**UTILITY OF ENDOBRONCHIAL ULTRASOUND-GUIDED TRANSBRONCHIAL NEEDLE ASPIRATION IN THE DIAGNOSIS OF LUNG DISEASES**

**Kamal A. Ata\*, Hamdy Ali\*, Ola A. Alkady\* and Rex C. Yung\*\***

\*Department of Chest Diseases, Sohag Faculty of Medicine, Sohag University, Sohag, Egypt. \*\*Department of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland, United States of America.

**ABSTRACT**

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a promising technique in the mediastinalstaging of non small cell lung cancer (NSCLC). However, itsrole in the diagnosis of different lung diseases has not beenwell studied. Using a prospective design, this study was conducted to assess the utility of EBUS-TBNA in the diagnosis of lung diseases. The study included 147 patients; with central or peripheral, localized or infiltrative lung lesions with or without mediastinal and/or hilar lymphadenopathy; of them 86 (58.5%) were males and 61 (41.5%) were females with a mean age of 62.1 years. All patients were subjected to: detailed clinical assessment, routine laboratory investigations, plain X-ray chest, chest computed tomography (CT) scan or positron-emission tomography-CT scans of lung and mediastinum, and endobronchial ultrasound (EBUS) examination using convex (linear) EBUS probe with EBUS-TBNA and cytological or histological examination of the obtained specimens. The rapid on site cytopathology evaluation (ROSE) was available during the procedure. The ultrasonographic characteristics of lymph nodes (LNs) as echogenecity (homogeneous or heterogeneous), intranodal septations, and intranodal vessels were recorded. In the 147 patients, EBUS-TBNA was done in 244 LNs and 13 lung mass lesions. No procedure-related complications were observed. The EBUS-TBNA cytology results of 244 biopsied LNs in 147 patients included: benign lesions in 142 LNs (58.2%) in 72 patients (49%) {included 30 LNs (21.1%) with granulomas in 18 patients (25%), out of them 16 patients had sarcoidosis}; malignant lesions in 64 LNs (26.2%) in 63 patients (42.9%); and non diagnostic results in 38 LNs (15.6%) in 12 patients (8.1%). There were insignificant relations between LN station and size and EBUS-TBNA cytology results **(**p>0.05). The recorded sonographic image characteristics of 147 LNs in 70 patients showed that 67 LNs (45.6%) were characterized as heterogeneous and 8 (5.4%) as homogeneous, intranodal vessel was observed in 24 LNs (16.3%), and intranodal septation was observed in 48 LNs (32.7%). There was significant relation between LN sonographic characteristics and EBUS-TBNA biopsy results (p=0.003). In 37 patients with NSCLC, 45 LNs were sampled for staging. Metastasis was detected in 14 (N1) LNs in 14 patients, and in 15 (N2) LNs in 13 patients, and in 7 (N3) LNs in 7 patients. The cytological results of EBUS-TBNA in 13 lung mass lesions were: malignancy in 9 lesions (69.2%), benign in 3 lesions (23.1%), and non diagnostic in 1 lesion (7.7%). There was insignificant relation between mass site and EBUS-TBNA biopsy results (p=0.5). The diagnostic yield of EBUS-TBNA was 91.8%. The overall sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy rate of EBUS-TBNA in distinguishing benign from malignant lesions were 94%, 100%, 100%, 93.8% and 97.1%, respectively. In conclusion, EBUS-TBNA is a safe and highly accurate procedure for diagnosis of both malignant and benign lung lesions and for examination and staging of mediastinal and hilar LNs in patients with lung cancer.

**INTRODUCTION**

 Pathologic pulmonary and, particularly, mediastinal processes may be difficult to detect with established diagnostic procedures. Also, the diagnosis of peripheral pulmonary lesions and indeterminate mediastinal lymph nodes (LNs) and masses constitutes a significant challenge.Options for tissue diagnoses include computed tomography-guidedpercutaneous biopsy, transbronchial fine-needle aspiration,mediastinoscopy, left anterior mediastinotomy, or video-assistedthoracoscopic surgery; however, these approaches have both advantagesand limitations in terms of tissue yield, safety profile, andcost.(1)

A general postoperative 5-y survival of 40 to 50% in lung cancer patients, despite imaging techniques such as computed tomography and magnetic resonance imaging, indicates the need for better diagnostic tools to improve preoperative staging(2). The objective of non small cell lung cancer (NSCLC) staging, when there is no evidence of distant metastases, is the evaluation of mediastinal LN involvement. Accurate staging of NSCLC is important not only to determine the patient's prognosis, but to aid in deciding on a treatment plan, as the presence of mediastinal LN involvement is diagnostic for stage III lung cancer and suggests inoperability and the need for treatment with chemotherapy, radiation, or both. If the patient does not have nodal involvement, surgery is the treatment of choice.(1,3)

 Bronchoscopy plays an important role in the diagnosis of various lung diseases, especially in the diagnosis and stagingof lung cancer. **Endobronchial** biopsy under direct visualizationcan provide a diagnosis in more than 90% of cases of lung cancer. However,the majority of lung cancers present with primary lesions outsidethe direct view of the bronchoscope, and the yield of transbronchialneedle aspiration (TBNA) for sampling the mediastinum varies widely(1,4).The pooled sensitivityfor TBNA in mediastinal stagingis 39%, and the pooled specificity is99%(5). The view from a bronchoscope islimited to the lumen and the internal surface of the airways;thus, expanding the bronchoscopist's view beyond the airwayscould vastly improve the diagnostic capabilities of diagnosticbronchoscopy(1).

Endobronchial ultrasound (EBUS) is a new minimally invasivetechnique that expands the view of the bronchoscopist beyondthe lumen of the airway.It allows visualization of the tracheobronchial tree with real-time ultrasound and permits visualization of the internal structure of pulmonary lesions, which may narrow the differential diagnosis(1,2). The **endobronchial** application of **ultrasound** was first describedin 1992(6). Since that time, major technological advances haveoccurred, with much published research now reported on the indicationsand diagnostic accuracy of EBUS.Today, EBUS is recognized as an accurate and minimally invasiveprocedure, developed for the diagnosis of parenchymal lung lesionsand the sampling of mediastinal LNs for lung cancerdiagnosis and staging. Two different techniques are available: radial EBUS and the newest development is the convex EBUS-TBNA scope with a curvilinear electronic transducer on the tip of a flexible videoscope.(1,2,4)

The new endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive staging method that has emerged as a potential alternative to mediastinoscopy in lung cancer staging. It is a real-time ultrasonographically visualized puncture that achieves a sensitivity of 92.5%, a negative predictive value of 91% and a diagnostic accuracy of 95% on average. Lymph nodes down to 5mm can be successfully sampled and there are no reports of major complications(7). The EBUS-TBNA can also be used in the diagnostic workup of patients with various intrapulmonary and intrathoracic lesions.(8,9)

**AIM OF THE WORK**

 The aim of this prospective study was to assess the utility of endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lung diseases.

