10TH ANNIVERSARY OF SCIENTIFIC STUDY ON EBUS-TBNA — A REVIEW
Looking beyond the bronchial wall.
The world’s first curved linear array ultrasonic bronchoscope was introduced to the market by Olympus in 2003. The development of the endoscope had started more than five years earlier based on a request from the well-known Danish thoracic surgeon Mark Krasnik to miniaturise existing EUS-FNA technology to be applied for diagnosis from within the bronchial system. Krasnik’s appeal was born out of the necessity to improve the results of mediastinal staging, which was not possible with traditional mediastinoscopy.

The success story of EBUS-TBNA starts in 2003 with a publication in the journal Thorax by Mark Krasnik and Peter Vilmann from Gentofte University Hospital, Denmark. This article gave the first description of the principle of EBUS-TBNA. In the same journal, in 2006, the Gentofte group, together with a group from the Thoraxklinik in Heidelberg and Harvard Medical School’s Beth Israel Deaconess MC, chronicled their study on 502 patients that showed that EBUS-TBNA resulted in 93% diagnostic yield, a sensitivity of 94%, specificity of 100% and accuracy of 94%, with PPV at 100% and NPV at 11%. A further interesting outcome of the study was that no significant difference between ultrasound diagnosis under local and general anaesthesia was identified.

Also in 2006, an international EBUS-TBNA focus group was formed by Felix J. F. Herth (Heidelberg), Mark Krasnik (Copenhagen), Kazuhiro Yasufuku (Chiba), Robert Rintoul (Cambridge) and Armin Ernst (Boston). This coalition published a description of how to do an EBUS-TBNA in the Journal of Bronchology thus offering a detailed description of local lymph node positions and orientation within the mediastinum. It was the first comprehensive reference tool for the growing number of EBUS-TBNA users. Besides being confirmed in larger series, EBUS-TBNA has been studied and compared to existing modalities like EUS-FNA (Vilmann et al., Endoscopy 2005 - 93 patients / Herth et al., American Journal of Respiratory and Critical Care Medicine 2005 - 160 patients, PET/CT (Yasufuku et al., Chest 2006 - 102 patients), classical TBNA and EUS-FNA (Wallace et al., JAMA 2006 - 138 patients).  

In 2007, the first publication evaluating EBUS-TBNA use outside of mediastinal staging was issued by a Japanese group from Chiba University (Wong and Yasufuku et al., European Respiratory Journal 2007 – 65 patients). EBUS-TBNA was proven to be a safe method allowing a high yield also for the diagnosis of sarcoidosis. In 2008, a different approach was described in a study on the use of the EBUS-TBNA endoscope for EBUS-guided miniforceps biopsy for histologic proof of lymphoma and/or sarcoidosis (Herth et al., Annals of Thoracic Surgery 2008 - 75 patients). With the strong acceptance of EBUS-TBNA as a reliable diagnostic tool for enlarged lymph nodes in patients with non-small cell lung cancer (NSCLC), it soon became clear that lymph nodes below the one centimetre range could also be sampled. This led to a study with 100 patients published in 2006 in the European Respiratory Journal (with joint data from the Thoraxklinik Heidelberg, Gentofte University Hospital and Harvard Medical School’s Beth Israel Deaconess MC) that showed that every sixth patient with no evidence of mediastinal disease on CT was diagnosed positive using EBUS-TBNA. EBUS-TBNA thus shows potential to avoid explorative thoracoscopies. Further studies imply that EBUS-TBNA should be used as a complementary tool to imaging technologies like CT and PET (EBUS-TBNA in the Radiologically and PET-Normal Mediastinum: Herth et al., Chest 2008 - 100 patients). In 2008, Hwangbo et al. showed that in cases with both CT- and PET-negative and -positive scans, EBUS-TBNA is an excellent tool for detecting mediastinal metastasis, thereby confirming that EBUS-TBNA is an effective invasive method following CT and PET scanning.

In a study by Armin Ernst et al. (Journal of Thoracic Oncology 2008 - 66 patients), it was shown that EBUS-TBNA can have a superior yield compared to cervical mediastinoscopy, which leads to the conclusion that mediastinoscopy is not necessarily of additional diagnostic benefit in evaluating negative EBUS-TBNA-staged lymph nodes. However, mediastinoscopy retains an important role, especially in operable patients, for assessing local mediastinal invasion and the exclusion of metastases in non-enlarged lymph nodes. Herth et al. evaluated EBUS-TBNA for re-staging in 124 patients with tissue-proven IIA-N2 disease after induction chemotherapy (Journal of Clinical Oncology 2008) and concluded that EBUS-TBNA is a valuable and practical tool for re-staging with a sensitivity of 76%, specificity of 100%, PPV of 100%, NPV of 20% and diagnostic accuracy of 77%. These results imply that negative results of EBUS-TBNA for re-staging should be confirmed by surgical re-staging.

With the compatibility of EBUS-TBNA and the Aloka Prosound alpha5 ultrasound processor, which was realised in prototypes in 2006, additional Doppler modes became available. Soon it was investigated whether the existing algorithm for flow resistance (resistance index by Pourcelot) allowed conclusions with respect to the dignity of lymph nodes. In 2008, a first reference value for normal lymph nodes was described by Herth et al. (Journal of Thoracic Oncology - 89 patients), and a consecutive study done by the same authors describes changes in flow resistance parameters in malignant lymph nodes.

