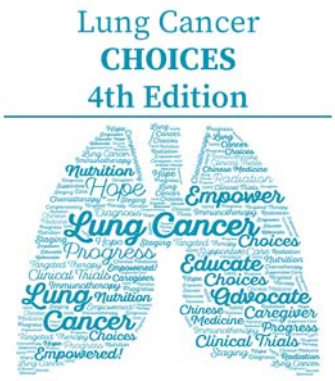


Chapter 1

The Diagnosis and Staging of Lung Cancer

Tze-Ming Chen, MD, FCCP

Introduction

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

Lung cancer survival is strongly associated with the stage of disease and the resulting application of appropriate treatment.

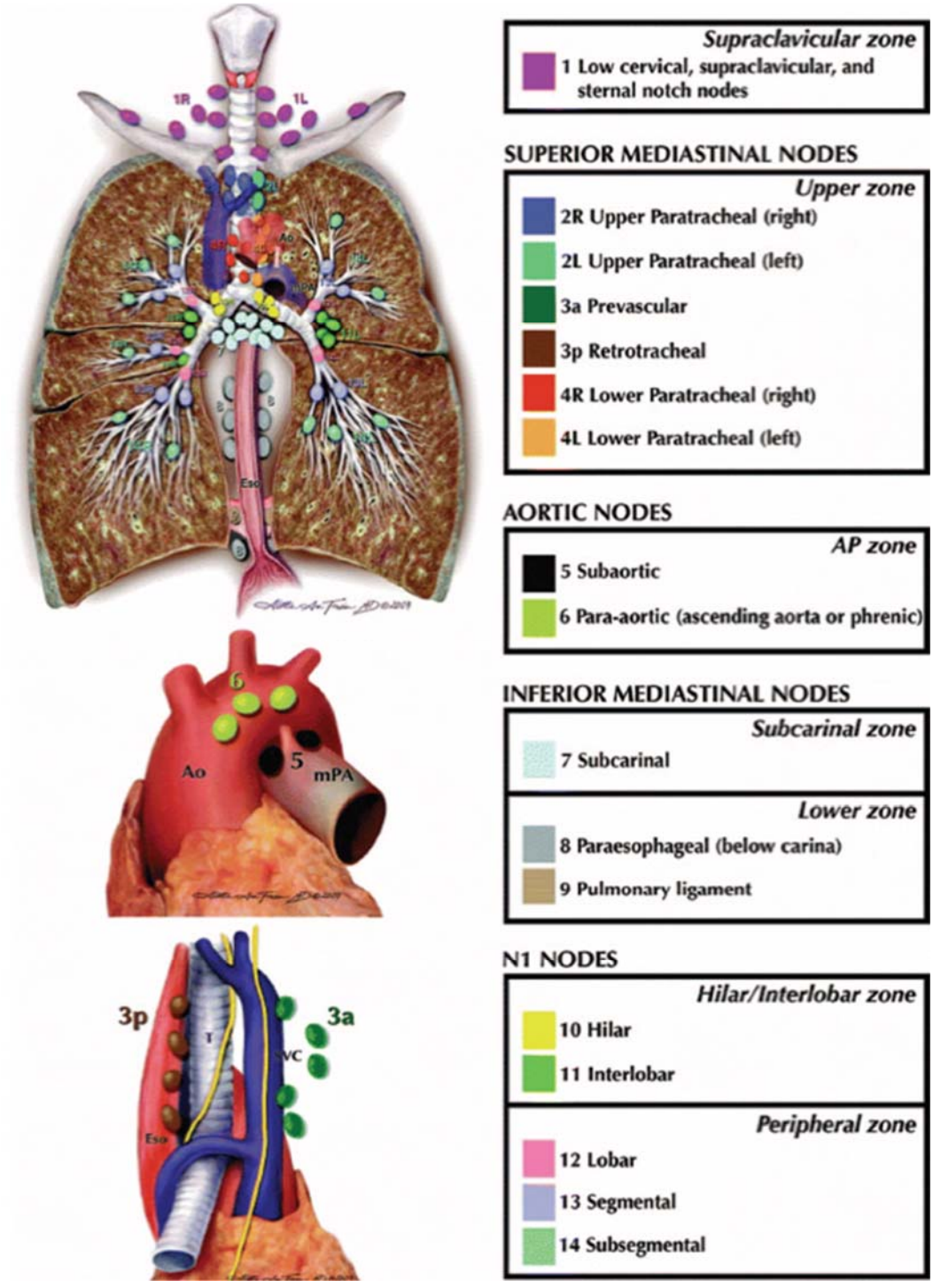
This chapter will review the current system for staging non-small cell lung cancer (NSCLC), the different diagnostic and staging options, and a brief discussion about the importance of mutation analyses in guiding treatment for patients with advanced-stage disease. I will then provide a summary of our center's approach towards lung cancer diagnosis and staging with supporting literature where available.