**PATIENTS AND METHODS**

**Study Subjects:**

This study was carried out, using a prospective design, in the Department of Pulmonary and Critical Care Medicine, Johns Hopkins University Hospital, Baltimore, Maryland, United States of America, during the period from December 2007 to December 2009. It included 147 patients who were referred for bronchoscopy and endobronchial ultrasound (EBUS) with a possible diagnosis of thoracic malignancies with or without possible loco-regional lymph node (LN) metastases. Informed written consent was obtained from all subjects and the study was approved by the Hospital Institutional Review boards (JHM IRB).

The study populations were patients with central or peripheral, localized or infiltrative lung lesions with or without intrathoracic, mediastinal and/or hilar, adenopathy who were indicated for bronchoscopy.

The indications for bronchoscopy and EBUS examination were:

1. Suspected thoracic malignancy (clinical or radiological abnormality).
2. Mediastinal and/or hilar adenopathy in computed tomography (CT) and/or positron-emission tomography (PET) scan.
3. Staging of known lung cancer lesions with mediastinal LN involvement.
4. Previously resected lung cancer lesions to search for recurrence in resection margin or second primary.
5. Preoperative assessment of patients with lung cancer to determine extent of endobronchial involvement.
6. Patients with radiological peripheral lung lesions.
7. Patients with clinical and radiological features suggestive of granulomatous lung diseases with hilar or mediastinal LN enlargement in CT scan or PET positive lesions.
8. Patients with known extrathoracic cancer with suspected lung or mediastinal metastasis.

**Diagnostic Procedures:** all patients were subjected to the followings:

1. Detailed clinical assessment including history and physical examination.
2. Routine laboratory investigations.
3. Radiological investigations including but not limited to :
* Plain X-ray chest.
* Chest CT scan: preferably with intravenous contrast enhancement with a single injection contrast on a multidetector-row CT.
* Positron-emission tomography-CT scans of lung and mediastinum: for evaluation of the primary lesion, and the presence or absence of hilar and mediastinal LNs with documentation of their numbers, sizes and locations.

The international TNM staging system for lung cancer defines the regional LNs, the N component, as follows: N0=no LN metastasis; Nl=metastasis to LNs in the peribronchial or the ipsilateral hilar region or both, including direct extension; N2=metastasis to ipsilateral mediastinal and subcarinal LNs; and N3=metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular LNs. For descriptive purposes, LN groups are classified into stations according to the international Mountain and Dresler(10) LN Classification System:-

* N2 nodes: all N2 nodes lie within the mediastinal pleural envelope:- station [1] Highest mediastinal nodes, [2] Upper paratracheal nodes, [3] Prevascular and retrotracheal nodes, [4] Lower paratracheal nodes, [5] Subaortic (aorto-pulmonary window) nodes, [6] Para-aortic nodes (ascending aorta or phrenic), [7] Subcarinal nodes, [8] Paraesophageal nodes (below carina), [9] Pulmonary ligament nodes
* Nl nodes: all Nl nodes lie distal to the mediastinal pleural reflection and within the visceral pleura:- station [10] Hilar nodes, [11] Interlobar nodes, [12] Lobar nodes, [13] Segmental nodes, [14] Subsegmental nodes.

According to the location of the primary tumor, the ipsilateral nodes are designated right (R) or left (L); to denote right- or left-sided stations

1. Endobronchial ultrasound (EBUS) examination: using convex (linear) EBUS probe with EBUS-guided transbronchial needle aspiration.
2. Postbronchoscopy clinical observation with recording of any complication.
3. Cytological or histological examination of the obtained specimens.

**Endobronchial Ultrasound (EBUS) Examination:-**

***Anaesthesia:*** all procedures were performed in the endoscopy suite under monitored anaesthesia care (conscious sedation, typically with intravenous midazolam). Patients also received nebulized lidocaine immediately before the procedure and topical lidocaine during the procedure.

***Technique:***

 Linear (convex) probe EBUS (CP-EBUS) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) were performed using an ultrasound biopsy bronchoscope Olympus linear-probe (BF-UC180F Olympus; Tokyo; Japan) connected to an ultrasound unit (EU\_C60 Olympus Ltd). The probe incorporates a convex transducer at the tip of flexible bronchoscope with a frequency of 7.5MHz and depth of penetration of 9cm that scans parallel to the insertiondirection of the bronchoscope, generating a 50-degree image. The outer diameter of the insertion tubeof the flexible bronchoscope is 6.7mm and that of the tip is6.9mm, making this scope bulkier than a standard therapeuticbronchoscope. For this reason, intubation using the oral routefor insertion was preferred. The angle of view is 80 degrees,and the direction of view is 35 degrees forward oblique. Ultrasoundimages were obtained by placing the probe in direct contactto the trachea or bronchial wall, or after inflating the balloonon the tip of the bronchoscope with saline. We used the water-filledballoon to improve the image quality. In addition, the ultrasoundimages were frozen, allowing for measurement of the lesionor LN in two dimensions. Ultrasound and the white-lightbronchoscopic images were viewed simultaneously. There was also a separate working channel through which the biopsy needle was extended, allowing for real-time biopsy. The bronchoscope was also supported by Doppler function for the identification of blood vessels. The Doppler was used prior to needle insertion to ensure that a suspected LN was not, in fact, a blood vessel.

 Tissue samples were obtained with a dedicated 22-gauge Vizishot needle (XNA-202C). The needle was protected by an outer sheath, which was seen on the endoscopic image and thus preventing it from being deployed within the lumen of the bronchoscope. Image processing was performed by an Olympus ultrasound processor (EU-60). Real-time visualization of the needle was possible on the ultrasound image. Optimal visualization was obtained by partially inflating the balloon with water once a LN had been located. Doppler scanning was used prior to needle puncture to exclude a blood vessel as the object of interest. Once we were confident that the structure in question was a LN, the 22 gauge needle was passed through the bronchial wall and into the LN. The needle was passed back and forth through the LN once a vacuum syringe (10-20cc) had been connected to the needle in order to aspirate lymphatic tissue either in the form of cells or actual tissue fragments.

