Review

Endobronchial Ultrasound

Daniela Gompelmann*, Ralf Eberhardt, Felix JF Herth

Thoraxklinik at University of Heidelberg, Germany

Abstract:
Endobronchial ultrasound (EBUS) has emerged as a routinely performed procedure in diagnostic bronchoscopy. Extending the view beyond the airway wall, EBUS provides evaluation of tumor involvement of tracheobronchial wall and mediastinum and plays an essential role as a guidance technique for peripheral pulmonary diseases. The latest development is the EBUS-transbronchial needle aspiration (TBNA) scope that allows performing real-time EBUS-TBNA of enlargerd hilar and mediastinal lymph nodes.

Keywords:
endobronchial ultrasound; bronchoscopy; diagnosis

INTRODUCTION

Today, endobronchial ultrasound (EBUS) has emerged as a routinely performed procedure in diagnostic bronchoscopy. First, endosonography was used in the field of gastrointestinal endoscopy. Particularly for staging tumors of the esophagus and cardia,[1] endosonography was performed with great success. Several studies have showed that endoscopic ultrasonography is superior to radiological imaging procedures in staging of patients with gastrointestinal carcinoma.[1,2] To imitate these results, endosonography within the airways was developed in the 1990s.

Providing the visualization of the tracheobronchial wall and parabronchial structures, EBUS can be used for diagnosis of benign diseases, but also for malignant diseases in particular. In generally, different EBUS probes and techniques can be distinguished: (1) 20 MHz mechanical radial ultrasound probes that are equipped with a dedicated balloon provide a view of the multilayer structure of the tracheobronchial wall and adjacent structures. These probes can be used for evaluation of tumor involvement of tracheobronchial or mediastinal tumor infiltration as well as for detection of enlarged hilar and mediastinal lymph nodes. (2) 20 MHz ultra-miniature radial ultrasound probes with a narrow insertion tube diameter present a tool in diagnosis of peripheral pulmonary lesions by guiding transbronchial lung biopsies. (3) The EBUS-scope is a linear ultrasonic bronchoscope with a 5-12 MHz convex transducer at the tip that provides a real-time transbronchial needle aspiration under simultaneous visualization of hilar and mediastinal lymphadenopathy.

*To whom correspondence should be addressed.
E-mail: daniela.gompelmann@thoraxklinik-heidelberg.de
Received: 2012-03-10; Accepted: 2012-05-02
doi: 10.7178/eus.02.003

EVALUATION OF TUMOR INVOLVEMENT OF TRACHEOBRONCHIAL WALL AND MEDIASTINUM

Endosonograhpy in the central airways by radial ultrasound probes provides the view beyond the lumen of airways and thus allows detecting parabronchial pathological processes in the mediastinum but also allows evaluating the tracheobronchial wall itself.

To achieve the contact to the central tracheobronchial wall, 20 MHz mechanical radial ultrasound probes, that can be advanced through the working channel of a standard flexible bronchoscope, are equipped with a balloon that can be filled completely with water. Thus a 360° view of the tracheobronchial wall and adjacent structures is provided. In 1990 and 1992, Hürter and his co-workers reported the results of the first use of endobronchial sonography.[3,4] They described a high echogenic and trilaminated tracheobronchial wall, the echo-rich and patchy lung parenchyma as well as the echo-poor solid mass of tumors. By development of probes with higher frequencies, it could be shown, that the normal central airways have a seven layer sonographic structure including the mucosa, submucosa, endochondrium, cartilage, perichondrium, connective tissue and adventitia. The destruction of this seven-layer structure suggests an inflammatory or malignant infiltration.[5]

Therefore, endobronchial ultrasound can be used to characterize suspicious mucosal lesions, to determine the

