Endobronchial Ultrasound-Guided Biopsy of Mediastinal and Hilar Lymph Nodes

A Word on False Positives

To the Editor:

The article by Wang Memoli et al in an issue of CHEST (December 2011) on the use of endobronchial ultrasound (EBUS) to predict lymph node metastasis due to lung cancer was well presented and helpful for the interpretation and diagnosis of metastatic carcinoma. The authors discussed the widely accepted criteria suggestive of metastatic malignancy, including a positive PET scan and a short-axis lymph node diameter > 1 cm on CT scan. Although these criteria are strongly suggestive, they do not prove that the patient in fact has metastatic nodal disease.

Further diagnostic or interventional studies may be necessary to confirm or disprove the presence of metastatic lung cancer. Such studies may include mediastinoscopy or needle biopsy either percutaneously or through EBUS. Each technique has limitations regarding its diagnostic accuracy and risk for complications. False-negative as well as false-positive results may be obtained. Each situation must be interpreted with this in mind for the benefit of the patient and the best therapeutic program to recommend.

We recently evaluated a patient with adenocarcinoma of the right-side lung. The PET scan was interpreted as positive for bilateral hilar and mediastinal node metastasis. EBUS biopsy specimens from both the right-side and the left-side paratracheal and hilar areas demonstrated malignant cells in the right-side biopsy specimen and none in the left. The patient was informed of this finding and told that nonoperative therapy was recommended. She came to us for a consultation. We believed, on review, that the nodes were negative and recommended surgery. During right-side thoracotomy, 18 hilar and mediastinal lymph nodes were removed along with the involved lobe. All lymph nodes were negative for tumor presence. On review of the original EBUS biopsy specimen, lymphoid cells were present along with malignant cells, thus leading to the diagnosis of nodal metastasis. In retrospect, it appears that the false-positive study suggesting metastatic disease resulted from the EBUS needle passing through the node and into the lung or parenchymal tumor, thus the misinterpretation of positive nodal metastasis and the different therapeutic program being recommended.

Response

To the Editor:

The correspondence from Dr Dieter regarding our article in CHEST on endobronchial ultrasound (EBUS) predictors of metastatic malignancy has pointed out an important issue related to all diagnostic procedures: the false-positive result. False-positive results by EBUS have been reported and are related to the proximity of the primary tumor to a hilar, thus more distal, lymph node. This occurrence is rare, as several prospective studies comparing EBUS to surgical staging (mediastinoscopy or lymph node dissection at lung resection) have not reported any cases of false-positive results.

Some practitioners argue that a false-positive result is a problem presumably because it would lead to unnecessary procedures where a lesion is diagnosed as lung cancer but at resection, is not. Dr Dieter argues the opposite: His patient would not have undergone a potentially curative surgical resection because of a nodal metastasis diagnosis based on EBUS. Although his case may raise concern and make practitioners wary of their EBUS results, we have questions regarding Dr Dieter’s example. Which right-sided lymph node was positive on EBUS, mediastinal or hilar? If it was a hilar lymph node, the stage would likely be one in which curative resection was still possible despite lymph node metastasis. What made him doubt the results of the EBUS? The PET scan findings were considered positive, which supported the assumption that there was lymph node metastasis. Prior to surgical resection, should the patient have been referred for surgical confirmation with a mediastinoscopy if the EBUS-based diagnosis was in doubt? Before sending the patient for a thoracotomy, another method more invasive than EBUS but less invasive than thoracotomy to evaluate the mediastinum could have been performed. Was the lymph node that was positive at EBUS among the 18 hilar and mediastinal lymph nodes that were removed? This would verify the false-positive finding of the node sampled at EBUS. Is there any long-term follow-up on the patient to determine whether she has had subsequent recurrence?

Another aspect to consider in this case is the accuracy of the positive EBUS biopsy specimen. Part of the learning curve of performing EBUS lies in the ability to distinguish a lymph node and its borders from the surrounding structures. If the bronchoscopist guided the biopsy needle through the lymph node into the adjacent malignant mass, the needle could have become contaminated, resulting in the false-positive biopsy finding. Understanding the borders of the lymph node and avoiding contamination of the needle is crucial in all staging procedures.

