Review: "Endosonographic Mediastinal Lymph Node Staging of Lung Cancer"

Moishe Liberman MD, PhD, John Sampalis PhD, André Duranceau MD, Vicky Thiffault RN, Rachid Hadjeres MD, Pasquale Ferraro MD

Chest Vol 146, No 2, pp. 389-397, 2014

Background:

Since first introduced in 2004[1], endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) has become a powerful tool for diagnosis and staging of lung cancer. The American College of Chest physicians, in its third edition guidelines for the diagnosis and management of lung cancer, recommended a needle-based technique (EBUS, EUS or combined EBUS/EUS) as a first step for invasive mediastinal staging for non-small cell lung cancer (NSCLC)[2]. In general, mediastinoscopy should be considered if the needle technique is negative and there remains a high clinical suspicion of nodal (N2/N3) disease. However, this recommendation is still debated[3].

Several important previous trials have addressed needle-based staging and mediastinoscopy. Annema and colleagues compared surgical staging alone vs combined EBUS-TBNA and EUS (referred to as endosonography) followed by surgical staging in node negative patients. They demonstrated an improved sensitivity in the group first undergoing endosonography (85 to 94% respectively) [4], and a significant reduction in unnecessary thoracotomies. Yasufuku et al performed simultaneous EBUS-TBNA and mediastinoscopy and compared the operating characteristics of the two procedures.[5], These authors performed systematic mediastinal staging with EBUS-TBNA and demonstrated similar sensitivity and accuracy of the two techniques. They concluded that EBUS-TBNA could potentially replace surgical staging of the mediastinum in NSCLC. Combined EUS and EBUS staging has not been directly compared to surgical mediastinoscopy in the same group of patients. In a recent *Chest* publication, Liberman and colleagues evaluated the performance of combined EBUS/EUS vs surgical mediastinoscopy in a cohort of patients with NSCLC.[6] All patients underwent both procedures.

Methods:

They enrolled 166 patients with suspected NSCLC and no confirmed extra thoracic involvement. They performed combined EBUS/EUS followed by mediastinoscopy in all patients. Only those with negative N2/N3 disease by all three techniques underwent surgical resection and lymph node dissection. The final results of lymph node dissection were compared to the results from each technique as a secondary outcome. In the previously mentioned study of Yasufuku et al systematic lymph node sampling of the mediastinum with EBUS was performed.[6] This requires sampling every lymph node with a short axis dimension greater than 5mm, at stations 2R, 2L, 4R, 4L, and 7, starting with the contralateral lymph nodes. Liberman et al. performed a selective lymph node sampling by endosonography of only nodes that are deemed suspicious by CT, PET or ultrasound. The PI supervised all procedures and presumably selection of endosonographic sites, which may limit the generalizability of the study. The authors used an LMA during EBUS, which allowed them access to the 2R station, a limitation described by Yasufuku[6] in intubated patients.

Results:

With regard to the primary outcome, adding EUS to EBUS improved the sensitivity, NPV and accuracy when compared to mediastinoscopy (EBUS: 72%, 88%, 91%; EUS: 62%, 85%, 88%; combined EBUS-EUS - 91%, 96%, 97% respectively). While there were 5 patients with negative endosonography and positive mediastinoscopy, there were 24 patients with negative mediastinoscopy and positive endosonography, who, otherwise, would have undergone unnecessary thoracotomy. The secondary outcome showed a comparable sensitivity, NPV and accuracy of any of the techniques, including EBUS-TBNA alone, compared to thoracotomy with lymph node dissection.

Discussion:

The sensitivity of EBUS/TBNA was low at 72% compared to mediastinoscopy, possibly due to the selective sampling of a low number of LN (2.2), compared to mediastinoscopy where the 4R, 4L and station 7 lymph nodes were sampled in almost every patient. The relatively low number of needle passes (2 to 3) used was based on an internal analysis of FNA yield from the previous 1000 procedures in their institution. However, according to Lee et al the sensitivity of EBUS-TBNA for differentiating benign from malignant lymph nodes was maximal after 3 samples in the absence of ROSE. [7] Their yield increased with each needle pass from 69.8% to 83.7% up to 95.3% after the third sample. It is unclear if performing only two needle passes may have affected the results. Molecular testing was not performed for these patients as they were considered possible surgical candidates, although endosonography has been validated as adequate for tumor genotyping in NSCLC.[8] Acquiring additional tissue for molecular testing may require additional passes. The authors had a relatively high percentage of inadequate samples through EBUS, which also likely lowered the sensitivity of EBUS. (80% for 2R, 86% for 4R, 81% for 4L, 84% for 7)