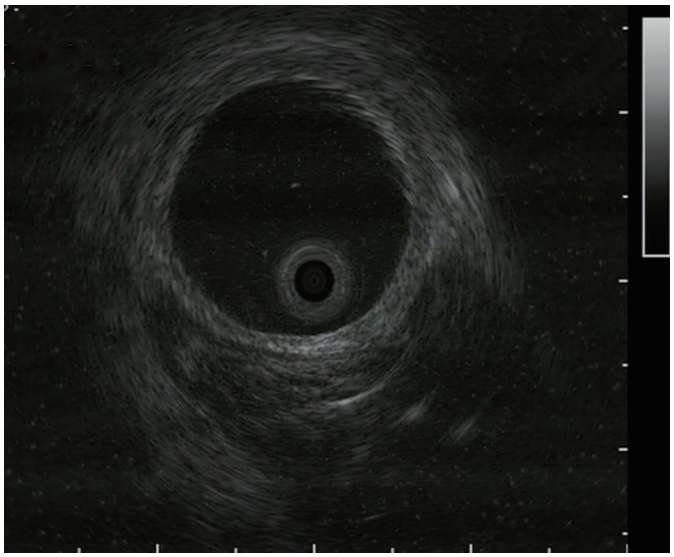

Figure 1. Normal tracheal wall with a clear border to the hypoechoic esophagus.

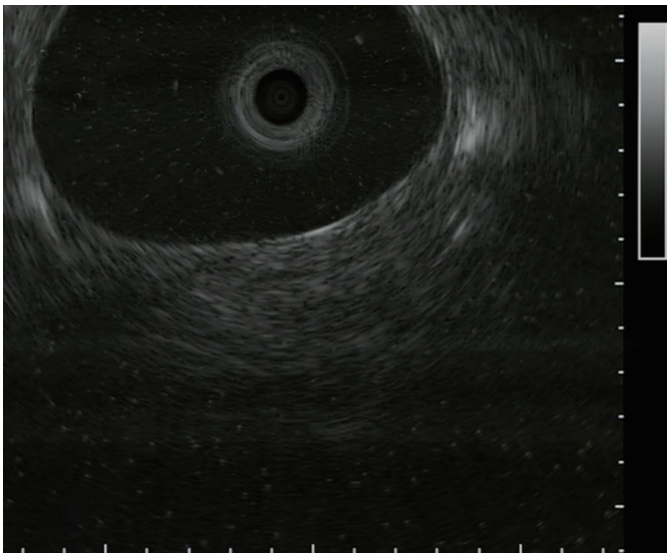

Figure 2. Infiltration of the tracheal wall by esophageal cancer. The normal structure of the airway wall is destroyed.

extension of early lung cancer and to assess the involvement of tracheobronchial wall or mediastinum in case of advanced malignant tumors that presents a critical factor regarding to therapeutic decision.

Nowadays, different bronchoscopic techniques, e.g. autofluorescence imaging (AFI) are provided to identify preneoplastic mucosal lesions and improve detection of early lung cancer. However, this diagnostic modality has a high sensitivity but the specificity of AFI with 60% leads to a high rate of false-positive results.[6] Therefore, EBUS can be used for further characterization of these AFI-positive mucosal lesions. In a study published in 2003, 74 patients with suspicious lesions on autofluorescence bronchoscopy, underwent EBUS for more accurate classification of the suspicious lesions.[7] In case of destruction of the multilayer structure of bronchial wall, thickening of the wall or parabronchial infiltration in the ultrasound image, the lesion was considered to be malignant. Malignancy was correctly diagnosed by AFI in 69%. In combination with EBUS, the sensitivity could be improved up to 97%.

Furthermore, EBUS does not only provide accurate classification of mucosal lesions, but also contributes to therapy decision. In case of localized tumor under 1 cm in diameter and without infiltration of the deeper layers of bronchial wall or lymph node enlargement evaluated by EBUS, endoscopic treatment like photodynamic therapy can be considered as curative therapy strategy in patients who cannot undergo surgery.[8]

EBUS has also a significance in the evaluation of involvement of tracheobronchial wall and mediastinal structures in case of advanced infiltrative cancers (Fig. 1, 2). One trial published by Herth *et al.* in 2003 covering 105 patients with central thoracic malignancies confirmed that EBUS is superior to chest computed tomography (CT) in evaluating airway involvement by central intrathoracic tumors.[9] All patients underwent CT followed by EBUS evaluation and subsequent surgical procedure. The histologic findings after surgery revealed an accuracy of 94% for EBUS and of 51% for CT.

In summary, EBUS in central airways presents a useful diagnostic method for characterization of suspicious mucosal lesions and for evaluation of infiltration of tracheobronchial wall and mediastinal structures by malignant tumors, thus determining the local tumor extension that is fundamental for therapy planning.