 The rapid on site cytopathology evaluation (ROSE) was available during the procedure and as determined by the cytologist, the adequacy of cytology specimens was defined by the presence of lymphocytes and inadequate or non diagnostic if there was no cellular components; but, blood, cartilage or bronchial epithelial cells only. The aspirated material was expelled onto the glass slides and smeared. Instead of routinely flushing all cells onto slides or into saline, the thin-wire needle trocar was used to push cells onto filter papers to create coagulum-clots for histology. The smears were air-dried and stained by a modified Giemsa (Diff-Quik) method. At least one air-dried smear was prepared from each aspiration pass and additional smears were fixed in 95% alcohol to be stained by the Papanicolaou method. Sections from the paraffin embedded cell block were stained with hematoxylin-eosin. Multiple passes, at least four, were performed until smeared aspirates were diagnostic of a disease condition and also showed an adequate amount of lymphoid tissue in LN samples. All smears were numbered with respect to the order of aspiration. Adequacy of the specimen and a preliminary diagnosis were rendered by a pathologist on site. In addition, bronchoalveolar lavage (BAL) was performed and the samples were sent for cytology and bacteriological examination. Cytological assessment was done and reported independently.

**Endobronchial ultrasound image characteristics of lymph nodes:**

The ultrasonographic characteristics on EBUS examination were studied in 124 LNs in 70 patients. The ultrasonographic characteristics recorded during EBUS examination were: echogenecity (homogeneous or heterogeneous), presence or absence of intranodal septations (figure 1 and 2), and presence or absence of intranodal vessel as examined by power Doppler mode (figure 3). After noting the ultrasonographic characteristics of the mediastinal or hilar LNs, EBUS-TBNA was done from the LNs, then all sonographic features of the LNs were compared to the final pathological result of the LN samples.

***Time of procedure:*** the total time of EBUS procedure was defined as the time from insertion of the bronchoscope to the retrieval of the bronchoscope after the procedure.



**Figure (2):** EBUS-TBNA in station 7 septated LN.



**Figure (1):** EBUS-TBNA in Rt. hilar LN.



**Figure (3):** Intranodal vessel in station 7 LN.

**Data Collection, Statistical Analysis and Outcome Measures:**

Collected data including complications, location of target lesions, and endobronchial puncture site for target lung masses were recorded. The LNs were systematically visualized by starting with N1 LNs followed by N2 nodes and finally N3 nodes. The LNs locations were classified according to the Mountain and Dresler(10) LN map**.**

 The real-time CP-EBUS-TBNA benign and non diagnostic biopsy results were confirmed byopen thoracotomy, mediastinotomy, thoracoscopy, mediastinoscopy, postmortem autopsy or clinical or CT follow-up for 6 months or more. A positive EBUS-TBNA result was considered as a true positive because the chance of contamination is very rare(11,12,13), so a positivecytologic result of malignancy was accepted as evidence andthe patients were treated accordingly.

 The sensitivity, specificity,negative and positive predictive values, and diagnostic accuracy were calculated using the standard definitions. The diagnostic yield defined as samples with definite malignant or benign pathology was calculated.  Data were analyzed using the statistical software (Statistical Package for the Social Sciences, SPSS; version 13.0; Chicago, IL). The results were compared using χ2 test and a probability level (p-value) of <0.05 was considered statistically significant.

**RESULTS**

The study included 147 patients, of them 86 (58.5%) were males and 61 (41.5%) were females, and their ages ranged from 17 to 93 years with a mean age of 62.07 ±13.25 years.In those 147 patients, 277 lymph nodes (LNs) and 13 lung mass lesions were examined by convex probe EBUS. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was done in 244 LNs in addition to 13 lung mass lesions. No procedure-related complications were observed.

The cytology results of EBUS-TBNA in patients included in the study are shown in table (1). Seventy-two patients (49%) had benign lesions, 63 (42.9%) had malignant lesions, and in 12 patients (8.1%) the procedure was non diagnostic.

**Table (1): Cytology results of EBUS-TBNA in patients included in the study.**

|  |  |
| --- | --- |
| **Result** | **Patients** |
| **No.** | **%** |
| **Malignant** Adenocarcinoma Squamous cell carcinoma Large cell carcinoma Small cell carcinoma Poorly differentiated NSCLC\*  Lymphoma  Neuroendocrine tumor  Poorly differentiated carcinoma  Metastasis from renal, oral  and rectal cancers  | 6316131676473 | 42.9 |
| **Benign** Granulomatous lung diseases  Benign lymphoid tissue  Acute inflammation  | 7218531 | 49 |
| **Non diagnostic** | 12 | 8.1 |
| **Total** | 147 | 100 |

\*NSCLC=non small cell lung cancer.

 The cytology results of EBUS-TBNA were divided according to biopsy target into:

* Mediastinal and hilar lymph nodes biopsy results, and
* Lung mass biopsy results**.**
1. ***Mediastinal and Hilar Lymph Nodes Biopsy Results:***

In 147 patients included in the study, 277 lymph nodes (LNs) were examined by convex probe EBUS and EBUS-guided TBNA was done in 244 LNs. The total number of LNs passes was 640 and the average number of EBUS-TBNA passes in each case was 4 while the range of passes was from 2 to 8 passes/case. The procedure time ranged from 15 to 80 minutes and the average time was 39 minutes.

The cytology results of 244 biopsied LNs in 147 patients are shown in table (2). Benign lesions were detected in 142 LNs (58.2%) in 72 patients (49%) which included 30 LNs with granulomas (21.1%) in 18 patients (25%). These 18 patients with granulomas included 1 case had tuberculous lymphadenitis, 1 case had Wegener’s granulomatosis and 16 had sarcoidosis. Malignant lesions were detected in 64 LNs (26.2%) in 63 patients (42.9%) while non diagnostic results were recorded in 38 LNs (15.6%) in 12 patients (8.1%) (the result was considered non diagnostic if the sample was not sufficient or the cytology result was only blood clot or bronchial epithelium).