Staging Background

The current staging system became the worldwide standard in 2017 which continues with the pre-existing method of assessing tumor size and its effect on the surrounding lung tissue or its

interaction with non-lung tissue (T), the extent of spread of lung cancer to lymph nodes (N) (Figure 1), and the presence or absence of metastatic spread of lung cancer outside of lung tissue (M).[1] The TNM classification system is then used to derive a stage of NSCLC, which ranges from localized disease (IA) to wide-spread disease (IV), providing information on expected prognosis and survival. Each edition builds on an international database of patients with lung cancer to provide a common basis for communicating the extent of cancer and prognosis.

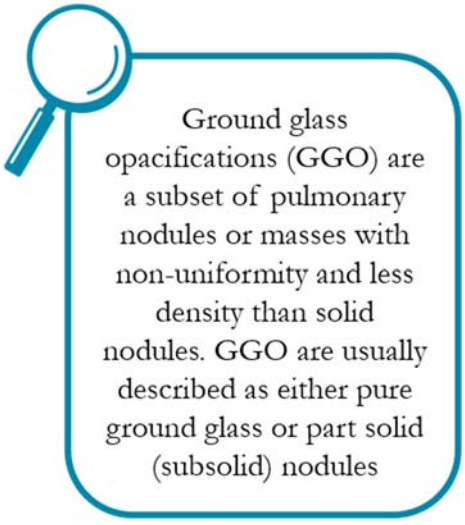
Figure 1: Schematic of the lymph node stations within the chest[1]



Diagnostic and Staging Modalities

PET is an imaging technique that captures the level of metabolic activity of different tissues. Patients are given an intravenous injection of 2-(18F) 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). Several studies have demonstrated the accuracy of PET for the diagnosis of lung cancer in pulmonary nodules and masses as well as for staging evaluation.[2-3] In 2009, a study demonstrated that combined PET-CT improves the selection of patients with known or suspected lung cancer for surgery by decreasing the number of patients with advanced-stage lung cancer undergoing surgery.[4] A subsequent retrospective study evaluating patients with clinical stage IA non-small cell lung cancer found PET-CT to have a sensitivity of 44%, a specificity of 83%, a positive predictive value of 78%, and a negative predictive value of 91% compared to surgery for detection of mediastinal lymph node metastases.[5] With the approval of lung cancer screening in the United States, PET-CT has a role in selected patients to aid in the risk stratification of indeterminate lung nodules measuring greater than 10mm in diameter or with evidence of growth if the lesion is less than 10mm.[6]

We now have more clarity regarding making decisions about which patients should undergo invasive mediastinal staging in the setting of negative PET-CT results. Recent research evaluated 284 consecutive patients with PET-CT staged T1 to 2, N0 non-small cell lung cancer who then underwent either endobronchial ultrasound or mediastinoscopy sampling of mediastinal lymph nodes.[7] 7% of these patients were found to have occult (hidden) N2 disease with PET-CT and EBUS / mediastinoscopy having negative predictive values of 92.9% and 96.3%, respectively. In addition, occult N2 disease was more likely to be present in patients with T2 disease compared with those with T1 disease (11.8% compared with 3.6%, p=0.009). Pure solid lesions were also more likely to have N2 disease compared to tumors with any ground glass (12.6% compared to 3.1%, P < 0.001). And patients with central tumors were more likely to have occult N2 disease compared to patients with peripheral lesions (17.5% compared with 4.4%, p < 0.001). Consequently, the authors recommend invasive mediastinal staging for patients with central and solid tumors, while those with peripheral ground glass lesions may not warrant such an approach.