DIAGNOSIS OF PERIPHERAL PULMONARY LESIONS

Diagnosis of peripheral pulmonary lesions still remains a dilemma in the daily routine of chest physicians. Pretest probability of malignancy and imaging tests are useful to characterize and differentiate between benign and malignant lesions; however histology is still required for definitive diagnosis. Ultra-miniature radial ultrasound probes provide a guidance system for approaching peripheral pulmonary lesions, thus increasing the diagnostic yield. These probes with a narrow insertion tube diameter can be introduced through a 2.0-mm working channel of a conventional flexible bronchoscope and advanced into the airway where the lesions are suspected. If the probe is inserted into the bronchi surrounded by peripheral lesions, a solid mass image appearing darker and more homogeneous (Fig. 3) replaces the typical snowstorm-like whitish ultrasound image that results from air-filled lung tissue. For marking the localization of the ultrasound probe, fluoroscopy or a guide sheath can be used. When using the latter method, the ultrasound probe is inserted into a guide sheath acting as an extended

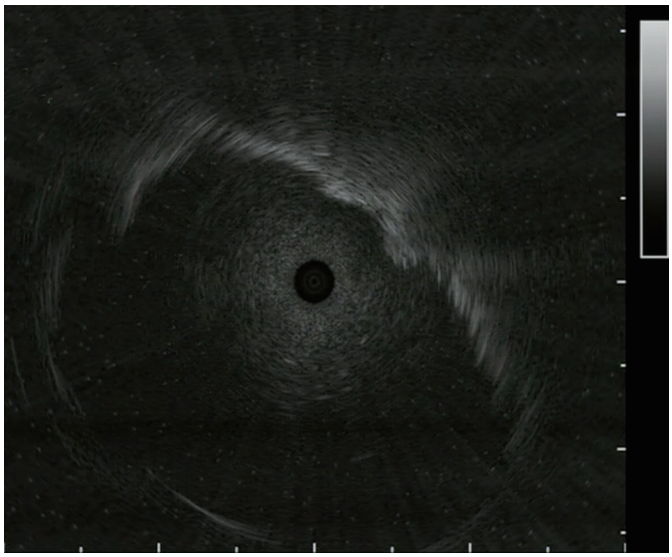

Figure 3. Ultrasound image shows the solid mass of a peripheral pulmonary lesion.

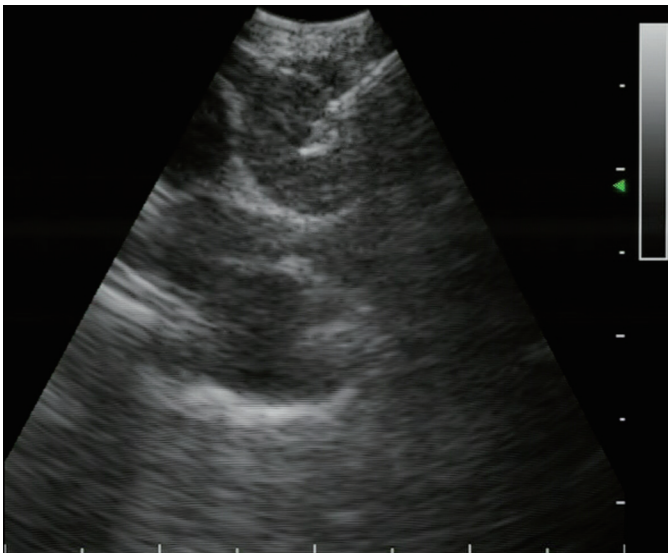

Figure 4. Endobronchial ultrasound-transbronchial needle aspiration. Needle is inserted within the lesion under simultaneous ultrasound control.

working channel prior to the procedure. After identifying the peripheral lesions, the probe is removed, whereas the guide sheath is left in place. Afterwards, transbronchial biopsy (TBB) can be performed.