Ultimately, false-positive results are rare. In most studies, when a positive result is obtained, that result is presumed to be a true
positive. The clinical implications of this should be evaluated to determine whether further study is needed to verify all positive results.

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Response

To the Editor:

I thank Dr Dieter for his interest in our article on endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and for this interesting case report. Our study was a report on the clinical effectiveness and determinants of diagnostic yield. For most patients, surgical confirmation of positive EBUS-TBNA cytology results is not warranted as part of the standard of care, so patients did not undergo routine surgical confirmation in our study when EBUS-TBNA results were positive. Thus, the false-positive rate cannot be determined. This was a necessary trade-off, since it would be impractical to obtain surgical biopsies on all cases in everyday practice.

There is, however, a good body of literature demonstrating that although false-positive EBUS-TBNA cases occur, they are very rare. Two separate meta-analyses reported a pooled specificity for EBUS-TBNA of 100%. In the meta-analysis by Adams et al, one case of a false-positive result was identified. However, it is important to note that some of the studies used in these meta-analyses did not include surgery as a reference standard when positive EBUS-TBNA results were available, so positive EBUS-TBNA results were by definition “true positive” in those studies. A more recent retrospective review found a specificity of 98.6% (95% CI, 92.4%-99.8%). A prospective observational study of 153 patients in which all patients had completed both EBUS-TBNA and mediastinoscopy, using thoracotomy as the reference standard, found that both EBUS-TBNA and mediastinoscopy had 100% specificity. As a consequence, positive EBUS-TBNA results should be viewed as sufficient evidence of nodal disease to guide treatment decisions in most patients.

The case reported by Dr Dieter highlights one potential cause of false-positive results—specifically, passing the EBUS-TBNA needle through the node and into an adjacent parenchymal lung tumor. The case description says that both right hilar and right paratracheal lymph nodes demonstrated malignant cells, but the lymph node stations were not specified. Similarly, it says there was a right-sided tumor, but the lobe is not specified, so it is difficult to draw conclusions. It seems most likely, based on the information provided, that the EBUS-TBNA positive lymph nodes were the 10R or 11R and the 4R, and the tumor was in the right upper lobe. If the tumor was in the right upper lobe, adjacent to the trachea, and extended into the area of the right mainstem bronchus and right upper lobe take-off, it is plausible that both 11R and 4R EBUS-TBNA samples could be falsely positive. Alternatively, it might have been only the 4R that was false positive, since the 11R would not have changed the decision on surgery. It is difficult to tell from the description provided. It would be useful to clarify what the findings were that led Dr Dieter and his team to identify the nodes as negative and to recommend surgery. Since review of the prior biopsy showed both lymph nodes and cancer, presumably it was the prior CT scan and PET scan images rather than the cytology results that provided this information. Tumor adjacent to but not directly invading the 4R and/or 10R or 11R lymph nodes might have been identified by CT/PET scan. Additional images would be useful to clarify this. If there was direct extension of the tumor into the 4R region, this would provide supporting evidence that this was indeed a false-positive result.

On balance, it is important to recognize that false-positive results do occur with EBUS-TBNA, but they are very rare. Proper technique is important to limit the number of false positive results. As Dr Dieter’s case points out, passing the EBUS-TBNA needle through a benign node into an adjacent paracervical tumor is one possible cause of false-positive results. Other causes include contamination from other lymph nodes or endobronchial disease. To limit the number of false-positive results when performing EBUS-TBNA, physicians should sample the highest lymph node stations first (ie, sample N3 nodes first, then N2, then N1) so as to avoid contamination of the needle with malignant cells. Similarly, any areas of endobronchial disease should only be biopsied after all necessary lymph node stations have been sampled. Finally, it is important to control the depth of needle penetration to ensure that the distance traversed is completely within the lymph node. Obtaining a clear posterior border of the lymph node on ultrasound is very important in this regard, as Dr Dieter’s case highlights, since it is possible to pass through a benign lymph node and into an adjacent area of tumor. This in turn can lead to false-positive results with resultant incidental upstaging.

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REFERENCES


