Endobronchial Ultrasound: A New Tool for Pulmonologists

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Introduction

The first description of direct visualization of tracheobronchial tree by Kollofrath O, assistant to Gustav Killian at the Poliklinik of Freiburg University, Germany, reads "On March 30th of this year I had the honor to assist my admired principal, Herrn Prof. Killian in extraction of a piece of bone from the right bronchus. This case is of such peculiarity with respect to its diagnostic and therapeutic importance that a more extensive description seems justified" [1]. For this Gustav Killian used esophagoscope as no dedicated tool existed to visualize the airway at that time. This case provided the proof that an instrument can not only be safely introduced in the human airway for visualization of airways, but it can also be used for therapeutic purpose. Later on, Chevalier Jackson introduced the direct ocular mechanism along with illumination and suction tubing which were attached to the esophagocope and the same principle was used for rigid bronchoscope [2]. Over subsequent years, many patients who had foreign body aspiration were treated by using the rigid bronchoscope [3]. However, the rigid bronchoscope could be used for visualization central airway only. Shigeto Ikeda, a Japanese thoracic surgeon, introduced the flexible instrument which used glass-fibres based optics, popularly known as fibre-optic flexible bronchoscope (FOB) [4]. The FOB had diameters of less than 6 mm, could be introduced to the distal airways and, its distal portion could be bent both anteriorly as well as posteriorly. Addition of FOB in the armamentarium of pulmonologists proved a great invention and subsequent years witnessed the invaluable contribution of FOB in diagnosis as well as management of lesions which were inside the airways. However, the assessment of lesions (lymph node) outside or adjacent to the large airways was still a problem. For assessment of these lesions computerized tomography (CT) scan was used. However CT scan was not a perfect modality to differentiate benign from the malignant ones. Since its introduction in flexible bronchoscopy in 1983 [5], conventional TBNA (cTBNA) has been technically well-established and has expanded its role in diagnosis of mediastinal lesions at different stations. cTBNA allows us to acquire samples from the subcarinal (station 7), paratracheal (station 2R and 4 R) and hilar (station 5) lymphnodes. cTBNA is guided by prior radiological examination and is done with "endobronchial vision", it is done without direct vision of the needle penetrating into the lesion. Most of the time, the bronchoscopist is "guessing" the depth of penetration with the constant fear that a mediastinal vessel may get punctured. Also, the yield form cTBNA is often poor (especially lymph node station other than 7, 2R and 4R) which may be attributed to inadequate penetration, poor angulations and improper puncture site. A successful penetration is indispensable in TBNA. Hence, real-time sampling is a logical development.

Invention of EBUS probe

Oesophageal endoscopic ultrasound (EUS) and fine needle aspiration (FNA) under its guidance had been in practice for gastrointestinal malignancies as well as accessible para-oesophageal lymphnodes since 1980s [6]. However, the probe was too big and was not suitable for use in the airways. It took more than a decade to develop an endobronchial ultrasound (EBUS) probe which could be inserted in to the airways [7, 8]. EBUS probe was based on the same principle as EUS probe. However, it was a convex probe (different from radial probe) and much smaller to allow adequate ventilation. The ultrasound probe was fitted to the tip of the bronchoscope. It also houses an inflatable balloon which can be inflated with saline to enhance the contact with the airway and hence improve the quality of ultrasound image. These modifications made the EBUS bronchoscope bulkier and stiffer than the conventional bronchoscope and hence, can only be introduced through oral route. EBUS bronchoscope provides two images simultaneously, the endobronchial image which is seen at obliquely angled view of 30 degree and ultrasound image which is angled forward at 90 degree parallel to shaft of the EBUS bronchoscope. Because of these features, more skill is required in navigating an EBUS bronchoscope. Also, the quality of images, are often suboptimal and require a second scope for the survey purpose. In this article "EBUS" stands for "convex probe" EBUS unless specified otherwise.

