph node station, in which both TBNA and PET results are available, is 100%. Therefore, a lymph node station, which is both TBNA and PET negative, does not need further invasive diagnostic investigation. Furthermore, PET was falsely negative in two patients in whom TBNA was positive. Both these patients had adenocarcinoma, which is known to have a low sensitivity with PET scanning.[49] The sensitivity of combined TBNA and PET scanning for enlarged lymph nodes was 100%, thus highlighting the value of an integrated approach.

DISCUSSION

TBNA is a well-established, simple and safe bronchoscopic technique that potentially reduces the number of higher risk surgical procedures such as mediastinoscopy and the diagnostic delays and financial costs associated with them.[50,51] TBNA is highly specific for detecting mediastinal lymph

node metastasis in patients with NSCLC, but that sensitivity depends critically on the prevalence of mediastinal lymph node involvement. The sensitivity of the technique is higher in patients with enlarged lymphadenopathy. TBNA is used most frequently to assess subcarinal nodes and paratracheal lymph nodes. It has been reported[8,52-54] that it is feasible to obtain adequate specimens via TBNA in approximately 80 to 90% of cases. Some studies have compared conventional versus EBUS-guided TBNA of lymph nodes and showed that ultrasound-guided TBNA significantly increases the yield of TBNA in some lymph node stations.[14,17] However, among those lymph nodes accessible to TBNA, the diagnostic yields obtained by conventional TBNA were similar and proved as effective as ultrasound-guided TBNA in the subcarinal and lower paratracheal areas where the majority of metastasis from NSCLC occurs.[55]

Recent American College of Chest Physicians (ACCP) guidelines[11] have demonstrated the overall sensitivity of TBNA at 78% with values ranging from 14 to 100%. The average FN rate was approximately 28% (range, 0 to 66%). The reported specificity and FP rates were 100% and 0%, respectively, although few studies confirmed positive TBNA results with further invasive procedures. Occasional FP results have been reported in series[7,56,57] in which this has been specifically examined with a confirmatory test (average, 7%). A recent study by Patel *et al*[58] showed that the success of TBNA increased significantly after using combined cytologic and histologic analysis of tissue specimens, with the yield for the successful sampling of mediastinal and hilar LNs increased from 53 to 91%. TBNA averted a surgical biopsy in 35% of the cases utilizing cytological analysis compared to 66% of cases using combined cytologic and histologic analysis.

Data by Harrow *et al*, Sharafkhaneh *et al*, and Wang *et al*[9,10,53] have shown that TBNA adds to the diagnostic yield of bronchoscopy. In one third of patients studied by Sharafkhaneh *et al*,[10] TBNA was the only test with a positive diagnostic yield. A positive TBNA usually obviates the need for mediastinoscopy for staging purposes. Melenka and colleagues[59] reported that using bronchoscopy and TBNA (alone or in combination with chest CT) was consistently the least expensive diagnostic option across a wide range of probabilities, test characteristics, and charges. Multiple studies[9,60] have shown higher TBNA yield for malignant lesions when compared to benign disease.

In a study by Szlubowski *et al*,[61] the TBNA technique was diagnostic in 67.1% of lung cancer patients and in 59.0% of patients with sarcoidosis. In the group of all lung cancer patients, specificity was 100%, sensitivity 88.5%, accuracy 91.8% and negative predictive value 77.9%, and in diagnosing of lymph nodes involvement in NSCLC was respectively 100%, 86.6%, 90.7%, and 76.6%. The high diagnostic yield was comparable for all mediastinal groups. In 80% of NSCLC patients with false negative results of TBNA, there was observed partial involvement of metastatic lymph nodes, confirmed by transcervical extended bilateral mediastinal lymphadenectomy (TEMLA). The diagnostic value of TBNA is very high in diagnostics of lung cancer, NSCLC staging, and sarcoidosis, but much lower in lymphomas, tuberculosis, and other non-malignant diseases.

