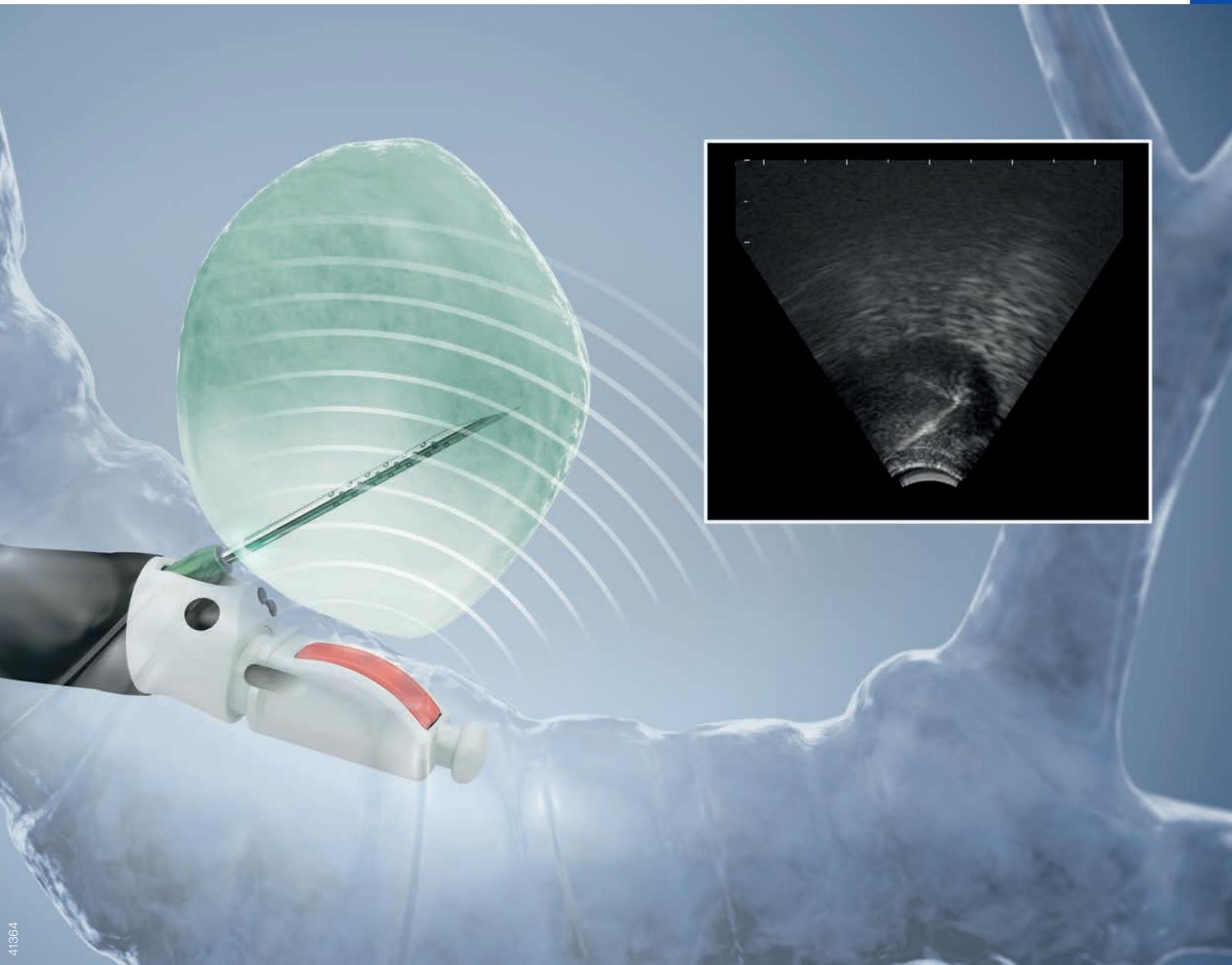


15th Anniversary of Scientific Study on EBUS-TBNA — a Review

Looking and Sampling beyond the Bronchial Wall



Scientific Study of EBUS-TBNA — a Review

The world's first curved linear array ultrasonic bronchoscope was introduced to the market by Olympus in 2004. 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 miniaturize 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 started in 2003 with a publication in the journal *Thorax* by Mark Krasnik and Peter Vilmann from Gentofte University Hospital, Denmark.¹ 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 Medical Center, 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%.² A further interesting outcome of the study was that no significant difference between ultrasound diagnosis under local and general anesthesia 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.³ 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 — 33 patients / Herth et al., *American Journal of Respiratory and Critical Care Medicine* 2005 — 160 patients), PET/CT (Yasufuku et al., *Chest* 2006 — 102 patients), and classical TBNA

and EUS-FNA (Wallace et al., *JAMA* 2008 — 138 patients).⁴⁻⁷

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-centimeter 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 Medical Center) that showed that every sixth patient with no evidence of mediastinal disease on CT was diagnosed positive using EBUS-TBNA.⁸ EBUS-TBNA thus shows potential to avoid explorative thorascopies. 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).⁹ 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.¹⁰

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).¹¹ 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 mini-forceps biopsy for histologic proof of lymphoma and/or sarcoidosis (Herth et al., *Annals of Thoracic Surgery* 2008 — 75 patients).¹²

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).¹³ 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.¹⁴ Also in 2007, in the same journal, the group reported chemosensitivity-related aberrant methylation profiling in samples obtained by EBUS-TBNA.¹⁵ In short, the group proved that samples gained by EBUS-TBNA allowed genetic evaluations of tumor cells from lymph nodes.

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.¹⁶ 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 restaging in 124 patients with tissue-proven IIIA-N2 disease after induction chemotherapy (*Journal of Clinical Oncology* 2008) and concluded that EBUS-TBNA is a valuable and practical tool for restaging, with a sensitivity of 76%, specificity of 100%, PPV of 100%, NPV of 20% and diagnostic accuracy of 77%.¹⁷ These results imply

that negative results of EBUS-TBNA for restaging should be confirmed by surgical restaging.

With the compatibility of EBUS-TBNA and the Aloka ProSound Alpha 5 ultrasound processor, which was realized 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.^{18,19}

In 2009 Tournoy et al. provided a detailed analysis of endosonographic 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.²⁰ In 2017 the 8th edition was published.