Yasufuku et al. from Chiba University in Japan have shown strong dedication to evaluating the benefits of EBUS-TBNA samples for immunohistochemical analysis and reported encouraging results with cell cycle-related proteins in chemotherapy patients (Thorax 2008). A year earlier, the same group had published in Chest that epidermal growth factor receptor (EGFR) mutation can be easily detected in metastatic lymph node samples from EBUS-TBNA. Also in 2007, in the same journal, the group reported chemosensitivity-related aberrant methylation profiling in samples obtained by EBUS-TBNA. In short, the group proved that samples gained by EBUS-TBNA allowed genetic evaluations of tumour cells from lymph nodes.

In 2009 Tournoy et al. provided a detailed analysis of endoscopicographic landmarks (where available), describing the anatomic borders of the lymph node stations as defined in the 7th edition of the IASLC’s TNM-staging nomenclature, which is relevant for correctly staging patients with lung cancer.

Building on the strong results of combined EUS-FNA and EBUS-TBNA procedures – a study published by Vilmann et al. in 2005 had already indicated their complementary nature – Annema et al. challenged the pre-dominant surgical staging algorithm by comparing the combined EBUS-TBNA and EUS-FNA with surgical staging and surgical staging alone. The results show that combining endosonographic and surgical staging resulted in greater sensitivity for mediastinal nodal metastases and fewer unnecessary thoracotomies. These results indicated that the combination of both procedures may be able to replace surgical staging as the primary staging method for patients with lung cancer.

Instead of using different scopes for EBUS-TBNA and EUS-FNA, two separate studies published in Chest in 2010 (Hwangbo et al. and Herth et al.) used only one bronchoscope for both procedures, starting via the trachea and continuing via the oesophageal route. They came to the conclusion that EBUS-TBNA and EUS-FNA are complementary methods and showed that both procedures can be performed with a single EBUS echoendoscope in one sitting by one operator. A further study in 2011, “Nonsurgical staging of the mediastinum: EBUS and EUS” conducted by Herth, stated that the combination of both procedures achieves a complete and accurate mediastinal staging. Therefore it can be expected that the implementation of combined EBUS-TBNA and EUS-FNA will reduce the need for surgical staging of lung cancer significantly.

The approach to take endobronchial ultrasound-guided lymph node biopsies with a transbronchial needle forceps (EBUS-TBNF), which was already investigated in smaller studies in 2008, was further studied by Herth et al. in 2011. The study showed that EBUS-TBNF is a safe procedure and provides diagnostic histological specimens of mediastinal lymph nodes.

The summary of scientific studies on EBUS-TBNA provided above clearly shows the procedure’s power in helping to improve mediastinal staging of lung cancer during the past 10 years. The technological development of less invasive staging and sampling devices continues to progress. With a growing number of interventional endoscopists using endosonography, we can expect further exciting developments in clinical practice in the years to come.
REFERENCES


Background: Transbronchial needle aspiration (TBA) is an established method for sampling mediastinal lymph nodes to aid in diagnosing lymphadenopathy and in staging lung cancers. Real-time endobronchial ultrasound (EBUS) guidance is a new method of TBA that may increase the ability to sample these nodes and hence to determine a diagnosis. A descriptive study was conducted to test this new method.

Methods: Consecutive patients referred for TBA of mediastinal lymph nodes were included in the trial. When a node was detected, a puncture was performed under real-time ultrasound control. The primary end point was the number of successful biopsy specimens. Diagnostic results from the biopsies were compared with operative findings. Lymph node stations were classified according to the recently adopted American Thoracic Society scheme.

Results: From 502 patients (316 men) of mean age 59 years (range 24–82), 572 lymph nodes were punctured and 535 (94%) resulted in a diagnosis. Biopsy specimens were taken from lymph nodes in region 2L (40 nodes), 2R (31 nodes), 3L (35 nodes), 4R (86 nodes), 4L (77 nodes), 7 (127 nodes), 10R (38 nodes), 10L (43 nodes), 11R (40 nodes) and 11L (33 nodes). The mean (SD) diameter of the nodes was 1.6 (0.36) cm and the range was 0.8–3.2 cm (SD range 0.8–4.3). Sensitivity was 94%, specificity 100%, and the positive predictive value was 100% calculated per patient. No complications occurred.

Conclusion: EBUS-TBNA is a promising new method for sampling mediastinal lymph nodes. It appears to permit more and smaller nodes to be sampled than conventional TBA, and it is safe.
Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration
Herth FFJ, Krasnik M, Yasufuku K, Rintoul R, Ernst A
J Bronchol 2006; 13: 84-91

The increasing use of minimally invasive techniques has renewed interest in transbronchial needle aspiration (TBNA) for obtaining biopsies of mediastinal lymph nodes. However, conventional TBNA relies on “blind” needle puncture guided only by static computed tomography scans.

The success of the technique is highly operator-dependent; reported sensitivities vary between 15% and 78%. In addition, many pulmonologists are so discouraged by the results of their initial experience that only 20% to 30% use TBNA. Here, we describe our technique for performing endobronchial ultrasound-TBNA using a curved linear array ultrasonic bronchoscope that allows aspiration biopsy under real-time ultrasound imaging.