The first EBUS-guided TBB was reported by Herth *et al.* in 2002.[10] A total of 50 patients with peripheral lesions underwent TBBs sequentially under fluoroscopic guidance and EBUS guidance. In 76% diagnostic material could be obtained by TBB under fluoroscopic guidance, whereas in 80% diagnosis could be established by EBUS-guided TBB. Although there was no significant difference in the diagnostic yield of these two methods, there was a trend for EBUS-guided TBB to be better than fluoroscopy-guided TBB for lesions < 3 cm in diameter. Since this publication, a lot of studies were performed evaluating diagnostic sensitivity of EBUS-guided TBB. In a meta-analysis published by Steinfordt *et al.* in 2011, 13 studies covering 1420 patients with peripheral nodules undergoing EBUS-guided TBB were summarized.[11] The results demonstrated a point specificity of 1.00. The point sensitivity of EBUS-guided TBB for pooled data was 0.73. Furthermore, a sub analysis revealed that the diagnostic yield is dependent on the lesion size. For lesions ≤ 20 mm in diameter, a diagnostic yield of 56.3% was observed, and for lesions > 20 mm, the diagnostic yield was 77.7%. However, EBUS-guided TBB is a safe method also for such small peripheral nodules with a higher sensitivity than fluoroscopy-guided TBB. Moreover, 2 out of these 13 studies evaluated the impact of number of biopsies on diagnostic yield and showed an improved yield to a plateau of 5 samples. However, it still remains unclear, if lobar position or the lesion´s pathology influence the diagnostic yield of EBUS-guided TBB. In these studies, different additional guidance techniques like fluoroscopy, guide sheaths or navigation systems were used. No significant influences of these various guidance devices on the sensitivity could be observed.

One recently published prospective, randomized trial also confirmed that there is no significant difference between the diagnostic yield of the EBUS-guided TBB under fluoroscopy using a prototype 3.4-mm thin bronchoscope and the EBUS-guided TBB using a 4.0-mm bronchoscope with a guide sheath.[12] 101 patients with a peripheral lesion of 26 mm in median diameter underwent the thin bronchoscopic method, and in 102 patients with a nodule of 27.5 mm in median diameter, the guide sheath method was performed. A histologic diagnosis was established in 65% using the thin bronchoscopic method and in 62% using the guide sheath method. Thus both methods have a similar diagnostic yield for evaluation of peripheral lesions.

Summarizing, EBUS alone or in combination with other guidance techniques increases the diagnostic yield of peripheral pulmonary lesions and thus decreases the need for surgical procedure or transthoracic needle aspiration.

HILAR AND MEDIASTINAL LYMPH NODE SAMPLING

There are many reasons for hilar and mediastinal lymph node enlargements including benign diseases like reactive lymphadenopathy, tuberculosis or sarcoidosis as well as malignant diseases like metastases of various primary cancer, lymphoma or thymoma. The most frequent indication for sampling hilar or mediastinal lymph nodes however is the assessment of hilar-mediastinal lymph node involvement in lung cancer. Lymph node involvement plays an important role regarding to survival of lung cancer patients. The 5-year survival rate for bronchogenic carcinoma with lymph

node metastases of 16% is very low compared to a 5-year survival rate of 49% in lung cancer without lymph node involvement.[8] Therefore, an accurate staging is crucial for treatment planning, thus determining the prognosis.

The first lymph node sampling through the main carina using a rigid bronchoscope was by Schiepatti, an Argentinian physician, in 1949.[13,14] In the following years, the technique of sampling paratracheal lymph nodes[15] was described and after the introduction of flexible needles, the technique was also performed by using a flexible bronchoscope. The first description of lung cancer staging by transbronchial needle aspiration was by Wang in 1983.[16] In the 1990s, mechanical ultrasound probes, that can be used within the central airways, were introduced providing to see beyond the wall and to evaluate parabronchial structures and thus enlarged hilar and mediastinal lymph nodes. After localization of the enlarged lymph nodes, conventional transbronchial needle aspiration (TBNA) could be performed. The latest development however is the EBUS-TBNA scope that provides to perform transbronchial needle aspirations under simultaneous ultrasound control. The EBUS-TBNA scope is a special ultrasound puncture bronchoscope. With a 5-12 MHz curvilinear transducer at its distal end, ultrasound images can be obtained by contacting the probe with the airway wall and thus provide to see beyond the bronchial wall.[13] Hence, lymph nodes or mediastinal solid tumors can be detected. With a color Doppler capability, it also allows to confirm blood vessels. For sampling the lymph nodes, a 21- or 22-G needle containing an inner stylet and surrounded by a flexible sheath is inserted through the 2.2-mm working channel and is advanced into the suspicious enlarged lymph nodes or masses for sampling under direct EBUS guidance. Afterwards, the stylet is removed and suction is applied at the proximal end of the needle. Then, the needle is passed in and out of the lymph nodes in a smooth motion (Fig. 4). After releasing suction, the needle can be withdrawn and the smears can be prepared. Lymph nodes in position 2, 4, 7, 10 and 11 can be assessed by TBNA. The complication rate of EBUS-TBNA, including infectious complications like lung abscess, mediastinitis[17] and pericarditis[18] as well as pneumothorax[19] is very low.