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.^{21,22}) used only one bronchoscope for both procedures, starting via the trachea and continuing via the esophageal 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

Scientific Study of EBUS-TBNA — a Review

and EUS-FNA will reduce the need for surgical staging of lung cancer significantly.²³

A review in 2016 by Bonta et al. confirmed this again. By introducing the EBUS scope into the esophagus (EUS-B) — following an EBUS procedure — the complete mediastinum and the left adrenal gland can be investigated in a single scope procedure by one operator. Additionally, in patients with suspected stage I/II sarcoidosis, EBUS-TBNA/EUS-FNA is the test with the highest granuloma detection rate.²⁴

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. in 2010 challenged the predominant surgical staging algorithm by comparing the combined EBUS-TBNA and EUS-FNA with surgical staging and surgical staging alone.²⁵ The results showed 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.

This is concluded in the 3rd edition of ACCP Guideline for lung cancer staging published in 2013.²⁶ Minimally invasive needle techniques to stage the mediastinum have become increasingly accepted and are the tests of first choice to confirm mediastinal disease in accessible lymph node stations. This is confirmed in the ESTS Guidelines.²⁷

Besides analysis of endosonographic characteristics of lymph nodes, elastography has also become more relevant in recent years. Ultrasound elastography is a new technique for describing the stiffness of tissue. In 2014 Izumo et al. evaluated the utility of endobronchial ultrasound elastography for mediastinal and hilar lymph nodes. They showed that endobronchial ultrasound elastography of mediastinal

and hilar lymph nodes is a noninvasive technique that can be performed reliably and may be helpful in the prediction of nodal metastasis during endobronchial ultrasound-guided transbronchial needle aspiration.²⁸ This was confirmed by Rozman et al. and Jiang JH in 2015.^{29,30}

As described above, molecular testing is possible with EBUS-TBNA samples. In 2015 Casadio et al. investigated the yield and applicability of molecular testing in the specimens obtained by EBUS-TBNA from patients with advanced non-small cell lung cancer (NSCLC). The study followed 306 consecutive patients with clinically diagnosed primary lung cancer who had the EBUS-TBNA procedure. EGFR and KRAS mutations as well as ALK rearrangement were evaluated. Molecular testing was possible in 96.9% of the samples obtained by EBUS-TBNA, which may allow targeted therapy.³¹

Also Nakajima et al. reported that molecular analyses such as the identification of EGFR mutation and ALK fusion gene detection are now being performed routinely with good sampling. They additionally remark that the application of EBUS-TBNA in pulmonary medicine and thoracic oncology is expanding with its role in the diagnosis of sarcoidosis, lymphoma, and tuberculosis. Especially for patients with early-stage sarcoidosis with adenopathy and minimal changes in the lung parenchyma, EBUS-TBNA has a significantly higher diagnostic yield compared to the conventional bronchoscopic modalities. Multidirectional analysis of samples obtained by EBUS-TBNA has allowed the assessment of lymphoma and molecular analysis in lung cancer.³²

In 2017 the first experiences with the 19G needle were reported. The diagnostic yield of the Flex 19G needle according to clinical cytopathology reports was 89% (42/47). The diagnosis and their respective diagnostic yield with the Flex 19G EBUS-TBNA needle were malignancy 24/27 (89%), sarcoidosis 13/14 (93%), and reactive lymph node hyperplasia 5/6 (83%).

All patients diagnosed with adenocarcinoma by the 19G needle had sufficient tissue for genetic testing.³³ In 2018 Garrison et al. analyzed the use of an additional 19G EBUS-TBNA needle for sampling. A 19G EBUS-TBNA needle was utilized following standard sampling with a 22G needle in 48 patients (50 sites) during the same procedure. Compared with 22G EBUS-TBNA alone, sampling with both the 22G and 19G EBUS needles resulted in an increase in diagnostic yield from 92% to 99% (P = 0.045). In select cases where additional tissue may be needed, sampling with a 19G EBUS needle following standard aspiration with a 22G needle results in an increase in diagnostic yield.³⁴

Also in 2017 Fujino et al. evaluated the new generation of EBUS bronchoscope. In comparison to the previous EBUS bronchoscope, the new generation has improved operability, selectivity of bronchial tree, access and detection of mediastinal/hilar lymph nodes.³⁵

This overview of scientific studies on EBUS-TBNA clearly shows the procedure's power in helping to improve mediastinal staging of lung cancer during the past 15 years. The technological development of less invasive staging and sampling devices continues to progress. With a growing number of interventional pulmonologists using endoscopic ultrasound, we can expect further exciting developments in clinical practice in the years to come.

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1

Preliminary Experience with a New Method of Endoscopic Transbronchial Real Time Ultrasound Guided Biopsy for Diagnosis of Mediastinal and Hilar Lesions

Krasnik M, Vilmann P, Larsen SS, Jacobsen GK
Thorax 2003; 58: 1083-1086

Background: The aim of the present study was to gain experience with a new method of endoscopic transbronchial ultrasonography with direct, real time guided fine needle aspiration biopsy (EBUS-FNA).

Methods: EBUS-FNA was performed in 11 patients. Selection of the patients for EBUS-FNA was based on computed tomographic (CT) scanning in 10 patients and on positron emission tomography in one. The ultrasonic bronchoscope used was a prototype with an outer diameter of 6.9 mm. The instrument has a small curved array transducer located in front of a 30° oblique forward viewing optic lens and a biopsy channel of 2 mm. The procedures were performed under general anaesthesia. EBUS-FNA was performed by direct transducer contact with the trachea or main bronchi with a prototype 22 gauge needle.

Results: A total of 15 lesions were punctured. No complications were experienced. Four lesions were targeted in region 10L, four in region 10R, one in region 4L, three in region 4R, one in region 1, one in region 7, and one in region 2R. The size of the lesions ranged from 7 mm to 80 mm. EBUS-FNA identified malignant cells in 13 lesions and benign cells in two.

Conclusions: EBUS-FNA is a promising technique for lymph node staging of lung cancer as well as for the primary diagnosis of solid lesions located adjacent to the trachea and main bronchi and not accessible by other methods apart from surgical intervention.

2

Real-Time Endobronchial Ultrasound Guided Transbronchial Needle Aspiration for Sampling Mediastinal Lymph Nodes

Herth FJF, Eberhardt R, Vilmann P, Krasnik M, Ernst A
Thorax 2006; 61: 795-798

Background: Transbronchial needle aspiration (TBNA) 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 TBNA 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 TBNA 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 (53 nodes), 3 (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 TBNA, and it is safe.