Simultaneously, conventional TBNA needle was also modified for the purpose of EBUS – TBNA. EBUS – TBNA needle assembly comes with multiple locking systems which help to fix it with EBUS bronchoscope and keep the needle and the sheath in position. The locking system avoids the risk of over insertion of the needle catheter and obviates the need of fixing the scope near the nose in jabbing technique. The EBUS – TBNA needle comes with internal stylet which is used to dislodge any debris present in the lumen. The EBUS – TBNA needle is available in 22 and 21 – gauge (21 and 22G) size. Larger size needle may provide the bigger tissue but is associated with more bleeding. The specimen adequacy or diagnostic yield is comparable with both sizes [9, 10]. At our centre we use 21G EBUS – TBNA needle.

Whilst, EBUS – TBNA needle is relatively more cumbersome than the cTBNA needles, yet the good diagnostic yield, even in small lesions, makes it an indispensible tool in the pulmonologist's armamentarium.

Utility of EBUS

Since its introduction, there have been multiple publications regarding the utility of EBUS – TBNA for various indications. Overall the utilities may be for malignant or benign lesions.

For malignant lesions

Staging of lung cancer: Quick and accurate nodal staging of lung cancer is required for the optimum management of these patients. Prior to introduction of EBUS, there were three modalities which were used in this setting – computerized tomography (CT) scan, positron emission tomographic (PET) scan and mediastinoscopy. Among these CT scan has very poor sensitivity and has already been replaced by PET scan wherever the facility is present. However, most of the time cytopathological or histopathological confirmation is required for nodal staging. In such setting, mediastinoscopy was the investigation of choice until a decade ago. Mediastinoscopy allows access to paratracheal nodes (station 2 and 4) and the subcarinal nodes (station 7). It may be extended to sample the subaortic (station 5) and paraaortic nodes (station 6), if required [11]. Mediastinoscopy has good sensitivity (78-81%) and negative predictive value (91%) [12-16]. However, it requires general anaesthesia, a thoracic surgeon and overnight admission. The procedure takes longer time to perform and is associated with small risk of major complication. Restaging, if required, is often challenging due to post-operative fibrosis.

With the advent of EBUS – TBNA, it is possible to sample almost all the lymph nodes adjacent to the airways, that is in the anterior and superior mediastinum (stations 2, 4, and 7) as well as intrapulmonary nodes (stations 10, 11, and 12) [17]. If we combine it with EUS – FNA, which can sample the nodes adjacent to the esophagus (2L, 4L, 5, 7, 8, 9) along with infra-diaphragmatic structures like the adrenal and the liver, a near complete assessment of all lymphnode stations is possible. However, it is extremely rare that a lung cancer metastasize to lymph node stations 8 and 9 without concurrent involvement of upper mediastinal nodes (stations 2, 4, or 7). Hence, routine addition of EUS to EBUS is not required for staging [18].

The comparative evaluation of EBUS – TBNA and mediastinoscopy

for staging of mediastinal lymph node was done, in a prospective study which included patients with potentially resectable NSCLC. It revealed that EBUS – TBNA achieve similar results as mediastinoscopy and can replace mediastinoscopy in such patients [19]. These observations were confirmed in a multicenter randomized controlled trial involving 241 patients with resectable lung cancer. The participants were randomized into either surgical staging or endosonography (EBUS – TBNA with or without EUS – TBNA) followed by surgical staging, for patients who did not reveal nodal metastases. The authors concluded that, a staging strategy combining endosonography and surgical staging compared with surgical staging alone resulted in greater sensitivity for mediastinal nodal metastases and fewer unnecessary thoracotomies [20]. There are many other well conducted studies which have established role of EBUS in this setting [19-22].

Similarly, EBUS has been shown to be better than CT scan as well as PET scan for staging of lung carcinoma. For instance, a prospective study compared EBUS – TBNA to CT staging in preoperative assessment of potentially operable lung carcinoma patients and has shown that EBUS – TBNA was superior to CT in sensitivity (92.3% and 80.0%, respectively) and specificity (100% and 70%, respectively) [23]. Similarly, EBUS – TBNA scored over PET scan for mediastinal staging of 117 patients with potentially operable non-small cell carcinoma (NSCLC) and showed better sensitivity (90% vs. 70%) and specificity (100% vs. 60%) [24]. These finding were confirmed by other researchers also [25]. Data have also demonstrated that preoperative EBUS could upstage patients with small, peripheral tumors and PET-CT scan-negative mediastinum [26].

