Endobronchial Ultrasound–guided Transbronchial Needle Aspiration for Diagnosing and Subtyping Lung Cancer: Is It Required in All Patients?

To the Editor:

We read with interest the study by Navani and colleagues (1) and concur with the authors that the cytology samples obtained from endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) can be used not only to diagnose lung cancer but also to subtype and perform mutation analysis. There is no doubt that EBUS-TBNA is an established modality for lymph nodal staging in patients being planned for surgical resection (2). However, we wish to know whether conduct of EBUS-TBNA from mediastinal lymph nodes for the sole purpose of diagnosing a lung malignancy is cost effective. In our experience and as shown in recent series (3, 4), the vast majority of patients with suspected lung cancer have endobronchial findings such as a growth or mucosal infiltration, especially if it is a central tumor. In these patients with endobronchial abnormalities, conventional bronchoscopy techniques such as endobronchial biopsy, bronchial washing, brush cytology, and endobronchial needle aspiration have a high sensitivity in clinching the diagnosis of lung cancer with rates approaching 90% (5, 6). Furthermore, the biopsy specimen would suffice both for subtyping and mutation analysis. The authors in their study do not mention the frequency of endobronchial abnormalities observed and whether an endobronchial biopsy was done or not. Did all the 774 suspected patients who underwent EBUS-TBNA have only mediastinal lymphadenopathy and no endobronchial abnormalities? This is important information that is essential in planning a cost-effective strategy, especially in resource-constrained settings. We believe that EBUS-TBNA for the purpose of diagnosing lung cancer should only be done when there are no endobronchial abnormalities seen, or when an endobronchial biopsy fails to provide a definitive diagnosis.

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Wanted: Lung Cancer Pathologists

To the Editor:

The interesting work by Navani and colleagues (1) led to different considerations of various key roles of pathologists in lung cancer. Historically, the definition of pulmonary pathologists referred to experts in nonneoplastic/interstitial diseases, conditions requiring excellent knowledge and interpretation of morphology together with clinical, laboratory, and imaging data.

However, the radical changes in management of patients with non–small cell lung cancer (NSCLC) based on careful histologic subtyping (2) and detection of molecular alterations of "druggable" oncogenic drivers (3) have increased the responsibilities of pathologists in routine practice. According to the "*tissue is the issue*" paradigm (4), the amount and quality of tumor tissue sampled by the bronchoscopist or radiologist is fundamental in allowing investigations predicting the best management of the lung cancer patient.

Nevertheless, the time has come to have pathologists dedicated to lung cancer in all pathology labs, as commonly happens elsewhere (i.e., hematopathology, soft tissue tumors, and breast cancer).

This facilitates a detailed diagnosis based on conventional morphology, limiting the use of immunostains (i.e., thyroid transcription factor-1 plus p63/p40), and an appropriate interpretation of "ambiguous" immunoprofiles (i.e., NSCLC expressing thyroid transcription factor-1 and p63 is an adenocarcinoma) (5), leading to a rate of NSCLC not otherwise specified of less than 10%, saving tissue for molecular analyses, and permitting enrollment in clinical trials requiring blank slides for biomarker analyses.

A dedicated pathologist is also the fulcrum in optimal tumor tissue handling. In fact, predictive factors are tested with different methods (i.e., extractive methods in detecting epidermal growth factor receptor mutations and fluorescence *in situ* hybridization for anaplastic lymphoma kinase rearrangement) that work differently when using cytology rather than biopsy (all mutations are better detected by cytology; fluorescence *in situ* hybridization is better standardized on biopsy; tumor cells microdissected from immunostained slides are perfectly suitable for molecular analyses providing DNA enrichment with few tumor cells) (6).

