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Lung Cancer Staging With Minimally Invasive Endoscopic Techniques

To the Editor: In their study of minimally invasive endoscopic staging of suspected lung cancer, Dr Wallace and colleagues1 concluded that endobronchial ultrasound-guided fine-needle aspiration (EBUS-FNA) has higher sensitivity than traditional transbronchial needle aspiration (TBNA). When evaluating the relative accuracy of a newer technique, it is important to ensure that the standard technique (in this case TBNA) is performed to recognized standards.

The authors acknowledge that rapid on-site cytological evaluation (ROSE) may increase the yield of TBNA2 but not of the ultrasound-guided techniques.3 The exclusion of ROSE from the study protocol may therefore have resulted in a suboptimized sensitivity of TBNA. Furthermore, the number of passes into the lymph node with traditional TBNA may also affect yield. The authors performed “at least 3” passes, while optimal yield may require 7 aspirates.2 These 2 factors combined may have biased the study toward the ultrasound-guided techniques.

In addition, it is important to recognize that TBNA has a role in lung cancer staging.4 The newer ultrasound techniques are not widely available outside the United States. Until they are, the yield from TBNA should be maximized based on the best available evidence.

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To the Editor: Dr Wallace and colleagues1 discussed the role of minimally invasive endoscopic diagnostic procedures in the work-up of enlarged and positron emission tomography (PET)–positive mediastinal lymph nodes in patients with suspected lung cancer. They compared 3 different endoscopic procedures (TBNA; endoscopic ultrasound-guided fine-needle aspiration, EUS-FNA; and EBUS-FNA) in 138 patients, reporting a high sensitivity (93%) and negative predictive value (97%) for the combination of EUS-FNA and EBUS-FNA. They concluded that these minimally invasive procedures may be a substitute for mediastinoscopy in selected cases. We would like to raise some concerns about this study.

First, according to the recent American College of Chest Physicians recommendations, “for patients with discrete mediastinal lymph node enlargement (and no distant metastases), a nonmalignant result from a needle technique [EUS-FNA, TBNA, EBUS-FNA] should be further confirmed by mediastinoscopy (regardless of whether a PET finding is positive or negative in the mediastinal nodes).” In the study by Wallace et al, only 42 of 99 patients (42%) with negative endoscopic results underwent a surgical biopsy. Thus, data on accuracy and specificity of these combined techniques were not assessed.

Second, it is likely that most physicians performing EUS-FNA in the chest are gastroenterologists since the method was originally developed in this specialty. Few centers may have the skills and the financial resources to offer EBUS-FNA and EUS-FNA. In this setting, TBNA has an important role because it can be performed by pulmonologists during the bronchoscopic procedure and with a low additional cost for the TBNA needle.

Third, nodal station 6 was diagnosed in 4 cases by EUS-FNA and in 1 case by EBUS-FNA. According to the regional lymph node classification for lung cancer staging,3 station 6 (paraortic nodes) includes nodes lying anterior and lateral to the ascending aorta and the aortic arch or the innominate artery. Anatomically, this nodal station would not seem to be directly reachable by EUS-FNA or EBUS-FNA, and it is not clear how the authors obtained the 5 ultrasound-guided specimens.

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To the Editor: Dr Wallace and colleagues concluded that the combination of EUS-FNA and EBUS-FNA achieved “near-complete” minimally invasive mediastinal staging in patients with suspected lung cancer. It was suggested that if EUS-FNA and EBUS-FNA were used to replace mediastinoscopy, 97% of patients would have been correctly labeled as negative. Although the concept of complete ultrasound-guided staging is both logical (both methods have a complementary diagnostic reach) and appealing (it is an ambulatory, minimally invasive strategy that is likely to be safe and cost-effective), there are a number of features of this study that require the data to be interpreted with caution.

First, this is a diagnostic study, not a lung cancer-staging study because only 75 of 138 patients (54%) turned out to have lung cancer. Second, almost half of the evaluated patients (47%) presented with a mediastinal mass only without radiological evidence of a primary lung tumor.

Third, the size of mediastinal nodes was not provided. It appears likely that a considerable proportion of patients presented with mediastinal masses: 10% of the patients with lung cancer were diagnosed with small-cell lung cancer, typically a bulky mediastinal disease. This implies that a rather different patient population was investigated compared with usual lung cancer patients who require mediastinal tissue staging. For these patients, we have demonstrated that additional staging of EUS-FNA compared with mediastinoscopy improves nodal staging and that staging by EUS-FNA alone reduces the need for surgical staging procedures.

Fourth, surgical-pathological verification of patients staged tumor-negative by EUS-FNA and EBUS-FNA was lacking in 58% of cases. Although follow-up computed tomography was available, this constitutes a major limitation to the reference standard.