**Table (2): Cytology results of EBUS-TBNA in biopsied LNs and in patients included in the study.**

|  |  |  |
| --- | --- | --- |
| **EBUS-TBNA****Result** | **Lymph nodes** | **Patients** |
| **No.** | **%** | **No.** | **%** |
| **Benign** | 142 | 58.2 | 72 | 49 |
| **Malignant** | 64 | 26.2 | 63 | 42.9 |
| **Non diagnostic** | 38 | 15.6 | 12 | 8.1 |
| **Total** | 244 | 100.0 | 147 | 100 |

The EBUS-TBNA was done in 244 mediastinal and hilar LNs in different locations (table 3). Most of the biopsies were from LNs station 4R and 7. Most of the benign and malignant lesions were found in LN stations 4R and 7. On the other hand, most non diagnostic results were found in LN station 4R. It was found that cytology results were irrelevant to LN station and also, the diagnostic yield was independent of LN station (p=0.244) (table 3).

**Table (3): Relation between LNs Locations and EBUS-TBNA results.**

|  |  |  |
| --- | --- | --- |
| **Lymph node** **station** | **EBUS-TBNA result** | **Total** |
| **Benign**  | **Malignant**  | **Non diagnostic** |
| **No.** | **%** | **No.** | **%** | **No.** | **%** | **No.** | **%** |
| **10L** | 2 | 1.4 | 3 | 4.7 | 0 | 0.0 | 5 | 2.1 |
| **10R** | 10 | 7.0 | 8 | 12.5 | 6 | 15.8 | 24 | 9.8 |
| **11L** | 15 | 10.6 | 1 | 1.6 | 2 | 5.3 | 18 | 7.4 |
| **11R** | 20 | 14.1 | 3 | 4.7 | 5 | 13.2 | 28 | 11.5 |
| **2R** | 1 | 0.7 | 1 | 1.6 | 1 | 2.6 | 3 | 1.2 |
| **4L** | 15 | 10.6 | 5 | 7.8 | 3 | 7.9 | 23 | 9.4 |
| **4R** | 40 | 28.2 | 22 | 34.3 | 14 | 36.8 | 76 | 31.1 |
| **7** | 39 | 27.4 | 21 | 32.8 | 7 | 18.4 | 67 | 27.5 |
| **Total** | 142 | 100.0 | 64 | 100.0 | 38 | 100.0 | 244 | 100.0 |
| **Chi-square** | 19.484 |
| **P-value**  | 0.244 |

The size of the LNs punctured by the real-time EBUS-TBNA ranged from 0.7 to 5cm and the mean LN size was 1.7cm. We divided LNs according to their sizes in CT scan into three groups: LNs <1cm (n=16, 6.6%), LNs 1-2cm (n=165, 67.6%), and LNs >2cm (n=63, 25.8%). Most of punctured LNs and most of the benign, malignant and non diagnostic results were found in LNs sized 1-2cm. There was insignificant relation between LN size and EBUS–TBNA cytology results (p>0.5) (table 4).

**Table (4): Relation between LN size and EBUS-TBNA cytology results.**

|  |  |  |
| --- | --- | --- |
| **Lymph Node** **size**  | **EBUS-TBNA result** | **Total** |
| **Benign**  | **Malignant**  | **Non diagnostic**  |
|  | **No.** | **%** | **No.** | **%** | **No.** | **%** | **No.** | **%** |
| **<1cm** | 9 | 6.3 | 1 | 1.6 | 6 | 15.8 | 16 | 6.6 |
| **1-2cm** | 97 | 68.3 | 40 | 62.5 | 28 | 73.7 | 165 | 67.6 |
| **>2cm** | 36 | 25.4 | 23 | 35.9 | 4 | 10.5 | 63 | 25.8 |
| **Total** | 142 | 100.0 | 64 | 100.0 | 38 | 100.0 | 244 | 100.0 |
| **Chi-square** | 0.008 |
| **P-value**  | >0.5 |

The ultrasonographic image characteristics of LNs (echogenecity, intranodal septations and intranodal vessel) were noted during EBUS-TBNA procedure in 147 LNs in 70 patients. For echogenecity, 67 LNs (45.6%) were characterized as heterogeneous and 8 (5.4%) as homogeneous. Intranodal vessel was observed in 24 LNs (16.3%) and intranodal septation was observed in 48 LNs (32.7%). By looking at the EBUS-TBNA results of these 147 LNs: a total of 106 LNs (72.1%) showed benign results and 27 (18.4%) showed malignant results while in 14 (9.5%) the procedure was non diagnostic. There was significant relation between LN sonographic characteristics and EBUS-TBNA biopsy results (p=0.003) (table 5).

**Table (5): Relation between LN sonographic characteristics and EBUS-TBNA cytology results.**

|  |  |  |
| --- | --- | --- |
| **Sonographic characteristics**  | **EBUS-TBNA cytology results** | **Total** |
| **Benign** | **Malignant** | **Non diagnostic** |
| **No.** | **%** | **No.** | **%** | **No.** | **%** | **No.** | **%** |
| **Homogeneous** | 6 | 5.7 | 2 | 7.4 | 0 | 0 | 8 | 5.4 |
| **heterogeneous** | 37 | 34.9 | 19 | 70.4 | 11 | 78.6 | 67 | 45.6 |
| **Intranodal vessel** | 21 | 19.8 | 3 | 11.1 | 0 | 0 | 24 | 16.3 |
| **Intranodal septations** | 42 | 39.6 | 3 | 11.1 | 3 | 21.4 | 48 | 32.7 |
|  **Total** | 106 | 100.0 | 27 | 100.0 | 14 | 100.0 | 147 | 100.0 |
| **Chi-square** | 20.07 |
| **P-value** | 0.003 |

**Endobronchial ultrasound-guided TBNA in staging of lung cancer:**

Thirty-seven patients with known non small cell lung cancer (NSCLC) or diagnosed by EBUS had EBUS-TBNA and 45 LNs were sampled for staging. Metastasis was detected in 14 (N1) LNs in 14 patients, and in 15 (N2) LNs in 13 patients, and in 7 (N3) LNs in 7 patients.

1. ***Lung Mass Lesions Biopsy Results:***

The EBUS-TBNA was done in 13 mass lesions in different locations (table 6). The total number of passes was 45 and the average number of passes was 3. The mass size in CT scan ranged from 2 to 6.5cm and the average mass size was 3.8cm. Cytological results of EBUS-TBNA in lung mass lesions were:

* Malignancy in 9 mass lesions (9/13, 69.2%): adenocarcinoma in 1 case, squamous cell carcinoma in 4 cases, poorly differentiated NSCLC in 2 cases, small cell carcinoma in 1 case, and large B cell lymphoma in 1 case.
* Benign in 3 lesions (3/13, 23.1%): granulomatous lung disease in 1 case, and benign respiratory epithelium in 2 cases.
* Non diagnostic in 1 lesion (1/13, 7.7%).

