A new model for the evaluation of cytology negative EBUS-TBNA negative lymph nodes found during lung cancer staging

Review of: **Nodal Staging in Lung Cancer: A Risk Stratification Model for Lymph Nodes Classified as Negative by EBUS-TBNA**
Matthew Evison, Julie Morris, Julie Martin, Rajesh Shah, Philip V. Barber, Richard Booton,and Philip A. J. Crosbie; Journal of Thoracic Oncology 2015. 10(1): 126-133

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Background

Lung cancer remains the most common cause of cancer death in the United States, with non-small cell lung cancer (NSCLC) being the most common form.[1] Successful treatment of NSCLC requires accurate staging of the mediastinum, often with the use of endobronchial ultrasound-guided needle aspiration (EBUS-TBNA)[2]. EBUS-TBNA is a well-established technique for staging the mediastinum with a positive predictive value close to 100%. The negative predictive value of EBUS-TBNA is lower and ranges from 78-91% in recent studies.[3-5] Given the relatively poor negative predictive value of EBUS-TBNA and the potential harm of performing an extensive resection procedure on a patient who is subsequently found to have non-operable disease the authors sought to develop risk prediction model which could be used to help select patients who have a negative EBUS-TBNA evaluation to go on for additional staging procedures.

Methods

Design: Retrospective analysis of a prospectively-collected database.
Database: Prospective data collected on all patients undergoing EBUS-TBNA at the University Hospital Manchester in the United Kingdom.
Patients: All patients undergoing EBUS-TBNA between March of 2010 and August of 2013 with pathologically or clinically-determined cases of primary lung cancer were included. All lymph nodes (LNs) had at least 6 months of clinical and radiological follow-up.

Nodal Characteristics Evaluated: Size in short axis on CT scan, maximum SUV of primary and LN(s) on PET/CT, US characteristic of LN during EBUS-TBNA (Echogenicity, Oval vs. Round Shape, Distinct vs. Indistinct Margins, Presence or Absence of a Central Hilar Structure, and the Presence or Absence of the Coagulation Necrosis Sign). The ultrasound characteristics were chosen based on prior work which had shown them to be associated with malignancy.[6]
Indications for Sampling: Initially the indications to sample a LN were short axis diameter of > 10 mm on CT or on endobronchial ultrasound, increase FDG uptake on PET/CT, presence of a central tumor, or the presence of abnormal signal characteristics on EBUS. Later on sampling was performed on all LNs measuring greater than 5 mm on EBUS.
Variables analyzed: All nodal characteristics evaluated above. In addition, the absolute LN SUV and LN SUV ratio.
Risk Stratification Model Development: All LN classified as negative (either definitely negative EBUS-TBNA sample or deemed inadequate on EBUS-TBNA but no additional evidence of malignancy on 6 months of follow-up) and were split into a validation and derivation cohort. A logistic regression model was then constructed using the derivation cohort. The model was then evaluated using the derivation cohort.
Interobserver Agreement Analysis: Two blinded EBUS-TBNA operators reviewed 50 randomly-chosen LN images and their classifications were compared.

Results

- 509 Patients (877 LNs) were included in the study with 306 negative LNs and 46 LNs with inadequate evidence of malignancy (352 LNs total).
    - 48 LNs classified as negative subsequently proven to be positive.
    - 329 LNs in negative LN pool with complete data included in the final analysis.
- Univariate analysis found increased risk of malignancy with LN size > 10 mm in short axis on CT, positive PET/CT LN imaging, increasing LN to primary tumor SUV ratio on PET/CT, and the adverse condition of all 5 US characteristics .
- Multivariate logistic regression analysis found that LN SUV > 4, SUV ratio 41-60 or > 60, and hetergenous echogenicity on US were predictive of malignancy.
- Unable to analyze presence of the coagulation necrosis sign 2/2 inadequate numbers.
- The authors created a scoring system summarized below:

	0	1	2

Echogenicity	Homogenous		Heterogeneous
SUV	≤ 4	> 4	
SUV Ratio	≤ 40	41-60	> 60

- Low risk defined as a summative score of ≤ 1.
- Using that cutoff the model had a sensitivity of 92.3%, specificity of 87.8%, positive predictive value of 64.9%, and a negative predictive value of 97.9% in the validation cohort.
- The interobserver variability for echogenicity was low, with an observed agreement of 93%, and a Kappa of 0.86.

Commentary

In this publication Dr. Evison et al. have developed a predictive model which is relatively easy to use in the setting biopsy negative adenopathy found during lung cancer staging. The model, developed using multivariate logistic regression utilizes a number of important factors including LN SUV values and echogenicity. This scoring system will need to be more validated, presumably in a prospective manner before it can be recommended as a tool to aide in the management of patients with suspicious but negative LNs on EBUS-TBNA. However, if validated it could provide multidisciplinary thoracic oncology programs with a powerful evidence-based tool to objectively evaluate LNs in question.

There are several strengths of this model as pointed out by the authors. The first is that it was developed with regard to individual LNs as opposed to on a per patient basis. The second is that the negative predictive value of the model is high, a critical feature given its goal of selecting suspicious LNs for further evaluation.

There are several limitations to this study the foremost of which is that it is a single-institution study. Second, not all patients underwent PET/CT as part of their evaluation and lymph nodes less than 1 cm on short axis measurement were not included. Finally, while the authors were able to demonstrate low interobserver variability in the determination of echogenicity characteristics the inherently subjective nature of this designation may be limiting when studied in other settings.

Overall, this study is an important first step in the development of scientific tools to help manage a high-stakes decision.

References

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