The first publications related to EBUS-TBNA were by Krasnik *et al.* in 2003[20] and by Yasufuku *et al.* in 2004[21]. Since then, several studies regarding to mediastinal staging of lung cancer by EBUS-TBNA were published and summarized in a different meta-analyses.[19,22] The meta-analysis published by Gu *et al.* in 2009 covering 11 studies with 1299 lung cancer patients showed that EBUS-TBNA had a pooled sensitivity of 0.93 and a pooled specificity of 1.00[19]. In 8 out of these 11 studies, the patients were selected on the basis on CT or positron emission tomography (PET)-CT positive results. In this subgroup a higher sensitivity with 0.94 could be observed. This meta-analysis also confirmed the safety of the EBUS-TBNA procedure. Only 1 pneumothorax in 1 out of the 1299 patients occurred and therefore the general complication rate was 0.07%. Another meta-analysis by Adams *et al.* in 2009 assessing 10 studies on accuracy of EBUS-TBNA revealed a sensitivity of 0.88[22]. Furthermore several trials comparing EBUS-TBNA to other methods of lymph node staging showed that the EBUS-TBNA has the highest value. In one prospective study 102 patients with proven or suspected lung cancer underwent CT, PET followed by EBUS-TBNA prior to surgery. The sensitivity and accuracy of EBUS-TBNA in the prediction of lymph node involvement with 92.3% and 98.0% was superior to those of CT with 76.9% and 60.8%, and PET with 80.0% and 72.5%.[23] Another prospective study compared the EBUS-TBNA to mediastinoscopy in 153 patients with proven or suspected non-small cell lung cancer.[24] The specificity of both, EBUS-TBNA and mediastinoscopy, were 100%. The sensitivity and accuracy for mediastinal lymph node staging for EBUS-TBNA were 81% and 93% compared to those of mediastinoscopy with 79% and 93%. Thus, there was no significant difference between these two diagnostic tools. Therefore, EBUS-TBNA is nowadays the first choice to evaluate the mediastinum.

However, one limitation of EBUS-TBNA is that not all mediastinal lymph nodes can be assessed. The lymph nodes in position 5, 6, 8 and 9 are not accessible by EBUS-TBNA. Hence, to achieve a complete mediastinal staging, two approaches, EBUS-TBNA and esophageal fine needle aspiration (EUS-FNA), must be combined.[25] Thereby, EBUS-TBNA and EUS-FNA can be performed with only one linear endobronchial ultrasound scope in one setting.[26, 27]

EBUS-TBNA does not only present an important diagnostic technique for mediastinal lymph node staging of lung cancer, but is also a useful diagnostic method in benign diseases such as sarcoidosis. A prospective study including 65 patients with hilar and mediastinal lymphadenopathy suspected for sarcoidosis confirmed that EBUS-TBNA is a safe technique for diagnosis of this benign granulomatous disease. The diagnostic yield of EBUS-TBNA was 91.8%.[28] Furthermore, one recently published trial showed that in case of sarcoidosis stage I and II EBUS-TBNA is superior to transbronchial lung biopsy of lung parenchyma that presented so far the standard diagnostic technique.[29]

In all these studies, EBUS-TBNA was performed by using a dedicated 21- or 22-G needle through which suction is applied. One recently published prospective study compared this EBUS-TBNA procedure to an EBUS-guided transbronchial needle capillary sampling (EBUS-TBNCS) without suction for assessing mediastinal lymphadenopathy due to benign or malignant diseases.[30] No differences in diagnosis or quality between samples obtained using EBUS-TBNA and samples obtained using EBUS-TBNCS were observed.

