those who have positive test results, can be as low as 15% (this means that 85% of the subjects with a positive test result will not have a TPE).9 The incidence of TPE is generally associated with the regional prevalence of tuberculosis.2 In the United States, only a small proportion of exudative pleural effusions are caused by tuberculosis.10

In TPE, a lymphocyte-dominant pleurisy, ADA is released in the presence of live intracellular Mycobacterium tuberculosis. It is thought that false-positive diagnoses of TPE by ADA level determination can be significantly reduced if ADA measurement is limited to lymphocytic pleural fluids. Theoretically, however, other lymphocyte-rich pleural effusions associated with live intracellular microorganisms also could have elevated ADA pleural fluid levels,11 including those caused by coccidioidomycosis and histoplasmosis, which are endemic mycoses in vast areas of the United States.

High levels of ADA also have been reported in noninfectious conditions associated with pleural fluid lymphocytosis, including malignant conditions (eg, adenocarcinomas, leukemias, and lymphomas) and collagen vascular diseases (eg, rheumatoid pleuritis and systemic lupus erythematosus).5,7 which make the test less useful in countries with a low prevalence of tuberculosis.12,13 Therefore, an increased ADA level should not be considered as an equivalent to the presence of mycobacteria in the pleural fluid or pleural biopsy specimens.2 A higher rate of false-positive test results can lead to the unnecessary administration of antituberculous therapy or a delay in making an alternative diagnosis.

In areas with a high prevalence of tuberculosis, the proportion of false-positive results will be obviously lower. However, a limitation of the test in this setting, as a sole method of diagnosis, is that culture results will not be available to guide antituberculous chemotherapy. Culture results are particularly necessary if drug-resistant tuberculosis is prevalent,10 an increasingly frequent scenario in countries with high rates of tuberculosis. Patients with drug-resistant tuberculosis may receive treatment with inefficient drugs due to the lack of availability of culture and drug-sensitivity results.

With the decline in the prevalence of TPE, the positive predictive value of pleural fluid ADA also declines, but the negative predictive value actually increases. Therefore, the measurement of the pleural fluid ADA level could be used to rule out a tuberculous etiology of lymphocytic pleural effusions, regardless of the rate of prevalence of the disease.5,4

In conclusion, the ADA assay should not be considered as an alternative to biopsy and culture, but rather as a screening test to guide further diagnostic procedures and management of an exudative pleural effusion of unknown origin.2,3

Rafael Laniado-Laborín, MD, MPH, FCCP
San Ysidro, CA

Endoscopic Ultrasound-Guided Fine-Needle Aspiration Staging of Lung Cancer

Is It Time To Go Beyond Cytology?

Endoscopic ultrasonography (EUS) is a unique imaging modality in which a high-frequency ultrasound transducer is incorporated into the tip of an endoscope to provide high-resolution images of
the GI wall and structures in close proximity to the GI tract. Linear echoendoscopes that can image parallel to the long axis of the instrument allow visualization of a projecting needle, relative to the adjacent tissue, making EUS-guided aspiration or intervention possible. Transesophageal EUS-guided real-time fine-needle aspiration (FNA) of mediastinal lymph nodes has become a clinically useful, minimally invasive, and safe method for detecting malignant lymph node invasion to stage the mediastinum.\(^1\)\(^,\)\(^3\) In patients with known non-small cell lung cancer (NSCLC) who have enlarged mediastinal lymph nodes on CT scan, the accuracy of EUS-guided FNA is approximately 96%.\(^1\) When a primary lung mass is suspected on CT, and enlarged mediastinal lymph nodes are seen in the posterior mediastinum, EUS-guided mediastinal FNA can provide a primary diagnosis and simultaneous staging information.\(^5\)\(^,\)\(^6\) Furthermore, EUS can also play a significant role in evaluating mediastinal lymphadenopathy of unknown origin with no primary lung mass on CT. Even when transbronchial FNA results are negative, EUS-guided FNA can provide a diagnosis of malignancy.\(^2\)\(^,\)\(^6\)

The current standards of lung cancer staging are based on either imaging, utilizing computed axial tomography, positron emission tomography (PET), or both, vs tissue-based staging that involves image-guided FNA, mediastinoscopy, or intraoperative staging. Image-guided transthoracic, bronchoscopic, and EUS-guided FNA greatly facilitate lung cancer staging by having the potential to precisely sample lung lesions and virtually all mediastinal lymph node stations. Imaging modalities alone, including chest radiography, CT, MRI, and PET identify lesions suspicious for cancer but cannot make a tissue diagnosis. Therefore, imaged-based staging has approximately a 10 to 20% inaccuracy. We have described a tissue-based algorithm for the diagnosis and TNM staging of lung cancer that uses procedures with the least invasiveness and cost with the highest diagnostic yields.\(^7\) For the anterior mediastinum, fluoroscopic, ultrasound, or CT-guided transthoracic FNA (which has a greater yield than bronchoscopy and is less invasive than mediastinoscopy) is our preferred primary technique for lymph node sampling.\(^8\) In the middle mediastinum, CT-guided transthoracic FNA is preferred for all nodal stations except subcarinal. EUS-guided FNA, which enables real-time transesophageal ultrasound-guided FNA within approximately 5 cm of the esophagus, is preferred for sampling subcarinal and posterior mediastinal lymph nodes because the yield is similar to CT-guided transthoracic FNA, with little or no risk of pneumothorax.\(^1\)\(^,\)\(^3\) The posterior mediastinum is also accessed by fluoroscopic-guided or CT-guided transthoracic FNA or video-assisted thoracic surgery.