3

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

Herth FJF, 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 with the technique 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.

4

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

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 transesophageal 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.

Abstracts

5

Transbronchial Versus Transesophageal Ultrasound-Guided Aspiration of Enlarged Mediastinal Lymph Nodes

Herth FJF, Lunn W, Eberhardt R, Becker HD, Ernst A
Am J Respir Crit Care Med 2005; 171: 1164-1167

Rationale: Transesophageal 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 53.2 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 approaches was: 2R: 19/13; 2L: 16/19; 3: 17/15; 4R: 19/12; 4L: 17/20; 7: 19/20; 10R: 18/9; and 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 to those of mediastinoscopy.

6

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 supraclavicular, 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.

7

Minimally Invasive Endoscopic Staging of Suspected Lung Cancer

Wallace MB, Pascual JMS, Raimondo M, Woodward TA, McComb BL, Crook JE, Johnson MM, Al-Haddad MA, Gross SA, Pungpapong S, Hardee JN, Odell JA
JAMA 2008; 299: 540-546

Context: In patients with suspected lung cancer, the presence of mediastinal lymph node metastasis is a critical determinant of therapy and prognosis. Invasive staging with pathologic confirmation is recommended. Many methods for staging exist; mediastinoscopy, an invasive procedure requiring general anesthesia, is currently regarded as the diagnostic standard.

Objective: To compare the diagnostic accuracy of 3 methods of minimally invasive endoscopic staging (and their combinations): traditional transbronchial needle aspiration (TBNA), endobronchial ultrasound-guided fine-needle aspiration (EBUS-FNA), and transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). In particular, we aimed to compare EBUS-FNA with TBNA.

Design, Setting, and Participants: Invasive staging of the mediastinum among consecutive patients with suspected lung cancer at a US academic medical center from November 2004 through October 2006.

Intervention: TBNA, EBUS-FNA, and EUS-FNA performed sequentially as a single combined procedure.

Main Outcome Measure: Sensitivity for detecting mediastinal lymph node metastases, using pathologic confirmation and 6- to 12-month clinical follow-up as the criterion standard.

Results: Among 138 patients who met all study criteria, 42 (30%) had malignant lymph nodes. EBUS-FNA was more sensitive than TBNA, detecting 29 (69%) vs 15 (36%) malignant lymph nodes ($P = .003$). The combination of EUS-FNA and EBUS-FNA (EUS plus EBUS) had higher estimated sensitivity (93% [39/42]; 95% confidence interval, 81%-99%) and negative predictive value (97% [96/99]; 95% confidence interval, 91%-99%) compared with either method alone. EUS plus EBUS also had higher sensitivity and higher negative predictive value for detecting lymph nodes in any mediastinal location and for patients without lymph node enlargement on chest computed tomography.

Conclusions: These findings suggest that EBUS-FNA has higher sensitivity than TBNA and that EUS plus EBUS may allow near-complete minimally invasive mediastinal staging in patients with suspected lung cancer. These results require confirmation in other studies but suggest that EUS plus EBUS may be an alternative approach for mediastinal staging in patients with suspected lung cancer.

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Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration of Lymph Nodes in the Radiologically Normal Mediastinum

Herth FJF, Ernst A, Eberhardt R, Vilmann P, Dienemann H, Krasnik M

Eur Respir J 2006; 28: 910-914

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can sample enlarged mediastinal lymph nodes in patients with nonsmall 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 two; all diagnoses were confirmed by surgical findings. The mean diameter of the punctured lymph nodes was 8.1 mm. The sensitivity of EBUS-TBNA for detecting malignancy was 92.3%, specificity was 100%, and the negative predictive value was 96.3%. No complications occurred.

In conclusion, endobronchial ultrasound-guided transbronchial needle aspiration can accurately sample even small mediastinal nodes, therefore avoiding unnecessary surgical exploration in one out of six patients who have no computed tomography evidence of mediastinal disease. Potentially operable patients with no signs of mediastinal involvement on computed tomography may benefit from pre-surgical endobronchial ultrasound-guided transbronchial needle aspiration and staging.

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Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration of Lymph Nodes in the Radiologically and Positron Emission Tomography-Normal Mediastinum in Patients with Lung Cancer

Herth FJF, Eberhardt R, Krasnik M, Ernst A

Chest 2008; 133: 887-891

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can reliably sample enlarged mediastinal lymph nodes in patients with non-small cell lung cancer (NSCLC), and in practice is mostly used to sample nodes visible on CT or positron emission tomography (PET). Few data are available on the use of endoscopic procedures to stage the mediastinum in clinical stage 1 lung cancer. The aim of the present study was to determine the results of EBUS-TBNA in sampling mediastinal lymph nodes in patients with lung cancer and a radiographically normal mediastinum and no PET activity.

From January 2004 to May 2007, patients highly suspicious for NSCLC with CT scans showing no enlarged lymph nodes (no node > 1 cm) and a negative PET finding of 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.

One hundred patients (mean age, 52.4 years; 59 men) were included. After surgery, 97 patients (mean age, 52.9 years; 57 men) had NSCLC confirmed and were included in the analysis. In this group, 156 lymph nodes ranging 5 to 10 mm in size were detected and sampled. Malignancy was detected in nine 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.

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

Hwangbo B, Kim SK, Lee HS, Lee HS, Kim MS, Lee JM, Kim HY, Lee GK, Nam BH, Zo JI

Chest 2009; 135(5): 1280-1287

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%, 59.8%, 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.

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Endobronchial Ultrasound: New Insight for the Diagnosis of Sarcoidosis

Wong M, Yasufuku K, Nakajima T, Herth FJF, Sekine Y, Shibuya K, Iizasa T, Hiroshima K, Lam WK, Fujisawa T
Eur Respir J 2007; 29: 1182-1186

A diagnosis of sarcoidosis should be substantiated by pathological means in order to thoroughly exclude other diseases. The role of real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the diagnosis of sarcoidosis has not been reported. The purpose of the present study is to evaluate the diagnostic yield of EBUS-TBNA in demonstrating the pathological features of sarcoidosis.