In the last years, a good quality of specimens increases in importance, because immunohistochemistry as well as mutational analysis is playing a more essential role in treatment of lung cancer. One study that included 156 patients with non-small-cell lung cancer undergoing EBUS-TBNA confirmed that epidermal growth factor receptor

(EGFR) mutations, k-ras mutations and p53 mutations can be analyzed in EBUS-TBNA samples, thus influencing therapeutic regimen and patients' outcome.[31] However, the literature related to the utility of FNA in lymphoproliferative disorders remains controversial.[32,33] One recently retrospective study confirmed that EBUS-TBNA combined with rapid-on-site-evaluation (ROSE) provides sufficient samples for diagnosis and classification of malignant lymphoma in patients with mediastinal lymphadenopathy.[33] Thereby, an appropriate smear with an adequate amount of cells seems to be a crucial prerequisite for diagnosing and classification.[33,34] For further improvement of the amount and thus the quality of the samples, the transbronchial needle forceps (transbronchial needle biopsy, TBNB) was developed, to increase the quantity of the obtained material by EBUS-TBNA that provides comprehensive histological examination, immunohistochemistry and mutational analysis. These needle forceps, that combine the feature of a needle as well as of a forceps and thus provide larger tissue samples, can be inserted through the working channel of an EBUS-TBNA scope. A pilot study published in 2011 evaluated the safety and efficacy of EBUS-TBNB to obtain tissue for the histological diagnosis of 50 patients with enlarged or PET-positive mediastinal lymph nodes.[35] In 42 out of the 50 patients (86%) a malignant or benign histological diagnosis could be established. The sensitivity, specificity and accuracy for EBUS-TBNB was 88%, 100% and 17% respectively.

In summary, EBUS provides a direct real-time EBUS-guided sampling of hilar and mediastinal lymph nodes and thus presents an essential diagnostic tool in lymphadenopathy due to malignant and benign diseases.

REFERENCES

1. Ziegler K, Sanft C, Semsch B, *et al*. Endosonography is superior to computed tomography in staging tumors of the esophagus and cardia. *Gastroenterol Suppl* 1988; A517.
2. Ziegler K, Sanft C, Zimmer T, *et al*. Comparison of computed tomography, endosonography, and intraoperative assessment in TN staging of gastric carcinoma. *Gut* 1993;34:604–10.
3. Hürter T, Hanrath P. Endobronchial sonography in the diagnosis of pulmonary and mediastinal tumors. *Dtsch Med Wochenschr* 1990; 115: 1899-905.
4. Hürter T, Hanrath P. Endobronchialsonography: feasibility and preliminary results. *Thorax* 1992; 47: 565-7.
5. Becker HD, Herth F. Endobronchial Ultrasound of the Ariways and the Mediastinum. In: Bolliger CT, Mathur PN (eds): Interventional Bronchoscopy. *Prog Respir Res* 2000; 30: 80-93.
6. Kennedy TC, McWilliams A, Edell E, *et al*. Bronchial intraepithelial neoplasia/early central airways lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; 132(3Suppl): 221S-233S.
7. Herth FJF, Becker HD, LoCicero J, *et al*. Endobronchial Ultrasound Improves Classification of Suspiscious Lesions detected by Autofluorescence bronchoscopy. *J Bronchol* 2003; 4: 249-52.
8. Goeckenjan G, Sitter H, Thomas M, *et al*. Prevention, diagnosis, therapy and follow-up of lung cancer. *Pneumologie* 2010; 64(Suppl 2): e1-164.
9 Herth F, Ernst A, Schulz M, *et al*. Endobronchial ultrasound reliably differentiates between airway infiltration and compression by tumor. *Chest* 2003; 123: 458-62.
10. Herth FJF, Becker HD. Endobronchial ultrasound-guided transbronchial lung biopsy in solitary pulmonary nodules and peripheral lesions. *Eur Respir J* 2002; 20: 972-4.
11. Steinfort DP, Khor YH, Manser RL, *et al*. Radial probe endobronchiale ultrasound for the diagnosis of peripheral lung cancer: systematic review and meta-analysis. *Eur Respir J* 2011; 37: 902-10.
12. Oki M, Saka H, Kitagawa C, *et al*. Randomized Study of Endobronchial Ultrasound-Guided Transbronchial Biopsy: Thin Bronchoscopic Method versus Gudie Sheath Method. *J Thorac Oncol* 2012; 7: 535-41.
13. FJF Herth. Transbronchial needle aspiration and endobronchial ultrasound. In: Strausz J, Bolliger CT. Interventional Pulmonology. *Eur Respir Monogr* 2010; 48: 45–8.
14. Schiepatti E. La puncionmediastinal a travesdeIespolontraqueal. *Rev As Med Argent* 1949; 663: 497-499.
15. Wang KP, Terry PB, Marsh B. Bronchoscopic needle aspiration biopsy of paratracheal tumors. *Am Rev Respi Dis* 1978; 118: 17-21.
16. Wang KP, Terry PB. Transbronchial needle aspiration in the diagnosis and staging of bronchogenic carcinoma. Am Rev Resir Dis 1983; 127: 382-5.
17. Huang CT. A rare constellation of empyema, lung abscess and mediastinal abscess as a complication of endobronchial ultrasound-guided transbronchial needle aspiration. *Eur J Cardiothorac Surg* 2011; 40: 264-5.
18. Haas AR. Infectious complications from full extension endobronchial ultrasound transbronchial needle aspiration. *Eur Respir J* 2009 ; 935-938.
19. Gu P, Zhao YZ, Jiang LY, *et al*. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. *Eur J Cancer* 2009; 45: 1389–96.
20. Krasnik M, Vilmann P, Larssen SS, *et al*. Preliminary experience with a new method of endoscopic transbronchial real time ultrasound guided biopsy for diagnosis of medastinal and hilar lesions. *Thorax* 2003; 58: 1083-6.
21. Yasufuku K, Chhajed PN, Skine Y, *et al*. Endobronchial ultrasound using a new convex probe: a preliminary study on surgically resected specimens. *Oncol Rep* 2004; 11: 293-6.
22. Adams K, Shah PL, Edmonds L, *et al*. Test performance of endobronchialultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: systematic review and meta-analysis. *Thorax* 2009; 64: 757–62.
23. Yasufuku K, Nakajima T, Motoori K, *et al*. Comparison of endobronchialultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. *Chest* 2006; 130: 710–8.
24. Yasufuku K, Pierre A, Darling G, *et al*. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. *J Thorac Cardiovasc Surg* 2011; 142: 1393-400.
25. Vilmann P, Krasnik M, Larsen SS, *et al*. Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. *Endoscopy* 2005; 37: 833–9.
26. Herth FJ, Krasnik M, Kahn N, *et al*. Combined endoscopic-endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes through a single bronchoscope in 150 patients with suspected lung cancer. *Chest* 2010; 138: 790-794.
27. Hangwbo B, Lee GK, Lee HS, *et al*. Transbronchial and transesophageal fine-needle aspiration using an ultrasound bronchoscope in mediastinal staging of potentially operable lung cancer. *Chest* 2010; 138: 795-802.
28. Wong M, Yasufuku K, Nakajima T, *et al*. Endobronchial ultrasound: new insight for the diagnosis of sarocidosis. *Eur*