There was insignificant relation between mass site and EBUS-TBNA biopsy results (p=0.564)(table 6).

**Table (6): Relation between mass site and EBUS-TBNA cytopathology results.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Mass Site\*** | **Cytopathology result** | **Total** | **Chi- square** | **P- value** |
| **Benign** | **Malignant** | **Non diagnostic** |
| **No.** | **%** | **No.** | **%** | **No.** | **%** | **No.** | **%** | 8.667 | 0.564 |
| **LLL** | 1 | 7.7 | 0 | 0.0 | 0 | 0.0 | 1 | 7.7 |
| **LMB** | 0 | 0.0 | 2 | 15.4 | 0 | 0.0 | 2 | 15.4 |
| **RLL** | 1 | 7.7 | 1 | 7.7 | 0 | 0.0 | 2 | 15.4 |
| **RML** | 1 | 7.7 | 2 | 15.4 | 1 | 7.7 | 4 | 30.7 |
| **RUL** | 0 | 0.0 | 3 | 23.1 | 0 | 0.0 | 3 | 23.1 |
| **RMB** | 0 | 0.0 | 1 | 7.7 | 0 | 0.0 | 1 | 7.7 |
| **Total**  | 3 | 23.1 | 9 | 69.2 | 1 | 7.7 | 13 | 100.0 |

\*LLL=left lower lobe, LMB=left main bronchus, RLL=right lower lobe, RML=right middle lobe, RUL=right upper lobe, RMB=right main bronchus.

**Follow up of all cases:**

**I- Patients with benign results:** of the 72 patients with benign results in 142 LNs and 3 lung masses:

1. Sixty patients (83.3%) with 120 LNs (84.5%) were confirmed to have benign lesions as follows:
* Forty patients with 83 LNs and 3 lung masses were confirmed by histology (surgery and mediastinoscopy).
* Two patients were confirmed by postmortem autopsy.
* Eighteen patients had clinical and CT scan follow up over a period of 6 months or more demonstrating a lack of clinical or radiologic disease progression, including patients with a diagnosis of sarcoidosis who were followed up as outpatients.
1. Four patients (5.6%) with benign LNs had false negative findings as they were found to have malignant lesions by mediastinoscopy and surgery.
2. Eight patients (11.1%) were lost to follow up.

**II- Patients with malignant results:** the 63 patients with malignant results, in 64 LNs and 9 lung masses, continued their treatment according to the histopathological diagnosis and staging results.

**III- Patients with non diagnostic results:** of the 12 patients with non diagnostic biopsy results in 38 LNs and 1lung mass lesion:

* Six patients were diagnosed later by mediastinoscopy (n=5) and repeated bronchoscopy with mediastinotomy (n=1) as benign lymphoid tissue including 2 granulomas cases.
* Three patients were followed up by CT scan over a period of 6 months and more which showed resolving lesions in 2 patients and non progressive lesion in 1 patient.
* Two patients were lost to follow up.
* One patient died.

There was no operative mortality or any surgical complications and mediastinoscopy was avoided in 86 patients.

The diagnostic yield of CP-EBUS-TBNA was 91.8%. The overall sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy rate of CP-EBUS-TBNA in distinguishing benign from malignant lesions were 94%, 100%, 100%, 93.8% and 97.1%, respectively.

**DISCUSSION**

Endobronchial ultrasound (EBUS) has emerged as a new diagnostic tool that allows the bronchoscopist to see beyond the airway so extending the diagnostic spectrum of bronchoscopic techniques. Due to a high diagnostic informative value, low effort and low risk, EBUS has become incorporated into routine practice in pulmonary centers and it has proved to be of increasing importance in the diagnosis of mediastinal mass and staging of lung cancer. Therefore, EBUS plays an important role in the new interdisciplinary guidelines on prevention, diagnostics, therapy and after care of lung cancer.(2,4)

 Linear (convex) probe EBUS allows a real-time EBUS-guided transbronchial needle aspiration (EBUS-TBNA). Although the main indication for EBUS-TBNA is lymph node (LN) staging and it is particularly useful for the evaluation of hilar and mediastinal LNs in cases of lung neoplasms with a sensitivity of more than 90% and specificity of 100%, it can also be used for diagnosis of intrapulmonary lesions, of unknown hilar and/or mediastinal lymphadenopathy, and of mediastinal tumors. It is a novel approach that has a good diagnostic yield with excellent potential in assisting safe and accurate diagnostic interventional bronchoscopy.(8,14)

This study was designed prospectively to evaluate the utility of the convex probe endobronchial ultrasound (CP-EBUS) with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the diagnosis of lung diseases.

In this study, EBUS-TBNA was used for biopsy of mediastinal and hilar LNs in addition to lung mass lesions. The sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy of EBUS-TBNA in distinguishing benign from malignant lung lesions were 94%, 100%, 100%, 93.8%, and 97.1%, respectively. Many studies(11,15-29) showed high diagnostic rates for EBUS-TBNA with sensitivities and negative predictive values of more than 90% and specificities of 100%. Our findingsare in concordance with findings from other large seriesof EBUS-TBNA cases.

The high diagnostic yield of EBUS-TBNA in this study can be attributed to availability of the rapid on site cytologic evaluation (ROSE) in all procedures. Another factor is the real-time visualization of the needle tract in the ultrasound plane during biopsy of LNs. We used ROSE in our series which in turn increased the diagnostic yield of CP-EBUS-TBNA to be 91.8%, also ROSE was helpful to decrease the number of passes. This finding is supported by those of other authors(22,30-33) who reported that ROSE is often used with EBUS-TBNA not only to confirm that diagnostic material is retrieved but also to identify positive biopsies immediately so that the procedure can be terminated. Therefore, use of ROSE in this manner will limit the number of stations sampled andwill significantly improve the diagnostic yield.

The EBUS-TBNA is useful in diagnosing and staging intrathoracic lymphadenopathy. It reaches multiple LN stations and can access LN stations either difficult or impossible to access by cervical mediastinoscopy, especially subcarinal (station 7) and hilar stations (10 and above)(1,20). In the present study, EBUS-TBNA biopsy was done in LNs with different sizes in different LN stations but it was found that biopsy success is independent of LN size (p>0.5) and LN station (p=0.24). These results agree with those of other investigators(31,34) who showed that the diagnostic yield of EBUS-TBNA in LNs of different sizes in the various LNs stations is similar. However,Gupta et al.(35) concluded that the factors which appear to influence the diagnosticyield of EBUS-TBNA include LN size and location (LNs 5mm and those in paratracheal location had a lower diagnosticyield).