Detecting brain metastases is challenging with PET-CT as FDG is avidly taken up by brain tissue. One retrospective study suggests this imaging modality may assist in selecting patients for brain MRI with a sensitivity of 72% and specificity of 100%.[8]

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. Therefore, it is important to obtain tissue confirmation 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 subcentimeter lung nodules as well as small lymph nodes.[9] In addition, some lung cancers, such as bronchioloalveolar carcinomas and carcinoid tumors have been reported to have negative PET imaging results.[10] Patients with poorly controlled diabetes mellitus or high blood glucose levels 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.[11] In addition, the change in activity with chemotherapy correlates with histopathologic response.[12]

Re-evaluation by PET/CT after neoadjuvant chemotherapy in a 2016 retrospective study of 17 patients with non-small cell lung cancer with N2 lymph node involvement demonstrated a sensitivity of 100% and specificity of 94%.[13]

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

EBUS-FNA is a minimally invasive technique that complements mediastinoscopy by its ability to access lymph node stations 2, 3, 4, 7, 10, and 11. (Table 1)

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	5
Extended Cervical Mediastinoscopy	6
VATS	Ipsilateral mediastinal lymph nodes

EBUS is a bronchoscopic technique that utilizes ultrasound to identify and permit real-time ultrasound-guided needle biopsy of paratracheal, hilar, and interlobar lymph nodes. In 2003 a group reported their initial experience with EBUS-FNA of mediastinal and hilar lesions under general anesthesia.[14] These investigators reported accurate sampling of lymph nodes from stations 1, 2, 4, 7, and 10, with nine diagnoses of malignancy and two diagnoses of benign disease. Subsequent studies have demonstrated that EBUS-FNA is a minimally invasive, highly accurate 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 that uses esophagogastroduodenoscopy to sample paraesophageal 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 structures below the diaphragm, including the celiac nodes, and the adrenal glands.

Studies evaluating EUS-FNA for lung cancer, excluding one, have demonstrated sensitivities and specificities for malignancy of 87% - 96% and 100%, respectively, which is comparable to EBUS-FNA.[15-16] Overall, these studies demonstrate that EUS is a valuable diagnostic and staging tool for patients with suspected or known NSCLC.

Guidance-assisted Bronchoscopy

One of the most significant limitations to using bronchoscopy for the diagnosis of early-stage lung cancer is the inaccuracy of bronchoscopy directed biopsy of lung nodules. Electromagnetic navigation can overcome this limitation for select lesions that are more than 1 to 1.5 cm in diameter. This system marries CT imaging with bronchoscopy allowing the physician to determine the position of the bronchoscope and a special guidance catheter within the lung of a patient. By performing pre-procedural planning, the physician is now able to maneuver a guidance catheter through a patient's airways to biopsy lung nodules that are concerning for cancer. In addition, the system allows the placement of fiducial markers around the lung nodule to facilitate treatment with stereotactic radiation.

The major limitations to the success of the procedure include:

- the patient's ability to tolerate bronchoscopy and its associated sedation,
- the size of the lesion of interest as well as its location,
- the experience of the physician performing the procedure, and,
- the actual biopsy is not performed under real-time visualization of the target.

In addition, this procedure is not recommended for patients who have an implanted cardioverter defibrillator or pacemaker due to potential interference between these devices and the electromagnetic field created by the bronchoscopy system.

Risks of the procedure include pain, bleeding, or a collapsed lung. However, these risks occur less frequently when compared to CT-guided biopsy or CT-guided placement of fiducial markers.