To refine this mental approach, it is a good practice to teach technicians how to differently prepare pulmonary cytology (e.g., to obtain a cell block from cytology aspiration) and to save biopsy tissue when cutting serial sections from paraffin-embedded blocks. It is also helpful to routinely simulate how best to handle the available tumor tissue in assessing predictive factors in different situations (i.e., a case with transbronchial fine-needle aspiration cytology only and a case having biopsy and cytology or only cytology on pleural effusion).

In this novel scenario of promising targeted therapies for NSCLC, another major issue is to have well-prepared, open-minded, and smart pathologists acting as playmakers, then "passing" to physicians detailed diagnoses and permitting predictive molecular analyses through tumor tissue–handling optimization.

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Reply: Lung Cancer Diagnosis and Staging Centers

From the Authors:

We thank Drs. Maturu, Agarwal, and Rossi for their interest in our article (1). Drs. Maturu and Agarwal question the cost effectiveness of endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) compared with standard bronchoscopy in the diagnosis of lung cancer. None of the patients included in our study had endobronchial disease, and we cannot agree with their statement that the vast majority of patients with lung cancer have abnormal endobronchial findings. Drs. Maturu and Agarwal also miss an important point regarding the utility of EBUS-TBNA in patients with lung cancer. Not only can EBUS-TBNA provide a lung cancer phenotype and genotype, but it also provides a highly accurate nodal stage, critical to determining the treatment options. EBUS-TBNA, therefore, provides considerable information in addition to that provided by bronchoscopy and may prevent the need for further investigations such as integrated positron emission tomography–computed tomography, endoscopic ultrasound–guided fine needle aspiration, and mediastinoscopy. We are currently investigating the clinical efficacy and cost effectiveness of EBUS-TBNA as an initial investigation after staging computed tomography scan in patients with suspected lung cancer (2).

We agree with Dr. Rossi that the personalization of advanced non–small cell lung cancer (NSCLC) management has adjusted the spotlight onto tissue acquisition techniques and their interpretation. A paradox currently exists whereby patients with metastatic disease (in whom cancer phenotyping and genotyping is mandatory for best outcomes) have the smallest biopsies, whereas patients with considerably larger surgically resected specimens currently do not have systemic treatment tailored to their tumor. Dr. Rossi highlights the key role that the pathologist plays in deciding treatment options for patients with advanced NSCLC as well as the demands now placed on small biopsy samples.

As well as the pathologist requiring more dedicated lung cancer expertise, the same may apply to pulmonologists. Evidence already exists that the presence of dedicated thoracic surgeons may result in better lung cancer outcomes (3). The number of centers using EBUS-TBNA as a diagnostic and staging tool continues to increase internationally. Although the learning curve to reach competency in the procedure may be short (4), the focus has been on procedure sensitivity, whereas the assessment of quality of samples generated has not yet been built into competency assessment.

The centers included in our study are recognized for their expertise in lung cancer management, and it is unclear whether the results seen in our study may be generalizable to centers without specific expertise in lung cancer. Dr. Rossi calls for pathologists dedicated to lung cancer in each laboratory that receives lung cancer samples. However, given current progress and the prospect of further genetic targets in NSCLC reaching clinical utility in the very near future, perhaps the time has come to consider centers dedicated to lung cancer imaging and tissue acquisition as well as pathological diagnostics. This model may optimize the patient experience for lung cancer diagnosis and staging, raise standards of diagnostics to a more uniform level, be cost effective, and facilitate recruitment to clinical trials.

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Bronchobiliary Fistula and Lithoptysis after Endoscopic Retrograde Cholangiopancreatography and Liver Biopsy in a Patient with Paroxysmal Nocturnal Hemoglobinuria

A bronchobiliary fistula (BBF) is a pathological communication between the hepatic bile ducts and the pulmonary bronchial tree. The etiology is most often secondary to postsurgical complications or trauma and patients present with biliptysis (bile in the sputum) (1–3). In contrast, lithoptysis (expectorated biliary stones) can be a rare complication of spilled gall stones after cholecystectomy (4). In this report, we present a rare case of the

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