In total, 65 patients with suspected sarcoidosis, with enlarged hilar or mediastinal lymph nodes on computed tomography, were included in the study. Patients with a suspected or known malignancy or previously established diagnosis of sarcoidosis were excluded. Convex probe endobronchial ultrasonography integrated with a separate working channel was used for EBUS-TBNA. Surgical methods were performed in those in whom no granulomas were detected by EBUS-TBNA. Patients were followed up clinically.

EBUS-TBNA was performed on a total of 77 lymph node stations in 65 patients. A final diagnosis of sarcoidosis was made for 61 (93.8%) of the patients. The remaining four patients were diagnosed as having Wegener's granulomatosis ($n = 1$) or indefinite ($n = 3$). In patients with a

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final diagnosis of sarcoidosis, EBUS-TBNA demonstrated noncaseating epithelioid cell granulomas in 56 (91.8%) of the patients. No complications were reported.

Endobronchial ultrasound-guided transbronchial needle aspiration proved to be a safe procedure with a high yield for the diagnoses of sarcoidosis.

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Endobronchial Ultrasound-Guided Miniforceps Biopsy in the Biopsy of Subcarinal Masses in Patients with Low Likelihood of Non-Small Cell Lung Cancer

Herth FJF, Morgan RK, Eberhardt R, Ernst A
Ann Thorac Surg 2008; 85: 1874-1878

Background: Transbronchial needle aspiration (TBNA) is used to sample mediastinal masses, but the value may be limited by the small specimen size obtained. In benign diseases and hematologic malignancies, the sample size from TBNA is often considered insufficient for diagnosis. We evaluated the safety and efficacy of obtaining histologic specimens from subcarinal masses using a 1.15-mm miniforceps under endobronchial ultrasound (EBUS) guidance and compared the diagnostic yield with TBNA alone.

Methods: Patients being evaluated for subcarinal lesions exceeding 2.5 cm (short axis) and without known or suspected non-small cell lung cancer were included. Bronchoscopy was performed, and EBUS-guided BNA of the lesion was performed first with a 22-gauge needle, followed by the 19-gauge needle. The miniforceps was then passed through the airway into the lesion (three to five passes) under real-time EBUS guidance. Three biopsy specimens were obtained.

Results: The study enrolled 75 patients (41 men; mean age, 51.5 years). Specimens were acquired from each patient using the three techniques and processed separately. A specific diagnosis was made in 36% of patients with the 22-gauge needle, 49% with the 19-gauge needle, and in 88% with the miniforceps. The increase in diagnostic yield with miniforceps was most significant in patients

with sarcoidosis (88% vs 36% for TBNA, $p = 0.001$) or lymphoma (81% vs 35%, $p = 0.038$). No complications occurred.

Conclusions: Miniforceps biopsy, performed under real-time EBUS guidance, can be used to obtain tissue specimens from subcarinal masses adjacent to the airway. The diagnostic yield for lymphoma and sarcoidosis is superior to TBNA alone, and the procedure appears safe.

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

Mohamed S, Yasufuku K, Nakajima T, Hiroshima K, Kubo R, Iyoda A, Yoshida S, Suzuki M, Sekine Y, Shibuya K, Farouk A, Fujisawa T
Thorax 2008; 63: 642-647

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 chemo-responsive and chemoresistant subgroups who might benefit from tailoring of chemotherapy.

Methods: The expression of six cell cycle-related proteins (pRb, cyclin D1, p16INK4A, p53, p21Waf1, Ki-67) in mediastinal lymph node specimens obtained by EBUS-TBNA was investigated by immunohistochemistry in 36 patients with pN2-NSCLC. Their predictive role(s) in the response to platinum-based chemotherapy was examined.

Results: Immunostaining was feasible in all studied specimens. Univariate analysis revealed that p53 and p21Waf1 expressions were significantly related to the response to chemotherapy ($p = 0.002$ and $p = 0.011$, respectively). Multivariate logistic regression analysis revealed that only p53 overexpression was associated with a poor response to chemotherapy ($p = 0.021$).

Conclusions: These results suggest that EBUS-TBNA is a feasible tool for obtaining mediastinal nodal tissue samples amenable for immunohistochemical analysis. Immunostaining of p53 in EBUS-TBNA-guided specimens may be useful in predicting the response to chemotherapy in patients with N2-NSCLC and helping in the selection of patients who might benefit from certain chemotherapeutic strategies.

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

Nakajima T, Yasufuku K, Suzuki M, Hiroshima K, Kubo R, Mohammed S, Miyagi Y, Matsukuma S, Sekine Y, Fujisawa T
Chest 2007; 132: 597-602

Background: The presence of somatic mutations in epidermal growth factor receptor (EGFR) predicts the effectiveness of EGFR tyrosine kinase inhibitors (TKIs). It would be ideal if an EGFR mutation could be detected in biopsy samples, since the majority of non-small cell lung cancer patients are inoperable at the time of presentation. We have reported the usefulness of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for the lymph node staging of lung cancer. EBUS-TBNA enables the sampling of histologic cores, which can be used for genetic analysis.

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.

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

Nakajima T, Yasufuku K, Suzuki M, Mohamed S, Sekine Y, Shibuya K, Takiguchi Y, Hiroshima K, Kimura H, Fujisawa T
Chest Meeting Abstracts 2007; 132: 466a

Purpose: Lung cancer remains to be the leading cause of cancer deaths despite the introduction of various chemotherapeutic agents. It would be ideal if the chemosensitivity can be predicted from biopsy specimens prior to treatment of lung cancer. Several types of aberrant methylation of DNA repair related genes are known to be associated with chemosensitivity. We have reported the usefulness of endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) for lymph node staging of lung cancer. The purpose of this study was to develop and analyze the feasibility of detecting aberrant methylation in samples obtained by EBUS-TBNA and to examine the correlation between multigene aberrant methylation profiling and response to chemotherapy.

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Methods: Thirty patients with primary non-small cell lung cancer diagnosed as metastatic carcinoma in hilar and/or mediastinal lymph node by EBUS-TBNA were enrolled. We evaluated the methylation status of a panel of six genes (FANCF, Reprimo, TMS1/ASC, Activated Protein-2alpha, CHFR, ATM) using methylation-specific PCR. Twenty-four patients with metastatic adenocarcinoma or squamous cell carcinoma received platinum-based combination chemotherapy and were evaluated for their response to chemotherapy following RECIST criteria.

