



Mediastinal staging in patients with radiographically normal lymph nodes

Review of: Endobronchial Ultrasound-guided Transbronchial Needle Aspiration for Systematic Nodal Staging of Lung Cancer in Patients with N0 Disease by Computed Tomography and Integrated Positron Emission Tomography-Computed Tomography

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Reviewers: Brian Shigenobu Furukawa MD¹, Nichole T. Tanner, MD, MSCR^{1,2}, Renda Soylemez Wiener, MD, MPH^{3,4}

1. Division of Pulmonary and Critical Care, Medical University of South Carolina
2. Health Equity and Rural Outreach Innovation Center, RHJ VA Hospital
3. The Pulmonary Center, Boston University School of Medicine
4. Center for Healthcare Organization & Implementation Research, ENRM VA Hospital

Objective:

Accurate pre-operative nodal staging of non-small cell lung cancer is crucial for developing an effective treatment regimen and preventing unnecessary surgical morbidity. Structural and functional imaging with CT and PET/CT is recommended as part of the initial clinical staging in those with non-small cell lung cancer (NSCLC),[1] but there are shortcomings in the diagnostic accuracy of these imaging modalities.[1-3] Because of this, lymph node (LN) abnormalities require further tissue confirmation with minimally invasive sampling techniques – the preferred method, where available. In those with a radiographically normal mediastinum, the current guidelines recommend tissue sampling when the tumor is central, is > 3cm in size, or there is evidence of N1 involvement.[1]

Several studies have shown endobronchial ultrasound (EBUS) transbronchial needle aspiration (TBNA) is an effective means for detecting occult nodal metastasis in NSCLC patients with a strong negative predictive value (87.7-100%) but a wide range of sensitivities (35 – 92.3%).[2, 4-6] These studies were limited by size, single imaging modalities, and were performed in those who were surgical candidates. In those patients with stage IA NSCLC who are poor operative candidates or those who refuse surgery, alternative therapies such as stereotactic body radiotherapy (SBRT) are available with similar local control rates.[7, 8] In those not able to undergo surgery, pre-therapy mediastinal staging may be desirable even in those without radiographic evidence of nodal involvement; a small study demonstrated a 16% prevalence of occult local metastasis in a radiographic normal mediastinum.[9] Ong and colleagues conducted

the following study to determine the utility of EBUS in radiographically N0 NSCLC patients undergoing surgical and non-surgical treatments.

Methods:

Design: Retrospective chart review of patients with NSCLC and radiographic N0 disease by both CT and PET-CT who underwent mediastinal staging via EBUS

Setting: Two major academic medical centers (Baylor College of Medicine and University of Texas MD Anderson Cancer Center).

Period of Enrollment: 2009 to 2014

Follow-up: 12 months

Patients Enrolled: 220 patients with NSCLC and radiographic N0 disease who underwent mediastinal staging via EBUS-TBNA. A radiographically normal mediastinum was defined as LN \leq 1 cm in the short axis and maximum standard uptake value \leq 2.5 by PET-CT. All LN \geq 5mm or those with concerning features for malignancy[10] were sampled with a minimum of 3 needle passes in a systematic order from highest to lowest stage (N3 to N1) with rapid on-site cytology examination (ROSE) available. Final determination of occult metastasis was determined by surgical pathology or radiographic follow-up to 12 months.

Main Results:

The overall incidence of occult metastasis was 22.3% (49). The sensitivity and negative predictive value (NPV) of EBUS-TBNA in radiographically N0 patients was 36.7% and 84.7%, respectively. There were 120 patients who were treated nonsurgically, with EBUS resulting in the upstaging of 18 (15%). Four patients were later found to have evidence of occult metastasis detected on subsequent imaging (false negative rate of 3.3%). Of the 100 patients who went on to surgical resection, 27 were upstaged. The false negative rate of EBUS in surgical patients was 27%, however 70% of these were in LN stations that are not accessible with EBUS (station 5-6 and intralobar). When these are excluded from the analysis, the resulting sensitivity and NPV increases to 60% and 93.4%, respectively, and the overall false negative rate decreases to 5.5%. Those patients discovered to have occult LN metastasis had statistically larger tumors, with almost half centrally located (inner one-third of the lung).

Conclusion:

The incidence of occult LN metastasis in NSCLC with a radiographically normal mediastinum is significant. Endobronchial ultrasound is a useful initial diagnostic tool but the modest sensitivity in this population is a limitation. Minimally invasive mediastinal staging should also be considered in patients with clinical stage IA NSCLC who are undergoing non-surgical therapies.

Commentary:

This study highlights several key points. First, the incidence of occult nodal metastasis in radiographically normal LN is significant and supports the findings of prior trials.[4-6] Second, EBUS is an effective means of diagnosing occult nodal disease in those with radiographic N0 disease and should be performed regardless of the treatment strategy (surgery vs .SBRT) as the presence of disease has both treatment and prognostic implications. Third, while the sensitivity of EBUS in this population is lower than previous EBUS staging trials in which there was a higher pretest probability for disease (based on abnormal imaging), it may be that in radiographic N0 patients metastatic foci can be microscopic and groups of LN in the same station can be both positive and negative thereby leading to missed diagnoses.[6]

This study is limited due to its retrospective nature. In addition, some of the nodes included did not meet the size definition of radiographically negative (largest 2.61 cm). It is not reported how many positive LN were > 1 cm, raising the question of what the true sensitivity is in radiographically normal nodes. Also important to note, is that in those who were upstaged by EBUS, the average primary tumor size was 3.9cm and almost half were centrally located. Based on size and location, the guideline recommendation would have been to proceed with EBUS staging despite the N0 status.

This manuscript adds to the growing body of literature in support of EBUS for proper clinical staging of radiographic N0 NSCLC, however several questions remain. Is a clinical stage IA peripheral tumor the appropriate cut-off not to pursue further mediastinal staging? Herth et al. reported that 7 of the 9 patients with nodal involvement had tumors < 3cm in size, but did not report if the location of the primary malignancy was peripheral or central.[5] Shingyoji and colleagues found a 16.6% incidence of N2 involvement in peripheral NSCLC with a radiographically normal mediastinum.[6] Should mediastinal staging always be performed in those with radiographic stage IA disease that are unfit for surgery? Co-morbidities precluding surgery may also preclude mediastinoscopy for staging and combined minimally invasive staging with EBUS and endoscopic ultrasound (EUS) may be a safe alternative. EUS can reach LN stations inaccessible by EBUS (eg level 5, 6) and these account for 10-30% of false negatives in this study and others.[6, 11] It has been shown that combined EBUS and EUS in the radiographically normal mediastinum was better than either modality alone,[12] however this approach outside of major medical centers may not be feasible.

The role for EBUS in the staging of LC is well established and Ong and colleagues remind us that staging of the radiographically normal is equally important especially in those who will pursue nonsurgical treatments.

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