Transbronchial Needle Aspiration (EBUS-TBNA) in the Evaluation of Mediastinal Lesions
Vilmann P, Krasnik M, Larsen SS, Jacobsen GK, Clementsen P
Endoscopy 2005; 37: 833-839

Background and Study Aims: It would be desirable to develop minimally invasive methods of tissue diagnosis from lymph nodes as well as solid lesions in the mediastinum. The aim of the present study was to test the combined method of transbronchial endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the evaluation of mediastinal lesions.

Patients and Methods: EUS-FNA and EBUS-TBNA were compared in 33 patients, for the staging of lung cancer in patients with an established diagnosis of non-small-cell lung cancer (n = 20) or for diagnosis of a suspicious mediastinal lesion in patients with suspected lung cancer (n = 13). EBUS-TBNA and EUS-FNA were unsuccessful in one patient each. The diagnoses were verified in 28 of the remaining 31 patients either at thoracotomy (n = 9) or during the clinical follow-up (n = 19).

Results: A total of 119 lesions were sampled by EUS-FNA (n = 59) and EBUS-TBNA (n = 60). EUS-FNA and EBUS-TBNA demonstrated cancer in 26 and 28 lesions, respectively, and benign cytology in 30 and 28 lesions, respectively. Suspicious cells were found in three and four lesions by EUS-FNA and EBUS-TBNA, respectively. When the 60 EBUS-TBNA samples were compared with the 59 EUS-FNA samples, 11 additional cancer diagnoses and three samples with suspicious cells were obtained by EBUS-TBNA that had not been obtained by EUS-FNA. Conversely, EUS-FNA diagnosed 12 additional cancer diagnoses, one suspicious and one specific benign diagnosis (sarcoidosis) in addition to EBUS-TBNA. With a combined approach (EUS-FNA + EBUS-TBNA) in 28 of the 31 patients in whom a final diagnosis was obtained in the evaluation of mediastinal cancer, 20 patients were found to have mediastinal involvement, whereas no mediastinal metastases were found in eight patients. The accuracy of EUS-FNA and EBUS-TBNA, in combination, for the diagnosis of mediastinal cancer was 100% (95% CI, 83 - 100%).

Conclusions: EUS-FNA and EBUS-TBNA appear to be complementary methods. A combined approach with both EUS-FNA and EBUS-TBNA may be able to replace more invasive methods for evaluating lung cancer patients with suspected hilar or mediastinal metastases, as well as for evaluating unclear mediastinal or hilar lesions.

Transbronchial versus Transesophageal Ultrasound-Guided Aspiration of Enlarged Mediastinal Lymph Nodes
Herth FFJ, Lunn W, Eberhardt R, Becker HD, Ernst A
Am J Respir Crit Care Med 2005; 171: 1164-1167

Rationale: Transbronchial and transbronchial, ultrasound-guided, fine-needle aspiration of enlarged mediastinal lymph nodes have become popular, but have never been compared directly.

Objectives: To compare the relative diagnostic yield and ability of the transesophageal and transbronchial approaches to reach abnormal mediastinal lymph nodes.

Methods: A total of 160 patients with enlarged lymph nodes in one of eight mediastinal lymph node stations underwent transbronchial and transesophageal biopsies in a crossover design. Each of the eight stations was allocated 20 patients. Two needle punctures were done with each approach.

Measurements: Percentage of successful biopsies, percentage of patients diagnosed, and biopsy time were measured from when the lymph node was identified with ultrasound.

Main Results: Among the 106 men and 54 women (mean age 63.2 years), transbronchial aspiration was successful in 85%, and transesophageal aspiration was successful in 78% (p = 0.2). For each station, the number of positive samples for the transbronchial/transesophageal approach was: 2R: 19/13; 2L: 16/18; 3: 17/15; 4R: 19/12; 4L: 17/20; 7: 18/20; 10R: 18/9; 10L: 17/18. Combining both approaches produced successful biopsies in 97% and diagnoses in 94% of patients. Mean biopsy times were 3.2 minutes for the transbronchial approach and 4.1 minutes for the transesophageal approach. The transbronchial approach was superior in nodes 2R, 4R, and 10R. No complications were encountered.

Conclusions: In experienced hands, enlarged mediastinal lymph nodes may be aspirated with either the transbronchial or transesophageal approach. These nonsurgical approaches have similar diagnostic yields, although the transbronchial approach is superior for right-sided lymph nodes. Combining both approaches provides results similar those of mediastinoscopy.

Comparison of Endobronchial Ultrasound, Positron Emission Tomography, and CT for Lymph Node Staging of Lung Cancer
Yasufuku K, Nakajima T, Motoori K, Sekine Y, Shibuya K, Hiroshima K, Fujisawa T
Chest 2006; 130: 710-718

Study objectives: To perform a prospective comparison of direct real-time endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA), positron emission tomography (PET), and thoracic CT for detection of mediastinal and hilar lymph node metastasis in patients with lung cancer considered for surgical resection.

Design: Prospective patient enrollment.

Setting: University teaching hospital.

Patients: One hundred two potentially operable patients with proven (n = 96) or radiologically suspected (n = 6) lung cancer were included in the study.