Results: Aberrant methylation was detected as follows: 9 cases of FANCF (30.0%), 14 cases of Reprimo (46.7%), 10 cases of TMS1/ASC (33.3%), 19 cases of Activated Protein-2 (63.3%) and no aberrant methylation was detected for CHFR and ATM. In response to chemotherapy, there were one CR, 6 PR, 12 SD and 5 PD cases. A comparison of the number of methylated genes to chemosensitivity revealed that the number of methylated genes was significantly smaller in the PD group than in the non-PD group ($p=0.0435$).

Conclusion: Aberrant methylation analysis can be performed in EBUS-TBNA samples obtained from metastatic lymph nodes in lung cancer patients. EBUS-TBNA allows genetic evaluations of tumor cells within the lymph node which may allow clinicians to predict chemosensitivity.

Clinical Implications: EBUS-TBNA samples provide molecular biological information which will be useful for the treatment of lung cancer. This raises the possibility of “tailored treatment” using the most effective chemotherapeutic agents.

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

Ernst A, Anantham 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 node 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 other 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 (93%) 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.

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

Herth FJF, Annema JT, Eberhardt R, Yasufuku K, Ernst A, Krasnik M, Rintoul RC
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 IIIA-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 IIIA-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, negative 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.

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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 examined 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, 42.2 years) were examined, and of these, 50 patients (24 female; 36 male; mean age, 44.7 years) had measurable RIs. PSV and ESV were measured in all visible nodes ($n = 196$) and an interpretable value was obtained in 127 nodes (2.5 nodes 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 5.1-6.3). 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.

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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.

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

Herth F, Eberhardt R, Mulay T, Anantham D, Ernst A
Chest Meeting Abstracts 2007; 132: 465c-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 nonmalignant) 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 visualize 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.

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Endoscopic and Endobronchial Ultrasonography according to the Proposed Lymph Node Map Definition in the Seventh Edition of the Tumor, Node, Metastasis Classification for Lung Cancer

Tournoy KG, Annema JT, Krasnik M, Herth FJF, van Meerbeeck JP
J Thorac Oncol 2009; 4(12): 1576-1584

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. Transoesophageal 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 map for the seventh edition of the tumor, node, metastasis classification for lung cancer.

Conclusion: Recognition of the new anatomic borders by EUS-FNA and EBUS-TBNA is relevant to correctly stage the patient with lung cancer. Although these borders and thus the exact lymph node stations can be identified in a large number of cases, there is a degree of uncertainty in some. The clinician should be aware of these when making a clinical interpretation.

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

Hwangbo B, Lee GK, Lee HS, Lim KY, Lee SH, Kim HY, Lee HS, Kim MS, Lee JM, Nam BH, Zo JI
Chest 2010; 138(4): 795-802

Objective: We performed this study to evaluate the role of transesophageal 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 transesophageal 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 64 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.

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Combined Endoscopic-Endobronchial Ultrasound-Guided Fine-Needle Aspiration of Mediastinal Lymph Nodes through a Single Bronchoscope in 150 Patients with Suspected Lung Cancer

Herth FJF, 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 endoscopically biopsied: 229 by EUS-FNA and 390 by EBUS-TBNA. Sensitivity was 89% for EUS-FNA and 92%

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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.

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Nonsurgical Staging of the Mediastinum: EBUS and EUS

Herth FJF

Semin Respir Crit Care Med 2011; 32(1): 62-68

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 imple-

mentation of minimally invasive endoscopic methods of EBUS-TBNA and EUS-FNA will reduce the need for surgical staging of lung cancer significantly.

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Linear Endobronchial and Endoesophageal Ultrasound: A Practice Change in Thoracic Medicine

Bonta PI, Crombag L, Annema JT

Curr Opin Pulm Med 2016 May; 22(3): 281-288

Purpose of Review: Linear endosonography, including intrathoracic lymph nodal sampling by endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) and endoesophageal ultrasound fine-needle aspiration (EUS-FNA), has an important role in the diagnosing and staging of lung cancer. Furthermore, endosonography is applied in the mediastinal evaluation of sarcoidosis, lymphoma, cysts, and nodal metastases of extrathoracic malignancies. Endosonography-related complications as well as sedation and training strategies are discussed. The purpose of this review is to summarize current practice, recent advances, and future directions.

Recent Findings: Lung cancer guidelines recommend endosonography — above mediastinoscopy — as the initial test for mediastinal nodal tissue staging. By introducing the EBUS-scope into the esophagus (EUS-B) — following an EBUS procedure — the complete mediastinum and the left adrenal gland can be investigated in a single scope procedure by one operator. In patients with suspected stage I/II sarcoidosis, EBUS-TBNA/EUS-FNA is the test with the highest granuloma detection rate. Diagnosing (recurrent) lymphoma is an increasingly accepted indication for endosonography. Systematic surveys showed that endosonography has a low complication rate. Simulator-based training and assessment tools measuring competency are important instruments to provide standardized and optimal implementation.

Summary: Endosonography is generally accepted as a powerful and safe diagnostic test for various diseases affecting the mediastinum. Large-scale implementation is needed.

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Mediastinoscopy vs. Endosonography for Mediastinal Nodal Staging of Lung Cancer: A Randomized Trial

Annema JT, van Meerbeeck JP, Rintoul RC, Dooms C, Deschepper E, Dekkers OM, De Leyn P, Braun J, Carroll NR, Praet M, de Ryck F, Vansteenkiste J, Vermassen F, Versteegh MI, Veselić M, Nicholson AG, Rabe KF, Tournoy KG

JAMA 2010; 304(20): 2245-2252

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 transesophageal 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.

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Diagnosis and Management of Lung Cancer, 3rd Ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, Harris LJ, Detterbeck FC
Chest 2013; 143(5)(Suppl): e211S-e250S

Background: Correctly staging lung cancer is important because the treatment options and prognosis differ significantly by stage. Several noninvasive imaging studies and invasive tests are available. Understanding the accuracy, advantages, and disadvantages of the available methods for staging non-small cell lung cancer is critical to decision-making.

Methods: Test accuracies for the available staging studies were updated from the second iteration of the American College of Chest Physicians Lung Cancer Guidelines. Systematic searches of the MEDLINE database were

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performed up to June 2012 with the inclusion of selected meta-analyses, practice guidelines, and reviews. Study designs and results are summarized in evidence tables.