The good diagnostic yield with this technique has brought it to the forefront as the first procedure for staging of lung cancer and has markedly reduced the need for mediastinoscopy and other surgical procedures [27].

For sub-typing of lung cancer and molecular studies: In today's era, adequate diagnosis of lung cancer requires ample specimen not only to identify malignant cells, but also for further sub-typing them using molecular testing. Initially, there was a concern that the quantity of sample obtained using EBUS may be insufficient for a complete molecular profiling of the tumor. However, there have been studies which demonstrated that the specimens obtained from metastatic lymphnodes with EBUS TBNA were adequate for pathological as well as molecular diagnosis such as EGFR mutation [28]. There is sufficient data which suggests that lung cancer tissue samples obtained by this technique can be successfully processed for molecular analysis for EGFR, KRAS, and ALK gene abnormalities among more than 90% of cases [29]. The tissue obtained by EBUS – TBNA can be used for immunohistochemistry, DNA mutation analysis, m-RNA and mi-RNA expression analysis and this method of tissue acquisition is not inferior to other specimen types [30].

Other malignancies: EBUS – TBNA has been used for diagnosis of intra-thoracic metastasis from extra-thoracic malignancies and lymphoma with a high diagnostic accuracy [31, 32]. For suspected lymphoma with isolated mediastinal lymph node enlargement, a prospective trial has shown that the diagnostic accuracy of EBUS

– TBNA was acceptable and a definite diagnosis could be made in 76% of the patients [32]. However, since the treatment of lymphoma often requires assessment of subtype and histological grade, the small volume of sample obtained by EBUS – TBNA is often insufficient.

Evaluation of airway wall: A frequent problem in patients with central intra-thoracic masses adjacent to the airway is in differentiating whether the airway wall is infiltrated by the tumor or it is merely an extrinsic compression. For this evaluation EBUS has been shown to be superior to CT scan with an accuracy of 94% and 51%, respectively [33]. Another prospective trial, comparing the usefulness of EBUS, computed tomography (CT) and magnetic resonance imaging (MRI) for the assessment of invasion of thyroid or esophageal cancer, showed that EBUS is the most useful technique for determining the depth and extent of tumor invasion into the airway wall [34].

For benign lesions

EBUS is often used to diagnose benign diseases causing mediastinal adenopathy such as sarcoidosis and tuberculosis (especially in endemic countries). Both these disorders are very close differential diagnosis in many patients and require, in addition to the clinico-radiological picture, a pathological confirmation. In a study to evaluate the utility of convex probe EBUS–TBNA as a modality for diagnosis of mediastinal lymphadenopathy, it was seen that EBUS–TBNA was diagnostic in 80.9% and 84.8% of patients with sarcoidosis and TB respectively [35]. In another prospective study comparing the diagnostic yield of EBUS–TBNA and TBLB through a flexible bronchoscope in patients with stage I and II sarcoidosis, it was seen that the diagnostic yield of EBUS–TBNA for stage I and II sarcoidosis is higher than for TBLB [36]. There have been randomized trials which also showed similar results [37, 38]. The GRANULOMA trial was a randomized study which included 304 consecutive patients with suspected pulmonary sarcoidosis who were subjected to either bronchoscopy or EBUS–TBNA. The diagnostic yield to detect granulomas for EBUS–TBNA was 80% as compared 53% for bronchoscopy [38].

EBUS–TBNA has been shown to have a high diagnostic yield in the investigation of suspected intra-thoracic TB [39]. In a prospective study, including 59 patients with suspected TB, the diagnosis of TB was confirmed in 41 patients [39]. Out of these 41 patients, EBUS–TBNA was helpful in confirming the diagnosis of tuberculosis in 35 and shown a sensitivity, specificity, positive and negative predictive values as 85%, 100%, 100% and 75%, respectively.

At our center the major indication of EBUS–TBNA is for the evaluation mediastinal lymph node enlargement due to TB or sarcoidosis. In our experience EBUS has a good diagnostic yield for diagnosis of these conditions [35].