EUS sample adequacy was markedly better (documented as 100% at stations 2R, 2L, 4R, 4L, and 7, although numbers of aspirates at each station vary markedly). Interestingly, EUS also identified one malignant left adrenal metastasis and one liver metastasis despite negative pre-procedure PET–CT scans in those regions (it is unclear whether these patients had N2/N3 disease). This may be an unrecognized advantage of EUS, and an area for further investigation. Eighty-eight LNs at station 5 were sampled by EUS and only 19 at station 4L. Some authors have argued that EUS cannot reach station 5, given that it lies lateral to the ligamentum arteriosum.[10] In general, studies of combined staging could benefit from clarification of this anatomy. Here, the differentiation remains unclear.

Liberman et al. directly compared endosonography to mediastinoscopy for invasive NSCLC staging and further confirmed a reduction in unnecessary thoracotomies with the use of endosonography. Interestingly, there were comparable results of the needle-based techniques compared to mediastinoscopy, even with selective sampling. This study adds to the evidence that endosongraphy is equivalent to mediastinoscopy for invasive mediastinal staging of NSCLC. It remains unclear if adding EUS to EBUS, provides additional diagnostic value. Further studies are needed to establish if there are specific patient subsets who may benefit from combined EUS and EBUS mediastinal staging.

Authors

Jad Harb MD
Fellow in Pulmonary and Critical Care
University of Vermont Medical Center

Christine Argento, MD, FCCP
Assistant Professor of Medicine
Interventional Pulmonology
Emory University

Momen M. Wahidi, MD, MBA
Director, Interventional Pulmonology and Bronchoscopy
Associate Professor of Medicine
Duke University Medical Center

C. Matthew Kinsey M.D., M.P.H.
Director, Interventional Pulmonary
Assistant Professor of Medicine
University of Vermont Medicine Center

References:

1. Yasufuku K, Chiyo M, Sekine Y, Chhajed PN, Shibuya K, Iizasa T, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. *Chest*. 2004;126:122-8.

2. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, Harris LJ, Detterbeck FC. Methods for Staging Non-small Cell Lung Cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2013;143:e211S–50S.

3. Wahidi MM, Ernst A. Point: Should UItrasonographic Endoscopy Be the Preferred Modality for Staging of Lung Cancer? Yes. *Chest* 2014;145:447–449.

4. Annema JT, van Meerbeeck JP, Rintoul RC, Dooms C, Deschepper E,Dekkers OM, et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. *JAMA*. 2010;304:2245-52.

5. Yasufuku K, Pierre A, Darling G, de Perrot M, Waddell T, Johnston M, da Cunha Santos G, Geddie W, Boerner S, Le LW, Keshavjee S. A prospective controlled trial of endobronchial ultrasound-

guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. *J Thorac Cardiovasc Surg* 2011;142:1393–400.e1.

6. Liberman M, Sampalis J, Duranceau A, Thiffault V, Hadjeres R, Ferraro P. Endosonographic mediastinal lymph node staging of lung cancer. *Chest* 2014;146:389–397.

7. Hee Seok Lee, MD; Geon Kook Lee, MD, PhD; Hyun-Sung Lee, MD, PhD; Moon Soo Kim, MD; Jong Mog Lee, MD; Hyae Young Kim, MD, PhD; Byung-Ho Nam, PhD; Jae Ill Zo, MD, PhD; and Bin Hwangbo. Real-time Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in Mediastinal Staging of Non-Small Cell Lung Cancer, How Many Aspirations Per Target Lymph Node Station? *Chest* 2008; 134:368–374

8. Folch E, Yamaguchi N, VanderLaan PA, Kocher ON, Boucher DH, Goldstein MA, Huberman MS, Kent MS, Gangadharan SP, Costa DB, Majid A. Adequacy of lymph node transbronchial needle aspirates using convex probe endobronchial ultrasound for multiple tumor genotyping techniques in non-small-cell lung cancer.
J Thorac Oncol. 2013 Nov;8(11):1438-44.

9. Yarmus L, Akulian J, Gilbert C, Feller-Kopman D, Lee HJ, Zarogoulidis P, Lechtzin N, Ali SZ, Sathiyamoorthy V. Optimizing endobronchial ultrasound for molecular analysis. How many passes are needed? *Ann Am Thorac Soc.* 2013 Dec;10(6):636-43.

10. Cerfolio RJ, Bryant AS, Eloubeidi MA. Accessing the aortopulmonary window (#5) and the paraaortic (#6) lymph nodes in patients with non-small cell lung cancer. *Ann Thorac Surg.* 2007 Sep;84(3):940-5.