Results: The sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis were approximately 55% and 81%, respectively, confirming that CT scanning has limited ability either to rule in or exclude mediastinal metastasis. For PET scanning, estimates of sensitivity and specificity for identifying mediastinal metastasis were approximately 77% and 86%, respectively. These findings demonstrate that PET scanning is more accurate than CT scanning, but tissue biopsy is still required to confirm PET scan findings. The needle techniques endobronchial ultrasound-needle aspiration, endoscopic ultrasound-needle aspiration, and combined endobronchial ultrasound/endoscopic ultrasound-needle aspiration have sensitivities of approximately 89%, 89%, and 91%, respectively. In direct comparison with surgical staging, needle techniques have emerged as the best first diagnostic tools to obtain tissue. Based on randomized controlled trials, PET or PET-CT scanning is recommended for staging and to detect unsuspected metastatic disease and avoid noncurative resections.

Conclusions: Since the last iteration of the staging guidelines, PET scanning has assumed a more prominent role both in its use prior to surgery and when evaluating for metastatic disease. Minimally invasive needle techniques to stage the mediastinum have become increasingly accepted and are the tests of first choice to confirm mediastinal disease in accessible lymph node stations. If negative, these needle techniques should be followed by surgical biopsy. All abnormal scans should be confirmed by tissue biopsy (by whatever method is available) to ensure accurate staging. Evidence suggests that more complete staging improves patient outcomes.

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Revised ESTS Guidelines for Preoperative Mediastinal Lymph Node Staging for Non-Small-Cell Lung Cancer

De Leyn P, Doooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, Turna A, Van Schil P, Venuta F, Waller D, Weder W, Zielinski M
Eur J Cardiothorac Surg 2014 May; 45(5): 787-798

Abstract: Accurate preoperative staging and restaging of mediastinal lymph nodes in patients with potentially resectable non-small-cell lung cancer (NSCLC) is of paramount importance. In 2007, the European Society of Thoracic Surgeons (ESTS) published an algorithm on preoperative mediastinal staging integrating imaging, endoscopic and surgical techniques. In 2009, the International Association for the Study of Lung Cancer (IASLC) introduced a new lymph node map. Some changes in this map have an important impact on mediastinal staging. Moreover, more evidence of the different mediastinal staging technique has become available. Therefore, a revision of the ESTS guidelines was needed. In case of computed tomography (CT)-enlarged or positron emission tomography (PET)-positive mediastinal lymph nodes, tissue confirmation is indicated. Endosonography [endobronchial ultrasonography (EBUS)/esophageal ultrasonography (EUS)] with fine-needle aspiration (FNA) is the first choice (when available), since it is minimally invasive and has a high sensitivity to rule in mediastinal nodal disease. If negative, surgical staging with nodal dissection or biopsy is indicated. Video-assisted mediastinoscopy is preferred to mediastinoscopy. The combined use of endoscopic staging and surgical staging results in the highest accuracy. When there are no enlarged lymph nodes on CT and when there is no uptake in lymph nodes on PET or PET-CT, direct surgical resection with systematic nodal dissection is indicated for tumours ≤ 3 cm located in the outer third of the lung. In central tumours or N1 nodes, preoperative mediastinal staging is indicated. The choice between endoscopic staging with EBUS/EUS and FNA or video-assisted mediastinoscopy depends on local expertise to adhere to minimal requirements for staging. For tumours >3 cm, preoperative mediastinal staging is advised, mainly in adenocarcinoma with high standardized uptake value. For restaging, invasive

techniques providing histological information are advisable. Both endoscopic techniques and surgical procedures are available, but their negative predictive value is lower compared with the results obtained in baseline staging. An integrated strategy using endoscopic staging techniques to prove mediastinal nodal disease and mediastinoscopy to assess nodal response after induction therapy needs further study.

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Endobronchial Ultrasound Elastography in the Diagnosis of Mediastinal and Hilar Lymph Nodes

Izumo T, Sasada S, Chavez C, Matsumoto Y, Tsuchida T:
Jpn J Clin Oncol 2014 Oct; 44(10): 956-962

Objective: Endobronchial ultrasound elastography is a new technique for describing the stiffness of tissue during endobronchial ultrasound-guided transbronchial needle aspiration. The aims of this study were to evaluate the utility of endobronchial ultrasound elastography for mediastinal and hilar lymph nodes, and to compare the elastographic patterns of lymph nodes with results from endobronchial ultrasound-guided transbronchial needle aspiration.

Methods: Seventy-five lymph nodes were evaluated. A convex probe endobronchial ultrasound was used with a new endoscopic ultrasound processor to assess elastographic patterns that were classified based on color distribution as follows: Type 1, predominantly non-blue (green, yellow and red); Type 2, part blue, part non-blue (green, yellow and red); Type 3, predominantly blue. The elastographic patterns were compared with the final pathologic results from endobronchial ultrasound-guided transbronchial needle aspiration.

Results: On pathological evaluation of the lymph nodes, 33 were benign and 42 were malignant. The lymph nodes that were classified as Type 1 on endobronchial ultrasound elastography were benign in 24/24 (100%); for Type 2 lymph nodes, 6/14 (46.9%) were benign and 8/14 (57.1%) were malignant; Type 3 lymph nodes were benign in 2/37 (5.4%) and malignant in 35/37 (94.6%). In classifying Type 1 as "benign" and Type 3 as "malignant," the sensitivity, speci-

ficity, positive predictive value, negative predictive value and diagnostic accuracy rates were 100, 92.3, 94.6, 100 and 96.7%, respectively.

Conclusions: Endobronchial ultrasound elastography of mediastinal and hilar lymph nodes is a noninvasive technique that can be performed reliably and may be helpful in the prediction of nodal metastasis during endobronchial ultrasound-guided transbronchial needle aspiration.

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Endobronchial Ultrasound Elastography Strain Ratio for Mediastinal Lymph Node Diagnosis

Rozman A, Malovrh MM, Adamic K, Subic T, Kovac V, Flezar M
Radiol Oncol 2015 Nov 27; 49(4): 334-340

Background: Ultrasound elastography is an imaging procedure that can assess the biomechanical characteristics of different tissues. The aim of this study was to define the diagnostic value of the endobronchial ultrasound (EBUS) elastography strain ratio of mediastinal lymph nodes in patients with a suspicion of lung cancer. The diagnostic values of the strain ratios were compared with the EBUS brightness mode (B-mode) features of selected mediastinal lymph nodes and with their cytological diagnoses.

