The Diagnosis and Staging of Lung Cancer

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Introduction

Lung cancer remains the leading cause of cancer-related mortality in the United States despite advances in chemotherapy and surgery. The evaluation of patients with suspected or known lung cancer requires accurate and preferably rapid diagnosis and staging to facilitate the optimal treatment regimen: surgery, surgery followed by chemotherapy, chemotherapy alone, or chemotherapy in conjunction with radiation therapy. Currently, staging requires the use of combined positron emission tomography - computed tomography (PET-CT) imaging, endobronchial ultrasound guided-fine needle aspiration (EBUS-FNA), endoscopic ultrasound guided-FNA (EUS-FNA), mediastinoscopy, thoracentesis, video-assisted thoracoscopic surgery (VATS), and or CT- or ultrasound-guided FNA.

In this article, we will review the different diagnostic and staging options. We will then provide a summary of our center's approach towards lung cancer diagnosis and staging with supporting literature where available.

Diagnostic and Staging Methods

Combined PET-CT

PET is an imaging modality that captures the level of metabolic activity of different tissues. Patients are given an injection of 2-(^{18}F)fluoro-2-deoxy-D-glucose (FDG) followed by imaging 60 minutes later. The degree of metabolic activity correlates with the level of FDG uptake which is reported as a standardized uptake value (SUV). A number of studies have demonstrated the accuracy of PET for the diagnosis of lung cancer in pulmonary nodules and masses[1,2,3,4,5] as well as for staging evaluation.[6,7] Fischer (2009) demonstrated that combined PET-CT is a better predictor of which patients with known or suspected lung cancer would benefit from surgery.[8] An earlier trial found similar benefits with PET imaging alone.[9]

Delayed PET imaging is also of interest. Cancers continue to absorb FDG over 1.5 to 5 hours.[10] Thus, an increase in the SUV of nodules, masses, or lymph nodes over time may suggest a cancer.[11,12,13]

It is important to realize that FDG uptake also occurs in inflammatory and infectious processes thereby limiting its ability to discriminate between these and cancers. Hara (2003) reported a mean SUV of 6.45 $\pm$ 2.30 for 14 patients with tuberculosis infections while 97 untreated patients with lung cancer had a mean SUV of 5.29 $\pm$ 2.72.[14] This emphasizes the importance of obtaining tissue to confirm the diagnosis of cancer for FDG-avid lesions.

False negatives can result from the limited spatial resolution of PET scanners affecting the accuracy of this test in pulmonary nodules less than a centimeter in diameter as well as in small lymph nodes.[7] In addition, certain cancers of the lung – i.e. bronchioloalveolar carcinomas and carcinoid tumors - have been reported to have negative PET imaging results.[15,16,17,18,19]

Patients with poorly controlled diabetes mellitus or elevated blood glucose levels at the time of imaging are also more likely to have false negative studies as a result of the elevated levels of endogenous glucose competing for uptake with FDG.

Cancers with low or negative PET signal appear to be associated with better prognoses.[20] In addition, the level of PET activity appears to correlate with prognosis[21] and the change in activity with chemotherapy correlates with cancer response to treatment.[22,23]

Endobronchial Ultrasound-Guided Fine Needle Aspiration (EBUS-FNA)

Prior to the development of EBUS-FNA, patients who were candidates for surgery for suspected or diagnosed lung cancer often required an additional staging procedure, specifically mediastinoscopy. However, mediastinoscopy is associated with a complication rate of as high as 2-3%, and more importantly is unable to sample posterior subcarinal (station 7), hilar (station 10), para-aortic (station 6), or aortopulmonary window (station 5) lymph nodes. Consequently, unresectable, advanced stage cancer has been reported in up to 10% of patients at the time of surgery precluding cancer removal.[24] EBUS-FNA is an alternative minimally invasive technique that complements mediastinoscopy by its ability to access lymph node stations 2, 3, 4, 7, 10, and 11 (Table 1).

EBUS is a bronchoscopic technique that utilizes ultrasound to identify and to permit real-time ultrasound-guided needle biopsy of paratracheal, hilar, and interlobar lymph nodes. Krasnik (2003) reported their initial experience with EBUS-FNA of mediastinal and hilar lymph nodes under general anesthesia.[24] These investigators reported accurate sampling of lymph nodes from stations 1, 2, 4, 7, and 10, with 9 diagnoses of cancer and 2 diagnoses of benign disease. Yasufuku published 2 studies evaluating EBUS performance in 2004 [25] and 2005 [26] reporting false negative rates of 4 to 5%. Additional studies report false negative rates of 4 to

10%.[27,28,29] These studies have demonstrated that EBUS-FNA is a minimally invasive alternative as well as a complementary procedure to mediastinoscopy for mediastinal and hilar staging, respectively, for known or suspected NSCLC.