By using the technique of EBUS-TBNA in this study, we confirmed our assumption that the use of EBUS for TBNA results in a high success rate for accessing LNs and a high diagnostic yield (91.8%). It allowed for reliable biopsy of even small nodes and nodes in difficult locations. As a matter of fact, when using EBUS, LN location and size did not influence the success of actually “hitting” the intended node. This is in contrast to conventional TBNA, where there is a significant difference in diagnostic success depending on node location. This gives additional creed to the assumption that imaging guidance is beneficial for TBNA.

Accurate diagnosis and staging of lung cancer are crucial for prognostic and therapeutic decision making. The most important application of EBUS is the use of CP-EBUS-TBNA to accurately stage the mediastinum in patients with non small cell lung cancer (NSCLC). It has the advantage of simultaneously obtaining the diagnosis and stage of lung cancer in a single procedure in the outpatient setting, especially in patients who present with a lung mass, mediastinal adenopathy, and no evidence of distant metastasis.(1) The EBUS-TBNA offers a minimally invasive alternative to mediastinoscopy with additional access to the hilar LNs, a better safety profile, and it removes the costs and hazards of theatre time and general anaesthesia with comparable sensitivity, although the negative predictive value of mediastinoscopy (and sample size) is greater. It obtains larger samples than conventional TBNA, has superior performance and theoretically is safer, allowing real-time sampling under direct vision. It can also have predictive value both in sonographic appearance of the nodes and histological characteristics. Therefore, EBUS-TBNA is indicated for NSCLC staging, diagnosis of lung cancer when there is no endobronchial lesion, and diagnosis of benign pulmonary and mediastinal lesions (especially tuberculosis and sarcoidosis). The procedure is different than for flexible bronchoscopy, takes longer, requires more training and is more expensive than conventional TBNA but can save costs by reducing the number of more costly mediastinoscopies.(36)

The important role of EBUS-TBNA in NSCLC staging was defined by many studies(17-26,31,32,37-45) with pooled sensitivity of 93% and specificity of 100%. In this study, we used EBUS-TBNA in staging of NSCLC. Metastasis was detected in 14 (N1) LNs in 14 patients, and in 15 (N2) LNs in 13 patients, and in 7 (N3) LNs in 7 patients.

In the present study, EBUS-TBNA showed good results not only in lung cancer, lymphoma or metastatic lesions diagnosis, or in staging of NSCLC but also in diagnosis of benign lung diseases especially granulomatous lung diseases as sarcoidosis. Of the 72 patients with benign results, 60 cases (83.3%) with 120 LNs (84.5%) were confirmed to be benign and 18 cases were diagnosed as granulomatous lung diseases (1 case had tuberculous lymphadenitis, 1 case had Wegener’s granulomatosis and 16 had sarcoidosis). These results are consistent with those of other investigators(46,47) who reported that EBUS-TBNA is a safe, minimally invasive tool for the primary diagnosis of pulmonary sarcoidosis as it has a high diagnostic yield, superior to that of standard TBNA, and it should be considered as an appropriate alternative diagnostic technique for patients with suspected pulmonary sarcoidosis**.**

It has been reported that sonographic features are useful imaging tool in the evaluation of cervical LN metastasis in head and neck cancers, breast cancers and thoracic malignancies(48,49).For prediction of malignant LNs in our series, we studied the ultrasonographic features as regards echogenecity, intranodal septations and intranodal vessels in 147 LNs in 70 patients and we found that there was a significant relation between LN ultrasonographic features and LN biopsy result (p=0.003). It was found that intranodal septation had a powerful correlation with benign LNs and a high negative predictive value for malignant involvement so that more invasive follow-up biopsies may be deferred which spares patients potential surgical complications.

To our knowledge, few studies were done on LN ultrasonographic characteristics for prediction of malignant LNs. Kurimoto et al.(50) evaluated the internal structures of 78 mediastinal and hilar LNs by B mode and power Doppler mode. They found that hyperechoic interface echo, internal echogenecity, aberrant vessels, subcapsularvessels, and focal absence of perfusion were useful to differentiatemetastatic LNs from those of sarcoidosis. On the other hand , Meltem and coworkers(51), in their study on the ultrasonographic features in benign and malignant mediastinal LNs, showed that although the absenceof a blood vessel and presence of an irregular margin of theLN had a more powerful correlation with malignancy,none of the features as the round shape, absence ofthe blood vessel, hypoechogenicity, heterogeneity,irregular and hyperechoic margin, presence of hyperechoic dots,septations and anechoic cystic cavities were found to be significantly correlated withthe malignant pathology (p>0.10).Fujiwara et al.(52) also studied image characteristics of 1061 LNs obtained by CP-EBUS for prediction of LN metastasis. They found that when LNs had the following features; >1cm in short axis, round shape, distinct margin, heterogeneous echogenecity, the absence of central hilar structure, or the presence of coagulation necrosis sign, they tended to suggest metastatic LNs**.** The accuracy of predicting metastatic property was 76.4% for size, 79.3% for shape, 65.7% for margin, 89.9% for echogenecity, 63.8% for the central hilar structure, and 86.0% for the coagulation necrosis sign**.**

Part of the attraction of EBUS-TBNA has been the lack of reported complications. Presumably, EBUS-TBNA is thought to have eliminated or reduced the potential of complications that were rarely associated with "blind" or conventional TBNA such as aortic puncture, pneumomediastinum and chylothorax. All authors of the published literature have not encountered complications related to EBUS-TBNA and to date no major complications have been reported in the literature(8).In the present study, there were no recorded complications with CP-EBUS and EBUS-TBNA.Other studies(3,9,14,20,53) also support this finding about the safety ofEBUS-TBNA.Although EBUS-TBNA is a safe method with no major complications, rare minor complications were recorded after the procedure as a case report of endobronchial polyp developed in a patient with tuberculous lymphadenitis(54).In other studies(55,56,57), there were recorded infective complications from EBUS-TBNA as pericardial effusion, lung abscess and mediastinal abscess. However, no complication required surgical intervention or a prolonged hospitalization.