Respir J 2007; 29: 1182-6.
29. Oki M, Saka H, Kitagawa C, *et al*. Prospective study of endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes versus transbronchial lung biopsy of lung tissue for diagnosis of sarcoidosis. *J Thorac Cardiovasc Surg* 2012; Epub ahead of print.
30. Casal RF, Staerkel GA, Ost D, *et al*. Randomized Clinical Trial of Endobronchial Ultrasound Needle Biopsy With and Without Aspiration. *Chest* 2011; Epub ahead of print.
31. Nakajima T. Multigene Mutation Analysis of Metastatic Lymph Nodes in Non-small Cell Lung Cancer Diagnosed by Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration. *Chest* 2011; 140: 1319-24.
32. Hehn ST, Grogan TM, Miller TP. Utility of fine-needle-aspiration as a diagnostic technique in lymphoma. *J Clin Oncol* 2004; 22; 3046-52.
33. Marshall CB, Jacob B, Patel S, *et al*. The utility of endobronchial ultrasound-guided transbronchial needle aspiration biopsy in the diagnosis of mediastinal lymphoproliferative disordes. *Cancer Cytopathol* 2011; 119:118-26.
34. Young NA, Moriarty AT, Haja JC, *et al*. Fine-needle aspiration of lymphoprolifertaive disorders – interpretations based on morphologic criteria alone: results from the College of America PathologisctsInterlaboratory Comparison Program in Nongynecologic Cytopathology. *Arch Pathol Lab Med* 2006; 130: 1766-71.
35. Herth F, Schuler H, Gompelmann D, *et al*. EBUS-guided lymph node biopsy (EBUS-TBNB) with a transbronchial needle forceps (TBNF) - a pilot study. *Eur Respir J* 2011; 39: 373-377.