Patients and Methods: This prospective, single-centre study enrolled patients with an indication for biopsy and mediastinal staging after a non-invasive diagnostic workup of a lung tumour. EBUS with standard B-mode evaluation and elastography with strain ratio measurement were performed before endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).

Results: Thirty-three patients with 80 suspicious mediastinal lymph nodes were included. Malignant infiltration was confirmed in 34 (42.5%) lymph nodes. The area under the receiver operating characteristic curve for the strain ratio was 0.87 ($p < 0.0001$). At a strain ratio ≥ 8 , the accuracy for malignancy prediction was 86.25% (sensitivity 88.24%, specificity 84.78%, positive predictive value [PPV] 81.08%, negative predictive value [NPV] 90.70%). The strain ratio is

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more accurate than conventional B-mode EBUS modalities for differentiating between malignant and benign lymph nodes.

Conclusions: EBUS-guided elastography with strain ratio assessment can distinguish malignant from benign mediastinal lymph nodes with greater accuracy than conventional EBUS modalities. This new method may reduce the number of mediastinal EBUS-TBNAs and thus reduce the invasiveness and expense of mediastinal staging in patients with non-small lung cancer (NSCLC).

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Endobronchial Ultrasound Elastography: A New Method in Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

Jiang JH, Turner JF Jr, Huang JA

J Thorac Dis 2015 Dec; 7(Suppl 4): S272-S278

Background: TBNA through the flexible bronchoscope is a 37-year-old technology that utilizes a TBNA needle to puncture the bronchial wall and obtain specimens of peribronchial and mediastinal lesions through the flexible bronchoscope for the diagnosis of benign and malignant diseases in the mediastinum and lung.

Methods: Since 2002, the Olympus Company developed the first generation ultrasound equipment for use in the airway, initially utilizing an ultrasound probe introduced through the working channel followed by incorporation of a fixed linear ultrasound array at the distal tip of the bronchoscope. This new bronchoscope equipped with a convex type ultrasound probe on the tip was subsequently introduced into clinical practice. The convex probe (CP)-EBUS allows real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of mediastinal and hilar lymph nodes. EBUS-TBNA is a minimally invasive procedure performed under local anesthesia that has been shown to have a high sensitivity and diagnostic yield for lymph node staging of lung cancer.

Results: In 10 years of EBUS development, the Olympus Company developed the second generation EBUS bronchoscope (BF-UC260FW) with the ultrasound image processor (EU-M1), and in 2013 introduced a new ultrasound image processor (EU-M2) into clinical practice. FUJII company has also developed a curvilinear array endobronchial ultrasound bronchoscope (EB-530 US) that makes it easier for the operator to master the operation of the ultrasonic bronchoscope. Also, the new thin convex probe endobronchial ultrasound bronchoscope (TCP-EBUS) is able to visualize one to three bifurcations distal to the current CP-EBUS.

Conclusions: The emergence of EBUS-TBNA has also been accompanied by innovation in EBUS instruments. EBUS elastography is, then, a new technique for describing the compliance of structures during EBUS, which may be of use in the determination of metastasis to the mediastinal and hilar lymph nodes. This article describes these new EBUS techniques and reviews the relevant literature.

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Molecular Testing for Targeted Therapy in Advanced Non-Small Cell Lung Cancer: Suitability of Endobronchial Ultrasound Transbronchial Needle Aspiration

Casadio C, Guarize J, Donghi S, Di Tonno C, Fumagalli C, Vacirca D, Dell'Orto P, De Marinis F, Spaggiari L, Viale G, Barberis M

Am J Clin Pathol 2015 Oct; 144(4): 629-634

Objectives: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive procedure that has revolutionized the diagnosis and staging of lung cancer. The goal of the present study was to investigate the yield and applicability of molecular testing in the specimens obtained by EBUS-TBNA from patients with advanced non-small cell lung cancer (NSCLC), comparing the results with a series of patients who underwent diagnostic surgical procedures in the same institution.

Methods: The study followed 306 consecutive patients with clinically diagnosed primary lung cancer who had the EBUS-TBNA procedure. EGFR and KRAS mutations were evaluated on cytologic specimens by Sanger sequencing and Cobas real-time polymerase chain reaction, whereas ALK rearrangement was tested by fluorescence in situ hybridization. The results were compared with those obtained from a series of 1,000 NSCLC surgical samples routinely analyzed.

Results: Molecular testing was possible in 96.9% of the samples obtained by EBUS-TBNA. EGFR (exons 18-21) mutations were found in 16.9%, KRAS mutation (exons 2-3) in 31.6%, and ALK rearrangement in 3.9% of the cases. In the surgical series, the mutations' distribution were 14.8%, 29.0%, and 3.4%, respectively. There were no statistical differences between the two series.

Conclusions: Our study demonstrates that EBUS-TBNA can be effectively used not just for diagnosis but also for complete mutational testing.

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Recent Advances in Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

Nakajima T, Yasufuku K, Fujiwara T, Yoshino I
Respir Invest 2016 Jul; 54(4): 230-236

Abstract: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive modality for sampling of mediastinal and hilar lymph nodes as well as pulmonary lesions adjacent to the airway. Guidelines for staging of lung cancer suggest that EBUS-TBNA should be considered the best first test of nodal staging for radiologically abnormal lymph nodes that are accessible by this approach. The application of EBUS-TBNA in pulmonary medicine and thoracic oncology is expanding with its role in the diagnosis of sarcoidosis, lymphoma, and tuberculosis. Especially for patients with early-stage sarcoidosis with adenopathy and minimal changes in the lung parenchyma, EBUS-TBNA has a significantly higher diagnostic yield compared to the conventional bronchoscopic modalities. Multidirectional analysis of samples obtained by

EBUS-TBNA has allowed assessment of lymphoma and molecular analysis in lung cancer. Histological evaluation with immunohistochemistry, flow cytometry, fluorescence in situ hybridization, and chromosome analysis can be performed if good-quality samples can be obtained. Molecular analyses such as identification of epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) fusion gene detection now are being performed routinely with good sampling. One of the advantages of EBUS-TBNA is the ability to perform repeat procedures in a minimally invasive way. Restaging of the mediastinum after induction therapy can be done safely and with ease compared to repeat surgical procedures. With improvement in molecular analysis technology, comprehensive gene expression analysis will become important in the management of patients with lung cancer. Further advances in EBUS technology and needles for tissue sampling likely will help bronchoscopists to acquire ideal tissue.