Radial Endobronchial Ultrasound Bronchoscopy (rEBUS)

An alternative approach is to utilize a radial endoscopic ultrasound. This device can be inserted through a standard bronchoscope and maneuvered into the lung tissue to help localize a lung nodule for biopsy. The major limitation with this modality is that the bronchoscopist must maneuver the probe to the nodule with studies suggesting that in 6 to 31% of cases, the lung nodule could not be visualized.[17-20] In addition, as with the electromagnetic navigational bronchoscopy system, the limitation of this technique is that the ultrasound probe is then removed so that a biopsy catheter can be inserted. Therefore, the biopsy is not under real-time visualization of the target.

If both technologies are available, using the guidance system to maneuver the catheter to the lesion of interest, followed by confirmation that the catheter is in the correct position using the radial ultrasound through the catheter, improves the accuracy of the biopsy. But this still leaves the operator without real-time imaging during the actual biopsy. [21]

Cervical and Anterior

Mediastinoscopy involves an incision at the base of the neck just above the suprasternal notch, followed by the insertion of a mediastinoscope 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 allows access to the para-aortic lymph nodes. (station 6) The video mediastinoscope permits easier handling and visualization during the procedure, as well as potential access to posterior subcarinal lymph nodes.[22-23]

The major limitations to performing mediastinoscopy are bleeding disorders, severe kyphosis, contraindications to general anesthesia, tracheostomy, or previous chest radiation. The scarring and fibrosis associated with radiation or prior procedures significantly increase the risk of damage to mediastinal organs and vasculature during attempted blunt dissection with the mediastinoscope.

Anterior mediastinoscopy (Chamberlain procedure) permits the evaluation of the aortopulmonary window lymph nodes. (Table 1) This involves an incision at the level of the 2nd or 3rd intercostal space to the left of the sternum and the placement of a mediastinoscope to visualize and biopsy visible lymph nodes. The procedure has not been extensively studied, but 2 studies have reported false negative rates of 0% and 11%.[24-25] It is generally well tolerated, and most patients can avoid an overnight hospital stay.

"When it is obvious that the goals cannot be reached, don't adjust the goals, adjust the action steps."
- Confucius

Thoracentesis

Patients with pleural effusions that layer at least 1 cm on lateral decubitus chest radiographs are easily assessed for malignancy by thoracentesis. This procedure requires only local anesthesia with 1% lidocaine and the placement of a temporary drainage catheter to remove the available pleural fluid. The procedure can be performed in an outpatient setting and is generally well tolerated by the patient. One often discussed complication is lung collapse, also referred to as pneumothorax. A prospective study of 506 thoracenteses in 370 patients reported 18 (4%) pneumothoraces.[26] Additional complications include, catheter insertion site pain, coughing, hemothorax, localized infection, intra-abdominal organ injury, and post-expansion pulmonary edema. Contraindications to performing thoracentesis include, bleeding disorders unless reversible, infection or abscess of the overlying skin, 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.[27] The rate of detection is dependent upon the type of carcinoma, the number of pleural fluid specimens obtained, and the extent of pleural involvement.[28]

Medical Thoracoscopy (Pleuroscopy)

Pleuroscopy is a procedure that allows access to the pleural space (the potential space between the inner surface of the chest wall and the outer surface of the lung) using an endoscope. In the setting of a diagnosis of or suspicion for lung cancer with a large pleural effusion, pleuroscopy can allow removal of pleural fluid for diagnosis and staging, while also potentially relieving shortness of breath, or chest discomfort, related to the presence of the fluid. In addition, if there are suspicious lesions seen on CT imaging or during the procedure along the inner chest wall lining, biopsies of these lesions can be done. Studies have demonstrated a high diagnostic yield for pleural effusions