Fromthis study it can be concluded that CP-EBUS-TBNA is a well tolerated, safe, highly accurate and cost effective procedure. It has high diagnostic yield and accuracy for diagnosis of both malignant and benign lung lesions and for mediastinal staging in patients with lung cancer. It allows real-time direct visualization of the area of interest while performing the biopsy and can access more sites and smaller LNs. Use of ROSE with EBUS-TBNA improves the diagnostic yield and the false negative rate. By incorporating findings of certain benignfeatures of LNs (as septations) during EBUS, more invasive follow-up biopsies may be deferredthus sparing patients potential surgical complications.So, EBUS-TBNA represents a fine alternativeto more invasive diagnostic procedures when conventional methodsfail to give the diagnosis in radiologically suspicious lesions as this minimally invasive diagnosticmodality can provide a final diagnosis without exposing the patientto the risk of complications from these invasive procedures.

**REFERENCES**

1. **Gomez M and Silvestri GA (2009).** Endobronchial ultrasound for the diagnosis and staging of lung cancer. The Proceedings of the American Thoracic Society; 6:180-186.
2. **Currie GP, Kennedy AM and Denison AR (2009).** Tools used in the diagnosis and staging of lung cancer: what's old and what's new? QJM; 102: 443-448.
3. **Szlubowski A, Kuzdzal J, Kolodziej M, et al. (2009).** Endobronchial ultrasound-guided needle aspiration in the non-small cell lung cancer staging Eur J Cardiothorac Surg; 35: 332-336.
4. [**Plekker**](http://erm.ersjournals.com/search?author1=D.+Plekker&sortspec=date&submit=Submit) **D,** [**Koegelenberg**](http://erm.ersjournals.com/search?author1=C.F.N.+Koegelenberg&sortspec=date&submit=Submit) **CF and** [**Bolliger**](http://erm.ersjournals.com/search?author1=C.T.+Bolliger&sortspec=date&submit=Submit) **CT (2010).** Different techniques of bronchoscopy. In Interventional Pulmonology. European Respiratory Society Monograph. Edited by Strausz J and Bolliger CT. Vol. 48: 1-17.
5. **Holty JE, Kuschner WG and Gould MK (2005).** Accuracy of transbronchial needle aspiration for mediastinal staging of non-small cell lung cancer: a meta-analysis. Thorax; 60: 949-955.
6. **Hurter T and Hanrath P (1992**). Endobronchial sonography: feasibility and preliminary results. Thorax; 47: 565-567.
7. **Antoni R, Susana P and Rosa L (2009).** Endobronchial ultrasound in lung cancer staging. Clin Pulm Med; 16: 275-280.
8. **Herth FJ (2010).** Transbronchial needle aspiration and endobronchial ultrasound. In Interventional Pulmonology. European Respiratory Society Monograph. Edited by Strausz J and Bolliger CT. Vol. 48: 45-58.
9. **Eckardt J, Petersen HO, Hakami-Kermani A, et al. (2009).** Endobronchial ultrasound-guided transbronchial needle aspiration of undiagnosed intrathoracic lesions. Interactive Cardiovascular and Thoracic Surgery; 9: 232-235.
10. **Mountain CF and Dresler CM (1997).** Regional lymph node classification for lung cancer staging. Chest; 111: 1718-1723.
11. **Yasufuku K, Nakajima T, Motoori K, et al. (2006).** Comparison of endobronchial ultrasound, positron emission tomography, and computed tomography for lymph node staging of lung cancer. Chest; 130: 710-718.
12. **Lee SH, Lee KG, Lee HS, et al. (2008).** Real-time endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal staging of non-small cell lung cancer: how many aspirations per target lymph node station. Chest; 134: 368-374.
13. **Jantz MA, Kulkarni V and Fernandez−Bussy S (2009).** Experience with endobronchial ultrasound for diagnosis of adenopathy and staging of intrathoracic malignancies. Am J Respir Crit Care Med; 179: A5792.
14. **Varela-Lema L, Fernandez-Villar A, and Ruano-Ravina A (2009).** Effectiveness and safety of endobronchial ultrasound–transbronchial needle aspiration: a systematic review Eur Respir J; 33: 1156-1164.
15. **Krasnik M, Vilman P, Larsen SS, et al. (2003).** Preliminary experience with a new method of endoscopic transbronchial real time ultrasound guided biopsy for diagnosis of mediastinal and hilar lesions. Thorax; 58: 1083-1086.
16. **Yasufuku K, Chhajed PN, Sekine Y, et al. (2004).** Endobronchial ultrasound using a new convex probe: a preliminary study on surgically resected specimens. Oncol Rep; 11: 293-296.
17. **Yasufuku K, Chiyo M, Sekine Y, et al. (2004).** Real-time endobronchial ultrasound guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. Chest; 126: 122-128.
18. **Rintoul RC, Skwarski KM, Murchison JT, et al. (2005).** Endobronchial and endoscopic ultrasound-guided real-time fine-needle aspiration for mediastinal staging. Eur Respir J; 25: 416-421.
19. **Herth FJ, Eberhardt R, Vilmann P, et al. (2006).** Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. Thorax; 61: 795-798.
20. **Herth FJ, Ernst A, Eberhardt R, et al. (2006).** Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically normal mediastinum. Eur Respir J; 28: 910-914.
21. **Herth FJ, Rabe KF, Gasparini S, et al. (2006).** Transbronchial and transoesophageal (ultrasound-guided) needle aspirations for the analysis of mediastinal lesions. Eur Respir J; 28: 1264-1275.
22. **Navani N, Kocjan G, Capitanio A, et al. (2009).** The utility of rapid on-site evaluation of samples from endobronchial ultrasound guided transbronchial needle aspiration. Am J Respir Crit Care Med; 179: A5788.
23. **Herth FJ, Eberhardt R, Krasnik M, et al. (2008).** Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically and positron emission tomography-normal mediastinum in patients with lung cancer. Chest; 133: 887-891.
24. **Herth FJ, Annema JT, Eberhardt R, et al. (2008).** Endobronchial ultrasound with transbronchial needle aspiration for restaging the mediastinum in lung cancer. J Clin Oncol; 26: 3346-3350.
25. **Vincent BD, El-Bayoumi E, Hoffman B, et al. (2008).** Real-time **endobronchial ultrasound-**guided transbronchial lymph node aspiration. Ann Thorac Surg; 85: 224-230.