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Flexible 19-Gauge Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration Needle: First Experience

Tyan C, Patel P, Czarnecka K, Gompelmann D, Eberhardt R, Fortin M, MacEachern P, Hergott CA, Dumoulin E, Tremblay A, Kemp SV, Shah PL, Herth FJF, Yasufuku K
Respiration 2017; 94(1): 52-57

Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a well-established first-line invasive modality for mediastinal lymph node staging in lung cancer patients and in the diagnostic workup of patients with mediastinal adenopathy. With the current 21- and 22-gauge (G) EBUS-TBNA needles, the procedure can be limited by the degree of flexibility in the needle and the size of the lumen in tissue acquisition.

Objective: We report our initial experience with a first-generation flexible 19G EBUS-TBNA (Flex 19G; Olympus Respiratory America, Redmond, WA, USA) needle with regards to efficacy and safety.

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Methods: The Flex 19G EBUS-TBNA needle was used in 47 selected patients with enlarged hilar and/or mediastinal lymphadenopathy at 3 centers. The standard Olympus EBUS scope with a 2.2-mm working channel was used in all cases.

Results: The diagnostic yield of the Flex 19G needle according to clinical cytopathology reports was 89% (42/47). The diagnosis and their respective diagnostic yield with the Flex 19G EBUS-TBNA needle were malignancy 24/27 (89%), sarcoidosis 13/14 (93%), and reactive lymph node hyperplasia 5/6 (83%). The mean short axis of the sampled lymph nodes was 19 ± 9 mm. No complications occurred except for 1 instance of moderate bleeding, which did not require intervention beyond suctioning and subsequently resolved. All 13 patients diagnosed with adenocarcinoma by the 19G needle had sufficient tissue for genetic testing.

Conclusion: EBUS-TBNA using the first-generation Flex 19G needle is feasible and safe with promising diagnostic yield while providing a greater degree of flexion with the Olympus EBUS scope. Additional clinical evaluations are warranted.

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Use of an Additional 19G EBUS-TBNA Needle Increases the Diagnostic Yield of EBUS-TBNA

Garrison G, Leclair T, Balla A, Wagner S, Butnor K, Anderson SR, Kinsey CM

J Bronchology Interv Pulmonol 2018 Oct; 25(4): 269-273

Background: Although endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has an excellent diagnostic yield, there remain cases where the diagnosis is not obtained. We hypothesized that additional sampling with a 19G EBUS-TBNA needle may increase diagnostic yield in a subset of cases where additional tissue sampling was required.

Methods: Indications for use of the 19G needle following 22G sampling with rapid on-site cytologic examination were: (1) diagnostic uncertainty of the on-site cytopathologist (eg, nondiagnostic, probable lymphoma, etc.), (2) non-small cell lung cancer with probable need for molecular genetic and/or PD-L1 testing, or (3) need for a larger tissue sample for consideration of inclusion in a research protocol.

Results: A 19G EBUS-TBNA needle was utilized following standard sampling with a 22G needle in 48 patients (50 sites) during the same procedure. Although the diagnostic yield between the needles was equivalent, the concordance rate was only 83%. The 19G determined a diagnosis in 4 additional patients (8%) and provided additional histopathologic information in 6 other cases (12%). Conversely, in 3 cases (6%) diagnostic information was provided only by the 22G needle. Compared with 22G EBUS-TBNA alone, sampling with both the 22G and 19G EBUS needles resulted in an increase in diagnostic yield from 92% to 99% ($P=0.045$) and a number needed to sample of 13 patients to provide one additional diagnosis. There were no significant complications.

Conclusions: In select cases where additional tissue may be needed, sampling with a 19G EBUS needle following standard aspiration with a 22G needle results in an increase in diagnostic yield.

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Human Ex Vivo Lung Evaluation of the Next Generation Convex Probe Endobronchial Ultrasound Bronchoscope

Fujino K, Ujiie H, Igai H, Kinoshita T, Lee C, Hindy S, Effat A, Yasufuku K

Chest 2017; Volume 152, Issue 4, A884

Purpose: Endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive modality for mediastinal lymph node staging of lung cancer. The aim of this study was to evaluate feasibility and improvement of the next generation convex probe endobronchial ultrasound (CP-EBUS) bronchoscope against the current CP-EBUS in ex-vivo human lungs. The prototype next generation CP-EBUS aims to make it easier to operate, to select bronchial tree, to puncture target LNs and to approach hilar LNs.

Methods: The prototype next generation CP-EBUS (BF-Y0063; Olympus, Tokyo, Japan), with a decreased forward oblique view (20 degrees), greater upward angulation range (160 degrees), and smaller distal rigid diameter (6.6 mm), was compared with the current CP-EBUS (35 degrees, 120 degrees, and 6.9 mm, respectively) in 8 ex-vivo human lungs. The operability, insertion ability, puncture ability, endoscopic and ultrasound images were assessed.

Results: A total of 8 ex-vivo human lungs were evaluated by 6 thoracic surgeons. The operability and bronchial selectivity were greater than CP-EBUS because of the decreased direction of view and increased angulation range. Although the maximum reach was not significantly different, increased angulation range enabled us to insert the CP-EBUS into the upper bronchial tree with ease. The average time for the detection of the majority of LNs with next generation CP-EBUS from the upper part of trachea set as a start point was significantly shorter (#4L; 11.3 sec. vs. 9.9, $P<0.05$, #7; 12.3 vs. 9.9, $P<0.01$, #10R; 18.6 vs. 13.5, $P<0.01$, and #11L; 25.8 vs. 19.2, $P<0.01$). As the puncture angle became sharper, lymph node puncture ability improved, especially accessibility to #4L and #10R was

easier with the next generation CP-EBUS. Next generation CP-EBUS was equal or greater in all respects, and was considered as acceptable for clinical use.

Conclusions: Next generation CP-EBUS has improved operability, selectivity of bronchial tree, access and detection of mediastinal/hilar lymph nodes.

Clinical Implications: The next generation CP-EBUS will allow better access and improved operability for assessment of mediastinal and hilar lymph nodes.