Endoscopic Ultrasound-guided Fine Needle Aspiration (EUS-FNA)

EUS is an additional minimally invasive ultrasound-based technique which uses esophagogastroendoscopy to sample para-esophageal lymph nodes. These include paratracheal (station 4), aortopulmonary window (station 5), posterior subcarinal (station 7), paraesophageal (station 8), and pulmonary ligament (station 9) lymph nodes (Table 1). Consequently, this technique complements both mediastinoscopy and EBUS-FNA with the additional advantage of being able to access stations 8 and 9 as well as subdiaphragmatic structures including the celiac nodes and the adrenal glands.

Studies evaluating EUS-FNA for lung cancer have demonstrated false negative rates of 4 to 14%, comparable to EBUS-FNA.[30,31,32,33,34,35,36] Overall, these studies demonstrate that EUS is a valuable diagnostic and staging tool for patients with suspected or known NSCLC.

Cervical and Anterior Mediastinoscopy

Mediastinoscopy starts with an incision at the base on the neck just above the sternum, followed by the insertion of a mediastinoscope behind the sternum along the length of the trachea to permit sampling of the paratracheal lymph nodes (stations 1, 2, 3, and 4) as well as anterior subcarinal lymph nodes (Table 1). An extended cervical mediastinoscopy is allows access to the para-aortic lymph nodes (station 6). The videomediastinoscope, introduced in 1994,[37] permits easier handling and visualization during the procedure as well as potential access to posterior subcarinal lymph nodes.[38,39]

A number of studies have evaluated the performance of mediastinoscopy. The largest was a review of all mediastinoscopies performed by the Cardiothoracic Surgery Division at Washington University School of Medicine between January 1988 and September 1998.[40] 1,745 patients underwent cervical mediastinoscopy with known or suspected lung cancer. 422 (24%) of these patients were found to have advanced disease by detection of cancer within lymph nodes surrounding the trachea. 107 patients were deemed non-surgical candidates due to comorbid conditions and 947 of the remaining 1,216 patients were found to have lung cancer after surgery. Lymph node involvement was detected at the time of surgery in 76 of the 947 patients representing an 8% false negative rate. 4 deaths (0.05%) and 12 complications (0.6%) occurred. Additional large studies report false negative rates of 3%[41] and 9%.[42] About half of the false negative results (42-57%) were due to lymph nodes that are not accessible by mediastinoscopy.[43]

The major limitations to performing mediastinoscopy are patients at high risk of bleeding or radiation therapy to the center of the chest. The scarring and fibrosis associated with radiation significantly increases the risk of damage to vital organs and vasculature located within the center of the chest during the procedure.

Anterior mediastinoscopy (Chamberlain procedure) permits the evaluation of the aortopulmonary window and paratracheal lymph nodes (Table 1). The procedure involves an incision between the 2nd and 3rd ribs entering the extrapleural mediastinal space and removing the lymph nodes under direct vision. The procedure has not been extensively studied but 2 studies have reported false negative rates of 0%[44] and 11%.[45] Complications include internal thoracic artery ligation and post-thoracotomy pain. It is generally well tolerated and most patients can avoid an overnight hospital stay.[43] This procedure has been supplanted largely by videoscopic techniques.

Thoracentesis

Patients with pleural fluid concerning for cancer may be candidates for thoracentesis. This procedure requires only local anesthesia with 1% lidocaine and the placement of a temporary drainage catheter into the pleural space to remove the available fluid. The procedure can be performed in an outpatient setting and is generally well tolerated by the patient. One often discussed complication is pneumothorax – lung collapse. A prospective study of 506 thoracenteses in 370 patients reported 18 (4%) pneumothoraces.[46] Additional complications include catheter insertion site pain, coughing, hemothorax – bleeding into the pleural space, localized infection, abdominal organ injury, and shortness of breath from the lung re-opening. Reasons to avoid thoracentesis include increased risk of bleeding unless reversible, infection or abscess of the skin at the insertion site, and the inability to localize a pocket of fluid for sampling.