26. **Koh MS, Tee A, Wong P, et al. (2008)**. Advances in lung cancer diagnosis and staging: Endobronchial ultrasound. Intern Med J; 38: 85-89.
27. **Tournoy KG, Rintoul RC, van Meerbeeck JP, et al. (2009).** EBUS-TBNA for the diagnosis of central parenchymal lung lesions not visible at routine bronchoscopy. Lung Cancer; 63: 45-49.
28. **Lee JE and Hwangbo B (2009).** Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lung cancer. Chest Meeting Abstracts; 136: 111S.
29. **Gilbert S, Wilson DO and Christie NA (2009).** Endobronchial ultrasound as a diagnostic tool in patients with mediastinal lymphadenopathy. Ann Thorac Surg; 88: 896-902.
30. **Alsharif M, Andrade RS, Groth SS, et al. (2008).** Endobronchial ultrasound-guided transbronchial fine-needle aspiration: the University of Minnesota experience, with emphasis on usefulness, adequacy assessment, and diagnostic difficulties. Am J Clin Pathol; 130:434-443.
31. **Ernst A, Anantham D, Eberhardt R, et al. (2008).** Diagnosis of mediastinal adenopathy: real-time **endobronchial ultrasound** guided needle aspiration versus mediastinoscopy. J Thorac Oncol; 3: 577-582.
32. **Block MI (2010).** Endobronchial ultrasound for lung cancer staging: how many stations should be sampled? Ann Thorac Surg; 89: 1582-1587.
33. **Cameron** **SE, Andrade RS and Pambuccian SE** **(2010).** Endobronchial ultrasound-guided transbronchial needle aspiration cytology: a state of the art review. Chest; 21: 6-26.
34. **Herth FJ, Becker HD and Ernst A (2003).** Ultrasound-guided transbronchial needle aspiration: an experience in 242 patients. Chest; 123: 604-607.
35. **Gupta A, Kennedy M, Casal R, et al. (2009).** Factors affecting the diagnostic yield of endobronchial ultrasound-guided transbronchial needle aspiration. Chest Meeting Abstracts; 136: 1S.
36. **Medford AR, Bennett JA and Agrawal S (2010).** Endobronchial ultrasound guided transbronchial needle aspiration Postgrad Med J; 86: 106-115
37. **Bauwens O, Dusart M, Pierard P, et al. (2008).** **Endobronchial ultrasound** and value of PET for prediction of pathological results of mediastinal hot spots in lung cancer patients. Lung Cancer; 61: 356-361.
38. **Kanoh K, Miyazawa T, Kurimoto N, et al. (2005).** **Endobronchial** ultrasonography guidance for transbronchial needle aspiration using a double-channel bronchoscope. Chest; 128: 388-393.
39. **Plat G, Pierard P, Haller A, et al. (2006).** **Endobronchial ultrasound** and positron emission tomography positive mediastinal lymph nodes. Eur Respir J; 27: 276-281.
40. **Yasufuku K, Chiyo M, Koh E, et al. (2005).** **Endobronchial ultrasound** guided transbronchial needle aspiration for staging of lung cancer. Lung Cancer; 50: 347-354.
41. **Groth SS, Whitson BA, D'Cunha J, et al. (2008).** Endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes: a single institution's early learning curve. [Ann Thorac Surg; 86: 1104-1109.](http://www.medscape.com/viewpublication/2627)
42. **Shrager JB (2010).** Mediastinoscopy: Still the Gold Standard.Ann Thorac Surg; 89: S2084-S2089.
43. **Tupayachi MG, Hosein PJ, Nguyen DM, et al. (2010).** Accuracy of endobronchial ultrasound-directed transbronchial needle aspiration for mediastinal staging in patients with non-small cell lung cancer. J Clin Oncol, ASCO Meeting Abstracts; 28: 7071.
44. **Natu S, Hoffman J, Siddiqui M, et al. (2010).** The role of endobronchial ultrasound guided transbronchial needle aspiration cytology in the investigation of mediastinal lymphadenopathy and masses, the North Tees experience J Clin Pathol; 63: 445-451.
45. **Wada H, Nakajima T, Yasufuku K, et al. (2010).** Lymph node staging by endobronchial ultrasound-guided transbronchial needle aspiration in patients with small cell lung cancer. Ann Thorac Surg; 90: 229-234.
46. **Garwood S, Judson M, Silvestri G, et al. (2007).** Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. Chest; 132:1298-1304.
47. **Tremblay A, Stather D, MacEachern P, et al. (2009).** A randomized controlled trial of standard vs endobronchial ultrasonography-guided transbronchial needle aspiration in patients with suspected sarcoidosis. Chest; 136: 340-346.
48. **Ahuja AT and Ying M (2005)**. Sonographic evaluation of cervical lymph nodes. Am J Roentgenol; 184: 1691-1699.
49. **Kim TH, Kang DK, Kim SY, et al. (2008).** Sonographic differentiation of benign and malignant papillary lesions of the breast. J Ultrasound Med; 27: 75-82.
50. **Kurimoto N, Inoue T, Tagaya R, et al. (2008).** Analysis of internal structures of mediastinal and hilar lymph nodes by endobronchial ultrasonography. Chest ACCP 74th Annual Meeting; 134: S34001.
51. **Meltem T, Gillespie C, Leh S, et al. (2008).** Analysis of endobronchial ultrasonographic features in benign and malignant mediastinal lymph nodes. Chest ACCP 74th Annual Meeting; 134: 13001.
52. **Fujiwara T, Yasufuku K, Nakajima T, et al. (2010).** The utility of sonographic features during EBUS-TBNA for lymph node staging in patients with lung cancer - A standard EBUS image classification system. Chest; 10.1378/chest.09-200610.1378/chest.09-2006.
53. **Steinfort DP, Johnson DF, Irving LB, et al. (2010).** Incidence of bacteraemia following endobronchial ultrasound-guided transbronchial needle aspiration. Eur Respir J; 36: 28-32.
54. **Gupta R, Park H, Kim H, et al. (2010).** Endobronchial inflammatory polyp as a rare complication of endobronchial ultrasound-transbronchial needle aspiration. Interactive Cardiovascular and Thoracic Surgery; 11: 340-341.
55. **Hass AR (2009).** Infectious complications from full extension endobronchial ultrasound transbronchial needle aspiration. Eur Respir J; 33: 935-167.
56. **Steinfort DP, Johnson DF, Irving LB, et al. (2009).** Infective complications from endobronchial ultrasound-transbronchial needle aspiration. Eur Respir J; 34: 524-525.
57. **Moffatt-Bruce SD and** Ross **P (2010). Mediastinal abscess** after endobronchial ultrasound with transbronchial needle aspiration: a case report. J Cardiothoracic Surgery; 5: 33.