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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