Pleural fluid analysis will obtain a diagnosis of metastatic adenocarcinoma in 70% of cases but only 20% of squamous cell carcinomas will be detected this way.[47] The rate of detection is dependent upon the type of cancer, the number of pleural fluid specimens obtained, and the extent of pleural involvement.[48]

Video-assisted Thoracoscopic Surgery

VATS or thoracoscopy is a surgical method that permits the surgeon to evaluate the pleural space and lymph nodes on the same side as the procedure. The surgery requires general anesthesia, single lung ventilation, and usually a short hospital stay but is usually well tolerated with an average complication rate of 2%.[49,50,51,52,53] The most common complication was prolonged lung collapse requiring chest tube management.

An important application of VATS is to directly visualize tumors that are radiographically staged as inoperable due to tumor invasion of vital chest organs and or blood vessels. Eggeling (2002) found that thoracoscopy upstaged 4 patients after discovering cancerous fluid within the chest cavity while down staging 6 patients thought to have vital organ invasion on computed tomography (CT).[51] The authors found that CT inaccurately predicted chest vital organ involvement in about 30% of cases and failed to detect involvement in about 35% of cases. This and additional publications[50,54] support the use of VATS to confirm T4 lesions designated by CT prior to categorizing the cancer as unresectable. Thoracoscopy can also evaluate the chest cavity for cancer in patients with fluid that remain negative for cancer on repeated thoracentesis or in patients with pleural abnormalities detected on CT. In addition, VATS provides an alternative approach to anterior and extended cervical mediastinoscopy for the evaluation of lymph node stations 5 and 6, respectively (Table 1).

Computed Tomography or Ultrasound Guided Fine Needle Aspiration

Patients with suspected or known NSCLC who are found to have abnormalities outside of the chest on PET-CT imaging should undergo tissue biopsy to confirm metastases. This can be achieved using CT-guided or ultrasound guided fine needle aspiration. The procedure is generally very well tolerated and can be performed in an outpatient setting.

Thoracic Tumor Board Diagnostic and Staging Algorithm

Our center has established a Diagnostic Thoracic Tumor Board that brings together the knowledge and expertise of physicians from pulmonary medicine, medical oncology, radiology, nuclear medicine, and thoracic surgery. The group has developed an evidence-based algorithm for the diagnosis and or staging of patients with suspected or known lung cancer (Figure 1). It is

our opinion that patients with suspected or known lung cancer receive rapid, cost-effective, accurate diagnosis and staging so that the appropriate treatment may be initiated in a timely manner. Our goal for all patients is to have a diagnosis and cancer stage within 7 days of referral and to have the appropriate treatment initiated within 14 days.

All patients we evaluate with suspected or known NSCLC and who are potential candidates for surgical resection undergo PET-CT for staging purposes. This practice is supported by 2 studies. Fischer (2009) published a prospective randomized trial evaluating the effect of combined PET-CT on the number of futile chest surgeries performed in patients with highly-suspected or newly diagnosed NSCLC.[8] Futile chest surgery was defined as a final diagnosis of a benign process, pathologically proven NSCLC stage IIIA-N2, IIIB, or IV disease, inoperable T3 or T4 disease, or recurrent cancer or death from any cause within 1 year of randomization. A significant decrease in futile chest surgeries was achieved using PET-CT pre-operatively compared to conventional staging (21 of 60 vs. 38 of 73, p=0.05). A similar result was reported in an earlier publication using PET.[9]

Diagnosis if not previously made and staging is achieved by biopsy of the FDG-avid lesion that would achieve the most advanced cancer stage. Biopsy methods for lymph nodes detected within the chest are described in Table 1. The preferred route of biopsy of mediastinal lymph nodes is to start with either EBUS or EUS depending upon the lymph node of interest. If the biopsy result is negative by EBUS or EUS, a confirmatory mediastinoscopy is necessary prior to proceeding to surgical resection.