Interventions: CT, PET, and EBUS-TBNA were performed prior to surgery for the evaluation of mediastinal and hilar lymph node metastasis. The convex probe EBUS, which is integrated with a convex scanning probe on its tip, was used for EBUS-TBNA.

Surgical histology was used as the “gold standard” to confirm lymph node metastasis unless patients were found inoperable for N3 or extensive N2 disease proven by EBUS-TBNA.
Main results: EBUS-TBNA was successfully performed in all 102 patients (mean age, 67.8 years) from 147 mediastinal and 53 hilar lymph nodes. EBUS-TBNA proved malignancy in 37 lymph node stations in 24 patients. CT identified 92 positive lymph nodes, and PET identified 89 positive lymph nodes (4 supracarvular, 63 mediastinal, 22 hilar). The sensitivities of CT, PET, and EBUS-TBNA for the correct diagnosis of mediastinal and hilar lymph node staging were 76.9%, 80.0%, and 92.3%, respectively; specificities were 55.3%, 70.1%, and 100%, and diagnostic accuracies were 60.8%, 72.5%, and 98.0%. EBUS-TBNA was uneventful, and there were no complications.

Conclusion: Compared to CT and PET, EBUS-TBNA has a high sensitivity as well as specificity for mediastinal and hilar lymph node staging in patients with lung cancer. EBUS-TBNA should be considered for evaluation of the mediastinum early in the staging process of lung cancer.

Minimally Invasive Endoscopic Staging of Suspected Lung Cancer


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Abstracts
Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration of Lymph Nodes in Patients with Lung Cancer

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can reliably sample enlarged mediastinal lymph nodes in patients with non-small cell lung cancer (NSCLC). To date, EBUS-TBNA has only been used to sample nodes visible on computed tomography (CT). The aim of the present study was to determine the accuracy of EBUS-TBNA in sampling nodes 1 cm in diameter.

NSCLC patients with CT scans showing no enlarged lymph nodes (no node >1 cm) in the mediastinum underwent EBUS-TBNA. Identifiable lymph nodes at locations 2r, 2l, 4r, 4l, 7, 10r, 10l, 11r and 11l were aspirated. All patients underwent subsequent surgical staging. Diagnoses based on aspiration results were compared with those based on surgical results.

In 100 patients (mean age 58.9 yrs; 68 males), 119 lymph nodes ranging 5–10 mm in size were detected and sampled. Malignancy was detected in 19 patients but missed in one patient. Mean diameter of the punctured lymph nodes was 7.9 mm. The sensitivity of EBUS-TBNA for detecting malignancy was 89%, specificity was 100%, and the negative predictive value was 98.9%. No complications occurred.

In conclusion, EBUS-TBNA can be used to accurately sample and stage patients with clinical stage 1 lung cancer and no evidence of mediastinal involvement on CT and PET. Potentially operable patients with no signs of mediastinal involvement may benefit from presurgical staging with EBUS-TBNA.

Application of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration Following Integrated PET/CT in Mediastinal Staging of Potentially Operable Non-small Cell Lung Cancer

Background: The role of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) following integrated PET/CT scanning in mediastinal staging of non-small cell lung cancer (NSCLC) has not been assessed.

Methods: We prospectively evaluated the diagnostic values of PET/CT scanning and EBUS-TBNA for mediastinal staging in 117 patients with potentially operable NSCLC with accessible mediastinal lymph nodes (diameter range, 5 to 20 mm) by EBUS-TBNA. Subgroup analysis according to histologic type was performed.

Results: Of 30 cases of mediastinal metastasis, 27 were confirmed by EBUS-TBNA and 3 were confirmed by surgery. EBUS-TBNA results confirmed all cases with true-positive PET/CT scan findings and six of nine cases with false-negative PET/CT scan findings. The sensitivity, specificity, positive predictive value, negative predictive value (NPV), and accuracy of EBUS-TBNA in the detection of mediastinal metastasis were 90.0%, 100%, 100%, 96.7%, and 97.4%, respectively. For PET/CT scans, the values were 70.0%, 59.6%, 37.5%, 85.2%, and 62.4%, respectively (p = 0.052; p < 0.001; p < 0.001; p = 0.011; p < 0.001, respectively). In adenocarcinoma (n = 55), EBUS-TBNA detected four of six cases with false-negative PET/CT scan findings, and the NPV was higher for EBUS-TBNA than for PET/CT scans (94.6% vs 77.8%, respectively; p = 0.044). In squamous cell carcinoma (n = 53), the NPV of EBUS-TBNA and PET/CT scans were similarly high (97.9% vs 96.3%, respectively; p = 0.689).

Conclusions: EBUS-TBNA was an effective invasive method following PET/CT scanning in the mediastinal staging of potentially operable NSCLC. In mediastinal PET/CT scan-positive cases, EBUS-TBNA was an excellent tool for detecting mediastinal metastasis. Even in mediastinal PET/CT scan-negative cases, EBUS-TBNA can be useful for confirming mediastinal metastases, especially in adenocarcinoma.
ABSTRACTS

13 Diagnosis of Mediastinal Adenopathy – Real-Time Endobronchial Ultrasound Guided Needle Aspiration versus Mediastinoscopy

Ernst A, Ananthan D, Eberhardt R, Krasnik M, Herth FJF
J Thorac Oncol 2008; 3: 577-582

Background: Real-time endobronchial ultrasound has increased the accuracy of conventional transbronchial needle aspiration biopsy in sampling mediastinal lymph nodes. Nevertheless, direct comparisons with mediastinoscopy are not available to determine the role of endobronchial ultrasound in pathologic staging.