What is required is a randomized controlled clinical trial in which complete ultrasound-guided staging (EUS-FNA and EBUS-FNA) is compared with optimal surgical staging (current standard of care). The patient population should be well defined to reflect current clinical respiratory practice. Only such a trial can answer the question of whether endoscopy staging of the mediastinum of patients with lung cancer is preferable.

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In Reply: Dr Navani and colleagues raise the issue of the optimal number of passes of the TBNA needle into each lymph node. In one study, up to 7 TBNA passes were needed to maximize the sensitivity, although in that study more than 80% of positive diagnoses were obtained by the third FNA pass. Another study of the relationship between number of passes and sensitivity using EUS-FNA found that 3 passes were needed to maximize the sensitivity. Given the need to make a fair head-to-head comparison, we chose a uniform number of passes (at least 3) for all 3 procedures. We accept that more passes by TBNA may have increased the yield, and it is appropriate in settings where EUS-FNA or EBUS-FNA are not available. Similarly, the use of ROSE is most helpful when ultrasound guidance is not available but does increase the cost and time needed for the procedure. In one study, ROSE did not increase the diagnostic yield compared with 3 empirical passes for EUS-FNA.

In response to Dr Galetta and colleagues, the American College of Chest Physicians recommendation does state that a negative result from EUS-FNA, TBNA, or EBUS-FNA should be followed by a mediastinoscopy, based largely on the relatively high negative rate of any single test (EUS-FNA, 19%; EBUS-FNA, 20%; TBNA, 28%; mediastinoscopy, 11%). In our study, EUS-FNA and EBUS-FNA resulted in a false negative rate of 3%. If our data are supported by subsequent studies, the recommendation for performing a mediastinoscopy after a negative EUS-FNA or EBUS-FNA should be reconsidered in most patients.

I agree that wider availability of equipment and training are needed. Regarding level-6 lymph nodes, our group has demonstrated the preliminary feasibility and safety of approaching these lymph nodes via transaortic FNA from the esophagus.
In reply to Dr Annema and colleagues, our study was broadly inclusive of patients with mediastinal disease, including both patients with lung cancer and patients presenting with an isolated mediastinal mass or lymphadenopathy. Studies of the accuracy of EUS-FNA and EBUS-FNA among patients with lung cancer only have both EUS-FNA and EBUS-FNA was superior to any single procedure and EBUS-FNA alone was superior to TBNA alone. Although we did not specifically evaluate patients with particularly bulky subcarinal lymph nodes, these nodes are easily and reliably sampled with TBNA.

Finally, I agree that a trial directly comparing EUS-FNA and EBUS-FNA with mediastinoscopy in a non–small cell lung cancer population is warranted.

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Intrafamilial Spread of Methicillin-Resistant Staphylococcus aureus Infections

To the Editor: In his Clinical Crossroads article, Dr Moellering discussed the natural history, risk factors, epidemiology, and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections, using the case of a man with a recurrent skin infection. He noted the risks of infection from close and intimate contact in settings where such infections have been documented (hospitals, nursing homes, prisons, and athletic contacts). However, only the patient mentioned his family (the site of the most prolonged and intimate contact for most patients) and 1-year-old son, “who’s been on [antibiotics] ever since birth.”

It seems likely that the son has only been treated empirically and never cultured, so it is probably unknown whether he has had MRSA. However, multiple family members can have simultaneous or serial infections with the same Staphylococcus organism. One such documented familial outbreak of MRSA began with a family member who was hospitalized; was identified later in the father of the family; and then continued through a 10-year-old son, the wife, and several other children.

The Clinical Crossroads article does not state whether the patient’s son was in day care, which has been shown to be a locus of MRSA, or in a play group, where he may have acquired his original infection. But it is plausible that the son’s failure to clear infection is due to inadequately treated MRSA and that the index patient’s recurrence of infection is because of re-infection from his son (or from his wife, who could be infected or a carrier). It is also possible that a previously methicillin-sensitive organism became methicillin-resistant because of recurrent use of ineffective antibiotics in the son without culture or testing of sensitivity.

If for this case the common focus of infection for MRSA is the family, then the treatment and eradication would be very different from what was discussed. Further studies of the epidemiology of MRSA, focusing on the family, are needed.

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In Reply: Dr Bloom’s points are well taken. Intrafamilial spread of methicillin-susceptible S aureus has been well documented. However, because of the relative novelty of problems with community-associated MRSA (CA-MRSA), similar intrafamilial spread of these organisms has been less clearly defined, although it is very likely that this is a significant and growing problem.

Recent studies of nasal carriage of CA-MRSA document surprisingly low rates of carriage despite widespread dissemination of these organisms in the community. This has suggested that spread from colonized persons may be less of a factor for CA-MRSA than for hospital-associated strains of MRSA. This may be changing, however; a striking increase in nasal carriage of MRSA among injection drug users has recently been documented. The possibility of spread of these organisms to humans from family pets and other animals is being examined as well. Finally, the role of antibiotic exposure as a selective factor for MRSA coloniza-