Conclusion

Lung cancer survival is strongly associated with the stage of disease and the resulting application of appropriate treatment. With the introduction of combined PET-CT, EBUS, and

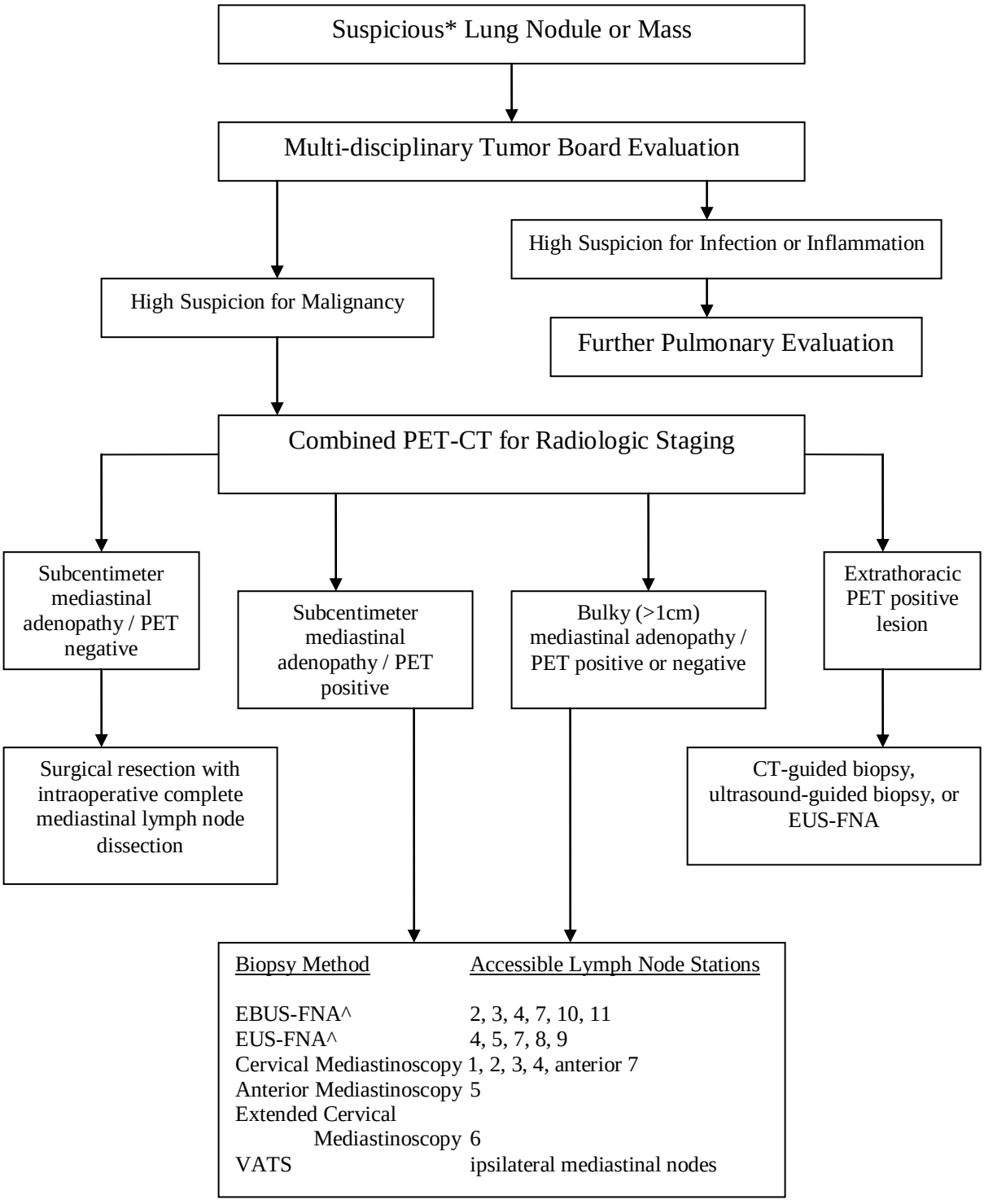
EUS to mediastinoscopy, patients can now be accurately staged avoiding unnecessary chest surgery. To improve the timely application of appropriate staging and diagnostic studies, a multidisciplinary panel of physicians is important and in our opinion essential.

Table 1.

Biopsy Method	Accessible Lymph Node Stations
EBUS-FNA	2, 3, 4, 7, 10, 11
EUS-FNA	4, 5, 7, 8, 9
Cervical Mediastinoscopy	1, 2, 3, 4, anterior 7
Anterior Mediastinoscopy	2, 4, 5
Extended Cervical Mediastinoscopy	6
VATS	Ipsilateral mediastinal lymph nodes

Figure 1.

Thoracic Tumor Board Diagnostic and Staging Algorithm



* Spiculated lesion on imaging, increasing size on serial computed tomography imaging, PET-avid lesion, significant smoking history, and or age greater than 50

^ preferred procedure but biopsies negative for malignancy require lymph node sampling for confirmation

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