Among benign lesions, sarcoidosis has the highest TBNA yield. Wang *et al*,[53] reported a 90% diagnostic TBNA yield with an 18-gauge needle in 20 patients with sarcoidosis. Positive TBNA in these patients obviated the need for more invasive procedures like mediastinoscopy. In the study by Bilaceroglu,[62] sensitivity, specificity, positive and negative predictive values, and accuracy of TBNA for TB were 83%, 100%, 100%, 38%, and 85%, respectively. The only complication, self-limiting hemorrhage of < 30 mL volume, occurred in 65 patients (77%), with a volume of < 5 mL in 59 patients (70%). Moreover, TBNA provided an immediate diagnosis in 78% of patients by histologic, cytologic, and bacteriologic (i.e., smear) specimens, and it was the only means of diagnosis in 68% of patients. Similarly, Harkin *et al*[63] could obtain a yield of 87% by TBNA in 23 procedures performed on HIV-positive patients with mycobacterial adenopathy, while achieving a rapid diagnosis in 74% and an exclusively diagnostic specimen in 48%.

Increasing education and experience can also improve TBNA performance and yield.[64-68] After serial educational interventions directed toward bronchoscopists and their technical staff, it has been shown that the yield with TBNA significantly increased from 21% to 48% in a 3-year period.[67] More recently, a similar rate of increase has been reported in sensitivity of TBNA from 33% to 81%.[68]

By endosonographic localization of lymph nodes, the results of TBNA can be significantly improved with a sensitivity up to 85%.[69] Herth *et al*,[70] investigated the results of an EBUS-guided TBNA compared to conventional TBNA showing that the yield of EBUS-TBNA is higher than conventional TBNA (85% vs 66%). In an additional analysis of lymph node stations without endoscopic landmarks (LN station 2, 3, 4 Mountain scheme), the detection technique is helpful to increase the yield. On the other hand, it also demonstrated that in the case of enlarged subcarinal nodes, a conventional TBNA has the same yield as TBNA after EBUS detection.[17]

In a randomized trial of 200 patients comparing conventional TBNA to EBUS-guided TBNA, Herth *et al*[17] demonstrated an overall diagnostic yield of 80% utilizing EBUS-guided TBNA v/s 71% ($P < 0.05$) utilizing conventional TBNA. In a study by Rintoul *et al*,[71] for the 18 patients who underwent EBUS-TBNA, the sensitivity, specificity and accuracy were 85%, 100%, and 89%, respectively. Yasufuku *et al*,[72] examined 70 patients with 58 mediastinal lymph nodes and 12 hilar lymph lymph nodes. The sensitivity, specificity, and accuracy of EBUS-TBNA in distinguishing benign from malignant lymph nodes were 95.7%, 100%, and 97.1%, respectively.

SUMMARY

TBNA is an efficient, cost-effective and safe method in the assessment of mediastinal lymphadenopathy.[20] For subcarinal lymph nodes, the diagnostic yield of conventional TBNA is similar to that of RP EBUS-guided TBNA.[17] Studies have revealed that lung cancer staging by TBNA has sensitivity and specificity close to mediastinoscopy with limited complication and reduces the need of mediastinoscopy.[11,62,68] TBNA is useful in making an initial diagnosis of N3 disease and also has the potential to identify malignant mediastinal lymph nodes that are negative for a PET scan. Combining TBNA results with PET improves the negative predictive value of each procedure alone.[48] The high negative predictive value of combined TBNA and PET for enlarged lymph nodes on CT scan has the potential to significantly reduce the need of mediastinoscopy by correctly identifying patients for neoadjuvant chemotherapy or direct surgical resection. Combination of TBNA/EBUS-TBNA and PET has the potential to allow adequate mediastinal staging of NSCLC with enlarged lymph nodes in most patients without the need for mediastinoscopy.[48] In recent decades, various newer modalities such as EBUS, EUS, and EMNB have evolved with an aim to increase the diagnostic yield and safety of bronchoscopic procedures.[73,74] However, all these modalities need specialized training, and are not easily be available in all facilities as cost is also a major factor. It is hence important to optimally utilize conventional TBNA along with routine bronchoscopy.

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