Objectives: To compare the diagnostic yield of endobronchial ultrasound against cervical mediastinoscopy in the diagnosis and staging of radiologically enlarged mediastinal lymph nodes stations accessible by both modalities in patients with suspected non-small-cell lung cancer.

Methods: Prospective, crossover trial with surgical lymph node dissection used as the accepted standard. Biopsy results of paratracheal and subcarinal lymph nodes were compared.

Results: Sixty-six patients with a mean age 60 +/- 10 years were studied. The prevalence of malignancy was 89% (59/66 cases). Endobronchial ultrasound had a higher overall diagnostic yield (91%) compared with mediastinoscopy (78%; p = 0.007) in the per lymph node analysis. There was disagreement in the yield between the two procedures in the subcarinal lymph nodes (24%; p = 0.011). There were no significant differences in the yield at all lymph node stations. The sensitivity, specificity, and negative predictive value of endobronchial ultrasound were 87, 100, and 78%, respectively. The sensitivity, specificity, and negative predictive value of mediastinoscopy were 68, 100, and 59%, respectively. No significant differences were found between endobronchial ultrasound (83%) and mediastinoscopy (82%; p = 0.083) in determining true pathologic N stage (per patient analysis).

Conclusions: In suspected non-small cell lung cancer, endobronchial ultrasound may be preferred in the histologic sampling of paratracheal and subcarinal mediastinal adenopathy because the diagnostic yield can surpass mediastinoscopy.

14 Endobronchial Ultrasound with Transbronchial Needle Aspiration for Restaging the Mediastinum in Lung Cancer

J Clin Oncol 2008; 26: 3346-3350

Purpose: To investigate the sensitivity and accuracy of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for restaging the mediastinum after induction chemotherapy in patients with non–small-cell lung cancer (NSCLC).

Patients and Methods: One hundred twenty-four consecutive patients with tissue-proven stage IIA-N2 disease who were treated with induction chemotherapy and who had undergone mediastinal restaging by EBUS-TBNA were reviewed. On the basis of computed tomography, 58 patients were classified as having stable disease and 66 were judged to have had a partial response. All patients subsequently underwent thoracotomy with attempted curative resection and a lymph node dissection regardless of EBUS-TBNA findings.

Results: Persistent nodal metastases were detected by using EBUS-TBNA in 89 patients (72%). Of the 35 patients in whom no metastases were assessed by EBUS-TBNA, 28 were found to have residual stage IIA-N2 disease at thoracotomy. The majority (91%) of these false-negative results were due to nodal sampling error rather than detection error. Overall sensitivity, specificity, positive predictive value, and diagnostic accuracy of EBUS-TBNA for mediastinal restaging after induction chemotherapy were 76%, 100%, 100%, 20%, and 77%, respectively.

Conclusion: EBUS-TBNA is a sensitive, specific, accurate, and minimally invasive test for mediastinal restaging of patients with NSCLC. However, because of the low negative predictive value, tumor-negative findings should be confirmed by surgical staging before thoracotomy.

15 Resistance Index in Mediastinal Lymph Nodes: A Feasibility Study

Herth FJF, Yasufuku K, Eberhardt R, Hoffmann H, Krasnik M, Ernst A
J Thorac Oncol 2008; 3: 348-350

Objective: The purpose of this study was to determine the range of Doppler ultrasonographic measurements of the resistance index in presumed normal mediastinal lymph node arteries.

Methods: Consecutive patients referred for bronchoscopy for various indications and normal CT findings in the mediastinum were included. The resistance index (RI) in mediastinal lymph node arteries was calculated with Color Doppler ultrasonography. The peak systolic velocity (PSV) and the end-diastolic velocity were measured, which allowed for calculation of the resistance indices in different lymph node stations and in each lymph node artery.

Results: Eighty-nine patients (32 female; 57 male; mean age, 42.7 years) were examined, and of these, 50 patients (24 female, 36 male; mean age, 44.7 years) had measurable RI. PSV and ESV were measured in all visible nodes (n = 196) and an interpretable value of 0.69 as the cut-off point for best discrimination was obtained in 127 nodes (2.5 nodal per patient). The median PSV was 15.6 cm/s (range, 8.9-23.2 cm/s, SD +/- 2.6, 25-75% percentile 13.8-17.5), and the median end-diastolic velocity was 5.8 cm/s (range, 3.6-11.4 cm/s, SD 1.15 cm/s, 25-75% percentile 5.1-8.3). The median RI values for arteries were 0.63 (range, 0.52-0.75, SD 0.04, 25-75% percentile 0.6-0.64) respectively. The Doppler measurements lasted on average 4.3 minutes and no complications were seen.

Conclusion: Color Doppler ultrasonography allows for quantification of velocities like PSV and ESV in mediastinal lymph node arteries, which in turn allow calculation of a resistance index. Knowledge of the resistance index’s normal range (which describes the resistance of the blood flow within the lumen of the lymph node artery) may be a useful adjunct to the ultrasonic assessment of the mediastinum.