In summary, EUS-guided FNA is particularly suited for the posterior mediastinal staging, with enlarged lymph nodes in the subcarina, aortopulmonary window, paraesophageal area, and para-aortic area being the most suitable locations for EUS-guided FNA. Recent data\(^9\) suggest that EUS-guided FNA may detect advanced mediastinal disease and avoid unnecessary surgical exploration in up to one in four patients who have no evidence of enlarged mediastinal lymph nodes on CT scan. While histologic tissue-based staging appears more accurate (95%), based on outcomes data, even early staging still predicts a relatively poor prognosis. Stage I has only a 60% 5-year survival, and stage II has only a 40% 5-year survival. Such poor outcomes suggest that either micrometastasis or havens of disease exist following resection for cure. Even though there is considerable prior negative data in regards to the utilization of adjuvant chemotherapy in NSCLC, data from recent randomized trials\(^10\)\(^–\)\(^13\) with demonstration of survival benefit increase the impetus to obtain more precise staging information.

In this issue of CHEST (see page 430), an aggressive application of EUS-guided FNA for staging lung cancer is presented by Wallace et al. The goal is to identify gene-expression patterns that may indicate the presence of metastasis or constitute an array that can predict outcomes and/or subclassifications that would allow better treatment stratification. The investigators have performed EUS-guided FNA sampling of all accessible lymph node stations during the preoperative evaluation of patients with known NSCLC. The EUS-guided FNA samples were then evaluated for both cytopathologic staging and gene expression-based profiling in six lung cancer-associated genes with expression determinants. Markers of gene expression are identified, such as KS1/4, with a high level of confidence to indicate the probability of micrometastases. This investigative team led by Wallace et al is well known and is to be commended for its continued work to attempt minimally invasive tissue-based staging of NSCLC to better predict therapy and outcomes. The group has coupled two relatively new techniques, namely EUS-guided FNA, with quantitative real-time reverse transcriptase-polymerase chain reaction for detection of rare gene transcripts that may indicate the presence of cancer cells in sampled mediastinal lymph nodes.

Unfortunately, this study is truncated, as there are no clinically relevant data presented to predict outcomes, survival, or response to adjuvant therapy. Likewise, the investigators admit that molecular marker overexpression alone is not definitive evidence of micrometastatic disease. The investigators speculate that overexpression of molecular markers
in lymph nodes may determine prognosis. They also speculate that a positive marker may indicate the need for systemic chemotherapy or radiotherapy.

Such data promise the potential for preoperative tissue/gene-based risk stratification, which most certainly will have some cut-off for risk/benefit for either neoadjuvant therapy or surgery. If EUS-guided FNA-based molecular and gene expression can be used to risk-stratify patients, this would be a tremendous aid to the clinician. Currently, balancing the patient’s premorbid condition with the need for either radiation, chemotherapy, or surgery vs risk stratification of the stage based on outcomes requires considerable judgment. One can only hope that improved staging and risk stratification would be coupled with more targeted therapeutic modalities.

All of us await the day when the “rosetta stone” of genetic classification vs accurate staging can be coupled with a outcomes-based therapeutic regimen that would allow matching of the patient’s therapy to the predicted risk/benefit ratio. Wallace et al have taken one of the first steps in this direction, which hopefully will lead to the needed giant leap in improving the treatment of lung cancer. Widespread availability of these new techniques coupled with prospective, randomized, multicenter outcomes trials are required to determine the impact of molecular marker positivity within mediastinal lymph nodes on treatment modalities and survival.

Manoop S. Bhutani, MD
Dennie V. Jones, Jr, MD
Joseph B. Zwischenberger, MD, FCCP
Galveston, TX

Dr. Bhutani is Professor of Medicine, Director, Center for Endoscopic Ultrasound, Co-Director, CERTAIN (Center for Endoscopic Research, Training and Innovation); Dr. Jones is an Associate Professor of Medicine and Interim Chief of Division of Hematology-Oncology; and Dr. Zwischenberger is Professor of Surgery, Medicine, Radiology, and Director of General Thoracic Surgery, University of Texas Medical Branch.

Correspondence to: Manoop S. Bhutani, MD, Professor of Medicine, University of Texas Medical Branch, 301 University Blvd, Route 0764, Galveston, TX 77555-0764; e-mail: mbsbhutan@utmb.edu

REFERENCES
2 Bhutani MS, Hawes RH, Hoffman, BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration for diagnosis of malignant lymph node invasion. Gastrointest Endosc 1997; 45:474–479

Transesophageal Echocardiography and Staging in Lung Cancer
A View From the Rear Window

Surgical resection is the main therapeutic procedure in the management of most cases of lung cancer. However, the feasibility of surgery as well as the choice of the proper surgical approach in the individual patient depend, among other conditions, on an accurate assessment of the extent of the tumor invasion of local structures, a process known as staging.1 Staging includes the assessment of the presence and extent of local spread of the tumor to adjacent structures such as the pleura, pericardium,