Newer applications of EBUS

Ultrasonographic image provided by EBUS can be used for assessment of the bronchial wall. It allows precise measurement of the thickness of different layers of bronchial wall. This information may be important for patients with bronchial asthma and can be used to assess the bronchial wall remodelling and its severity [40]. It has also been used for diagnosis of intravascular lesions like pulmonary artery tumour embolisms [41, 42] and sarcoma [43]. A new technique recently introduced in the EBUS is elastography to assess the stiffness of the tissue. This technique, like others, first made its debut in the endoscope before being integrated with the EBUS scope. The elastography is based on the principle that malignancy makes tissues less deformable. Compression of surrounding structures produces a deformity or strain effect that is inversely related to the hardness of the pathologic tissue, harder tissues are less deformable than softer tissues. This technique had been used successfully with endoscopy to differentiate with some accuracy between benign and malignant pancreatic masses and lymph nodes [44]. Recently, EBUS elastography has been used for mediastinal and hilar lymph nodes for prediction of nodal metastasis [45]. The initial results suggest that it may have the potential to improve the diagnostic yield of EBUS, as has already been demonstrated in gastrointestinal endoscopy.

Radial EBUS: A further advancement

Peripherally situated lesions present another diagnostic dilemma for the pulmonologist. All such patients cannot be advised surgery as the lesions may be benign. To avoid surgery in all cases, it is necessary to obtain a tissue for diagnosis using a minimally invasive technique. For such lesions conventional flexible bronchoscopy as well as convex probe EBUS were not useful and the lesions often remained outside of the reach of the bronchoscopist [46]. The advancement in technology has led to development of a thin radial probe housing a rotating ultrasound transducer. This can go to peripherally located lesions. The rotating ultrasound produces a 360° ("radial") ultrasound image of the airway. It is advanced into the bronchial segment till a characteristic ultrasound image is seen depicting the solid lesion. TBLB is then performed from this bronchus. Radial EBUS – TBNA sampling does not have the advantage of real time sampling since it is performed by sequential sampling.

The diagnostic yield for peripheral lesions is increased with use of radial probe endobronchial ultrasound (EBUS) to a level comparable to percutaneous sampling [47]. Though the diagnostic yield is still less than that reported with CT guided percutaneous needle biopsy or aspiration, the major advantage of radial probe EBUS is its safety. The reported incidence of pneumothorax in percutaneous interventions is more than 25% with patients requiring prolonged hospital stay and /or intercostal drainage for management [48-50] while with radial EBUS pneumothorax occurred in 1% and only 0.4% required intercostal tube placement [47]. This favourable safety profile has prompted pulmonologist to use radial EBUS as the first line in investigating peripheral lesion while, percutanoeus techniques are resorted to only in cases where either the lesion could not be identified using radial probe or the sample was insufficient or non-diagnostic.

Requirement of Training for EBUS

The guidelines for competency in EBUS set forth by the European Respiratory Society (ERS), / American Thoracic Society (ATS) [51] and American College of Chest Physicians (ACCP) [52]

and recommended that the trainee should perform 40 to 50 procedures before doing it independently. However, studies have demonstrated that there is a wide range of time over which EBUS–TBNA competence is attained and even experienced bronchoscopists vary in their speed of learning [53, 54]. Hence, performance of a set number of procedures does not guarantee competence in the technique.

A recent CHEST expert panel report suggests that professional societies and certifying agencies move from a volume-based certification system to skill acquisition and knowledge-based competency assessment [55]. It also recommended that that simulation specifically be integrated into a structured bronchoscopy teaching curriculum and that high-fidelity simulation due to its cost should be offered in regional simulation centres, which should be accessible to all training programs. It has been shown that EBUS–TBNA simulator use leads to rapid acquisition of skills comparable with that obtained with conventional training methods and EBUS–TBNA simulators show promise for training and simultaneously minimize the burden of procedural learning on patients [56].

Conclusion

EBUS has proven to be a great invention in the field of intervention pulmonology leading to a major change in the practice related management of the many malignant as well benign lung diseases. It has changed the diagnostic workup for diagnosis, staging and restaging of lung cancer and has almost replaced the invasive procedures such as mediastinoscopy. Similar usefulness has been seen in tuberculosis, sarcoidosis and some other diseases. However, due to the inherent design of the EBUS scope it poses some difficulty for learners and requires considerable training for this. The learning can done directly on the patients or using EBUS simulator. Considering the fact that the scope of EBUS is growing day by day, once learnt, no pulmonologist would like to stay away from EBUS.

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