16 Resistance Index through EBUS in Enlarged Mediastinal Lymph Nodes Correlates with Malignant Involvement

Herth F, Eberhardt R, Mulay T, Ananthan D, Ernst A
Chest Meeting Abstracts 2007: 132: 466c-466c

Purpose: The vascular resistive index (RI) is measured by Doppler ultrasound and can be correlated with certain disease states. The range of RI in enlarged mediastinal lymph nodes is not known.

Methods: Consecutive patients with enlarged mediastinal LN were examined. Recruitment continued until 100 patients who had RI measurements was achieved. RI measurements were performed using EBUS-TBNA Duplex Doppler ultrasound (Aloka Alpha 5, Aloka, Japan). All patients underwent surgical lymph node sampling to establish the relationship between histology (malignant or non-malignant) and RI.

Results: 152 pts were examined to include 100 in whom we were able to measure RI (54 male, 46 female, mean age 49 years). In 52 patients, we were not able to visualise vessels within the lymph nodes and no RI measurement was possible. The histology revealed malignancy in 70 cases and the RI was significantly higher in those than in patients without malignancy. Using the Youden Index we calculated a RI of 0.69 as the cut-off point for best discrimination (sensitivity 91.4 %, specificity 90 %, p< 0.001). The AUC was 0.965 with an excellent discriminatory power (95 % confidence interval 0.931 to 0.998).
Conclusion: An increased RI appears to be highly correlated with malignant histology in mediastinal lymph nodes.

Clinical Implications: It may be possible to safely avoid further histological sampling when EBUS-TBNA produces a non-malignant biopsy result in lymph nodes with a low RI.

Analysis of Cell Cycle-Related Proteins in Mediastinal Lymph Nodes of Patients with N2-NSCLC Obtained by EBUS-TBNA: Relevance to Chemotherapy Response

Methods: DNA was extracted from paraffin-embedded samples, and the EGFR mutation was confirmed by direct sequencing. Results: Forty-three cases were eligible for analysis and in 11 cases, EGFR mutation (25.6%) was detected; one case was a single point mutation (L858R) of exon 19, nine cases were point mutations (L858R) of exon 21, and one case was a double point mutation (L858R + L861V). All cases with EGFR mutations were confirmed by direct sequencing.

Conclusions: EGFR mutation can easily be detected in metastatic lymph nodes sampled by EBUS-TBNA. EBUS-TBNA allows genetic evaluations of tumor cells within the lymph node and may provide us with indications for EGFR-TKI therapy in the near future.

Assessment of Epidermal Growth Factor Receptor Mutation by Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

Methods: The expression of six cell cycle-related proteins (p16, cyclin D1, p16INK4A, p53, p21Waf1, Ki-67) in mediastinal lymph node specimens that can be used for immunohistochemical analysis, and to stratify patients with molecular-based pN2-NSCLC into chemoresponsive and chemoresistant subgroups who might benefit from tailoring of chemotherapy.

Chemosensitivity-Related Aberrant Methylation Profiling of Non-Small Cell Lung Cancer by Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

Methods: The purpose of this study was to develop and analyze the feasibility of detecting EGFR mutations in samples obtained by EBUS-TBNA. Forty-six patients with primary lung cancer in whom metastatic adenocarcinoma in the hilar and/or mediastinal lymph node was diagnosed by EBUS-TBNA were enrolled into the study. DNA was extracted from paraffin-embedded samples, and the EGFR mutation was analyzed in exons 19 and 21 using a newly developed loop-hybrid mobility shift assay. The results were confirmed by direct sequencing.

Results: Forty-three cases were eligible for analysis and in 11 cases, EGFR mutation (25.6%) was detected; one case was an in-frame deletion (E746-A750del) of exon 19, nine cases were point mutations (L858R) of exon 21, and one case was a double point mutation (L858R + L861V). All cases with EGFR mutations were confirmed by direct sequencing.

Conclusions: EGFR mutation can easily be detected in metastatic lymph nodes sampled by EBUS-TBNA. EBUS-TBNA allows genetic evaluations of tumor cells within the lymph node and may provide us with indications for EGFR-TKI therapy in the near future.

Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is an accurate tool for lymph node staging of non-small cell lung cancer (NSCLC). Most patients with NSCLC require systemic chemotherapy during their treatment, with relatively poor responses. If the response to chemotherapy could be predicted, ideally at the time of the initial bronchoscopic examination, the therapeutic benefit could be maximised while limiting toxicity. A study was therefore undertaken to investigate the feasibility of EBUS-TBNA for obtaining tissue samples from mediastinal lymph nodes that can be used for immunohistochemical analysis, and to stratify patients with molecular-based pN2-NSCLC into chemoresponsive and chemoresistant subgroups who might benefit from tailoring of chemotherapy.

Methods: The expression of six cell cycle-related proteins (p16, cyclin D1, p16INK4A, p53, p21Waf1, Ki-67) in mediastinal lymph node specimens that can be used for immunohistochemical analysis, and to stratify patients with molecular-based pN2-NSCLC into chemoresponsive and chemoresistant subgroups who might benefit from tailoring of chemotherapy.

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Methods: The expression of six cell cycle-related proteins (p16, cyclin D1, p16INK4A, p53, p21Waf1, Ki-67) in mediastinal lymph node specimens that can be used for immunohistochemical analysis, and to stratify patients with molecular-based pN2-NSCLC into chemoresponsive and chemoresistant subgroups who might benefit from tailoring of chemotherapy.

Abstract: Accurate assessment of lymph node involvement is a critical step in patients with non-small cell lung cancer in the absence of distant metastases. The International Association for the Study of Lung Cancer has proposed a new lymph node map, which provides precise anatomic definitions for all intrathoracic lymph nodes. Transosophageal endoscopic ultrasound with fine-needle aspiration and endobronchial ultrasound with transbronchial needle aspiration are two minimally invasive techniques that are increasingly implemented in the staging of non-small cell lung cancer. Therefore, recognition of the proposed anatomic borders by these techniques is very relevant for an accurate clinical staging. We here discuss the reach and limits of endoscopic ultrasound in the precise delineation and approach of the intrathoracic lymph nodes according to the new lymph node classification. In conclusion, recognition of the new metastasis classification for lung cancer is very relevant for an accurate clinical staging. We here discuss the reach and limits of endoscopic ultrasound in the precise delineation and approach of the intrathoracic lymph nodes according to the new lymph node classification. In conclusion, recognition of the new metastasis classification for lung cancer.

Mediastinoscopy vs. endosonography for mediastinal nodal staging of lung cancer: a randomized trial


Context: Mediastinal nodal staging is recommended for patients with resectable non-small cell lung cancer (NSCLC). Surgical staging has limitations, which results in the performance of unnecessary thoracotomies. Current guidelines acknowledge minimally invasive endosonography followed by surgical staging (if no nodal metastases are found by endosonography) as an alternative to immediate surgical staging.

Objective: To compare the 2 recommended lung cancer staging strategies.

Design, setting, and patients: Randomized controlled multicenter trial (Ghent, Leiden, Leuven, Papworth) conducted between February 2007 and April 2009 in 241 patients with resectable (suspected) NSCLC in whom mediastinal staging was indicated based on computed or positron emission tomography.

Intervention: Either surgical staging or endosonography (combined transosophageal and endobronchial ultrasound [EUS-FNA and EBUS-TBNA]) followed by surgical staging in case no nodal metastases were found at endosonography. Thoracotomy with lymph node dissection was performed when there was no evidence of mediastinal tumor spread.

Main outcome measures: The primary outcome was sensitivity for mediastinal nodal (N2/N3) metastases. The reference standard was surgical pathological staging. Secondary outcomes were rates of unnecessary thoracotomy and complications.

Results: Two hundred forty-one patients were randomized, 118 to surgical staging and 123 to endosonography, of whom 65 also underwent surgical staging. Nodal metastases were found in 41 patients (35%; 95% confidence interval [CI], 27%-44%) by surgical staging vs 56 patients (46%; 95% CI, 37%-54%) by endosonography (P = .11) and in 62 patients (50%; 95% CI, 42%-59%) by endosonography followed by surgical staging (P = .02). This corresponded to sensitivities of 79% (41/52; 95% CI, 66%-88%) vs 85% (56/66; 95% CI, 74%-92%) (P = .47) and 94% (62/66; 95% CI, 85%-98%) (P = .02). Thoracotomy was unnecessary in 21 patients (18%; 95% CI, 12%-26%) in the mediastinoscopy group vs 9 (7%; 95% CI, 4%-13%) in the endosonography group (P = .02). The complication rate was similar in both groups.

Conclusions: Among patients with (suspected) NSCLC, 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.

Transbronchial and Transosophageal Fine Needle Aspiration Using an Ultrasound Bronchoscope in Mediastinal Staging of Potentially Operable Lung Cancer


Objective: We performed this study to evaluate the role of transbronchial endoscopic ultrasound with bronchoscope-guided fine-needle aspiration (EUS-B-FNA) following endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the mediastinal staging of lung cancer.

Methods: In this prospective study, we applied transbronchial and transosophageal ultrasonography using an ultrasound bronchoscope on patients with confirmed or strongly suspected potentially operable non-small cell lung cancer. Following EBUS-TBNA, EUS-B-FNA was used for mediastinal nodes that were inaccessible or difficult to access by EBUS-TBNA. The accessibility by EBUS-TBNA and EUS-B-FNA to mediastinal nodal stations having at least one node ≥ 5 mm was also checked.

Results: In 150 patients, we performed EBUS-TBNA and EUS-B-FNA on 299 and 84 mediastinal nodal stations, respectively. Among 143 evaluable patients, EBUS-TBNA diagnosed mediastinal metastasis in 38 patients, EUS-B-FNA identified mediastinal metastasis in three additional patients. Surgery diagnosed mediastinal metastasis in four more patients. The sensitivity, negative predictive value, and diagnostic accuracy of EBUS-TBNA in the detection of mediastinal metastasis were 84.4%, 93.3%, and 95.1%, respectively. These values for the combined approach of EBUS-TBNA and EUS-B-FNA increased to 91.1%, 96.1%, and 97.2%, respectively, although the differences were not statistically significant (P = .332, P = .379, and P = .360, respectively). Among 473 mediastinal nodal stations having at least one node ≥ 5 mm that were evaluated, the proportion of accessible mediastinal nodal stations by EBUS-TBNA was 78.6%, and the proportion increased to 84.8% by combining EUS-B-FNA with EBUS-TBNA (P = .015).

Conclusion: Following EBUS-TBNA in the mediastinal staging of potentially operable lung cancer, the accessibility to mediastinal nodal stations increased by adding EUS-B-FNA and an additional diagnostic gain might be obtained by EUS-B-FNA.
Combined Endoscopic-Endobronchial Ultrasound-Guided Fine-Needle Aspiration of Mediastinal Lymph Nodes Through a Single Bronchoscope in 150 Patients With Suspected Lung Cancer

Herth FJ, Krasnik M, Kahn N, Eberhardt R, Ernst A
Chest 2010; 138(4): 790-794

Background: For mediastinal lymph nodes, biopsies must often be performed to accurately stage lung cancer. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) allows real-time guidance in sampling paratracheal, subcarinal, and hilar lymph nodes, and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) can sample mediastinal lymph nodes located adjacent to the esophagus. Nodes can be sampled and staged more completely by combining these procedures, but to date use of two different endoscopes has been required. We examined whether both procedures could be performed with a single endobronchial ultrasound bronchoscope.

Methods: Consecutive patients with a presumptive diagnosis of non-small cell lung cancer (NSCLC) underwent endoscopic staging by EBUS-TBNA and EUS-FNA through a single linear ultrasound bronchoscope. Surgical confirmation and clinical follow-up was used as the reference standard.

Results: Among 150 evaluated patients, 139 (91%; 83 men, 56 women; mean age 57.6 years) were diagnosed with NSCLC. In these 139 patients, 619 nodes were biopsied: 229 by EUS-FNA and 390 by EBUS-TBNA. Sensitivity was 89% for EUS-FNA and 92% for EBUS-TBNA. The combined approach had a sensitivity of 96% and a negative predictive value of 95%, values higher than either approach alone. No complications occurred.

Conclusions: The two procedures can easily be performed with a dedicated linear endobronchial ultrasound bronchoscope in one setting and by one operator. They are complementary and provide better diagnostic accuracy than either one alone. The combination may be able to replace more invasive methods as a primary staging method for patients with lung cancer.

Nonsurgical staging of the mediastinum: EBUS and EUS
Herth FJ
Semin Respir Crit Care Med 2011; 32(1):62-8

Abstract: A tissue diagnosis is frequently needed for accurate lung cancer staging of mediastinal nodes as well as the assessment of mediastinal masses. Noninvasive imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), positron-emission tomography (PET), and PET-CT provide some answers but no tissue diagnosis. Transbronchial needle aspiration (TBNA), a safe procedure that is performed during routine bronchoscopy, has a high impact on patient management.

Unfortunately, TBNA remains underused in current daily practice, mainly due to the lack of real-time needle visualization. The introduction of echo-endoscopes has overcome this problem. Endobronchial ultrasound-guided TBNA (EBUS-TBNA) allows real-time controlled tissue sampling of paratracheal, subcarinal, and hilar lymph nodes. Mediastinal lymph nodes located adjacent to the esophagus can be assessed by esophageal ultrasound-guided fine needle aspiration (EUS-FNA). Owing to the complementary reach of EBUS-TBNA and EUS-FNA in assessing different regions of the mediastinum, recent studies suggest that complete and accurate mediastinal staging can be achieved by the combination of both procedures. It is expected that implementation of minimally invasive endoscopic methods of EBUS-TBNA and EUS-FNA will reduce the need for surgical staging of lung cancer significantly.

Endobronchial ultrasound-guided lymph node biopsy with transbronchial needle forceps: a pilot study
Eur Respir J. 2012; 39(2):373-7

Abstract: One limitation of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the size of the available needles, frequently yielding only cells for cytological examination. The aim of this pilot study was to evaluate the efficacy and safety of newly developed needle forceps to obtain tissue for the histological diagnosis of enlarged mediastinal lymph nodes. Patients with enlarged, positron emission tomography (PET)-positive lymph nodes were included.

The transbronchial needle forceps (TBNF), a sampling instrument combining the characteristics of a needle (bevelled tip for penetrating through the bronchial wall) with forceps (two serrated jaws for grasping tissue) was used through the working channel of the EBUS-TBNA scope. Efficacy and safety was assessed. 50 patients (36 males and 14 females; mean age 51 yrs) with enlarged or PET-positive lymph nodes were included in this pilot study. In 48 (96%) patients penetration of the bronchial wall was possible and in 45 patients tissue for histological diagnosis was obtained. In three patients TBNF provided inadequate material.

For patients in whom the material was adequate for a histological examination, a specific diagnosis was established in 43 (86%) out of 50 patients (nonsmall cell lung cancer: n=24; small cell lung cancer: n=7; sarcoidosis: n=4; Hodgkin’s lymphoma: n=4; tuberculosis: n=2; and non-Hodgkin’s lymphoma: n=2). No clinically significant procedure-related complications were encountered. This study demonstrated that EBUS-TBNF is a safe procedure and provides diagnostic histological specimens of mediastinal lymph nodes.