If the pleural effusion is refractory and causing symptoms as described above, medical thoracoscopy can also assist with pleurodesis. These interventions can also be performed during a video-assisted thoracoscopic surgery, as described in the next section of this chapter but a medical thoracoscopy is usually more limited in its scope and more easily tolerated. It is usually performed by a pulmonologist under conscious sedation with local anesthesia, or the patient can undergo general anesthesia. Successful pleurodesis reported in recent publications ranges between 78% and 88% for malignant effusions with a lower success rate for malignant effusions related to lung cancer (72.3%).[29-30]

Complications of medical pleuroscopy include pain usually from the chest tube placed at the end of the procedure, infection, bleeding, a persistent air leak resulting from a tear of the visceral pleural surface or subcutaneous emphysema which is the result of air entering the subcutaneous tissue. More serious but rare complications include death, development of fluid in the lung when it re-expands after the fluid has been removed, or air entering the bloodstream. If cancer is present in the pleural space, there is also a risk of seeding the surgical site with cancer cells resulting in tumor growth through the site. This complication is more common with mesothelioma.

In summary, a medical thoracoscopy is a diagnostic option for pleural effusions that remain undiagnosed despite thoracentesis as well as a therapeutic approach for pleurodesis in refractory pleural effusions.

Video-Assisted Thoracoscopic Surgery

VATS or thoracoscopy is a surgical method that permits the surgeon to evaluate the pleural space and ipsilateral lymph nodes. The procedure requires general anesthesia, single lung ventilation, and usually a short hospital stay but is usually well tolerated with an average complication rate of 2%.[31] The most common complication was prolonged air leaks.

An important application of VATS is to directly visualize tumors that are radiographically staged T4. Several studies support the use of VATS to confirm T4 lesions designated by CT prior to categorizing the cancer as unresectable.[32] Thoracoscopy can also evaluate the pleural space for malignancy in patients with pleural effusions that are cytologically negative on repeated thoracentesis or in patients with pleural abnormalities detected on CT. In addition, VATS provide 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 Ultrasonography Guided Fine Needle Aspiration

Patients with suspected or known NSCLC who are found to have extra-thoracic disease on PET-CT imaging should undergo tissue biopsy to confirm a metastatic focus. 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.

Targetable Mutations in Lung Cancer

The diagnostic evaluation of a patient with suspected lung cancer in the early 21st century includes 3 specific goals:

1. Does the patient have lung cancer and if so, what type of lung cancer is present?
2. What is the pathologic stage of lung cancer?
3. If appropriate, are specific mutations present in the lung cancer that could be targeted by a specific therapy?

Using the techniques described above, the ideal for an individual patient would be to achieve these 3 goals in a single procedural setting. Currently, this is possible but as the number of targetable mutations increases, we may reach a point where a separate diagnostic procedure is needed to obtain enough tissue for all the testing needed to determine the most appropriate first-line treatment.

Thoracic Tumor Board Diagnostic and Staging Algorithm

Today, most cancer centers have Tumor Boards which have been shown to improve the staging of cancer. Our center has established a Diagnostic Thoracic Tumor Board that brings together the knowledge and expertise of physicians from pulmonology, oncology, radiology, nuclear medicine, and thoracic surgery. The group has developed an evidence-based algorithm for the diagnosis and staging of patients with suspected or known lung cancer (Figure 2). It is our opinion that patients with suspected or known lung cancer should 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 to evaluate for mediastinal disease and possible distant metastases. 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 thoracotomies performed in patients with highly-suspected or newly diagnosed NSCLC.[9] Futile thoracotomy 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 malignancy or death from any cause within 1 year of randomization. A significant decrease in futile thoracotomies 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.[10]

Diagnosis if not previously made and staging is achieved by biopsy of the PET-avid lesion that would achieve the most advanced TMN stage. Biopsy methods for lymph nodes 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 recommended prior to proceeding to surgical resection.

The reasons above are the reason our team believes so strongly in the importance of having a multidisciplinary panel of physicians to improve the timely application of appropriate staging and diagnostic studies.

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 thoracotomies.

Questions to Ask Your Doctor about Your Lung Cancer Diagnosis

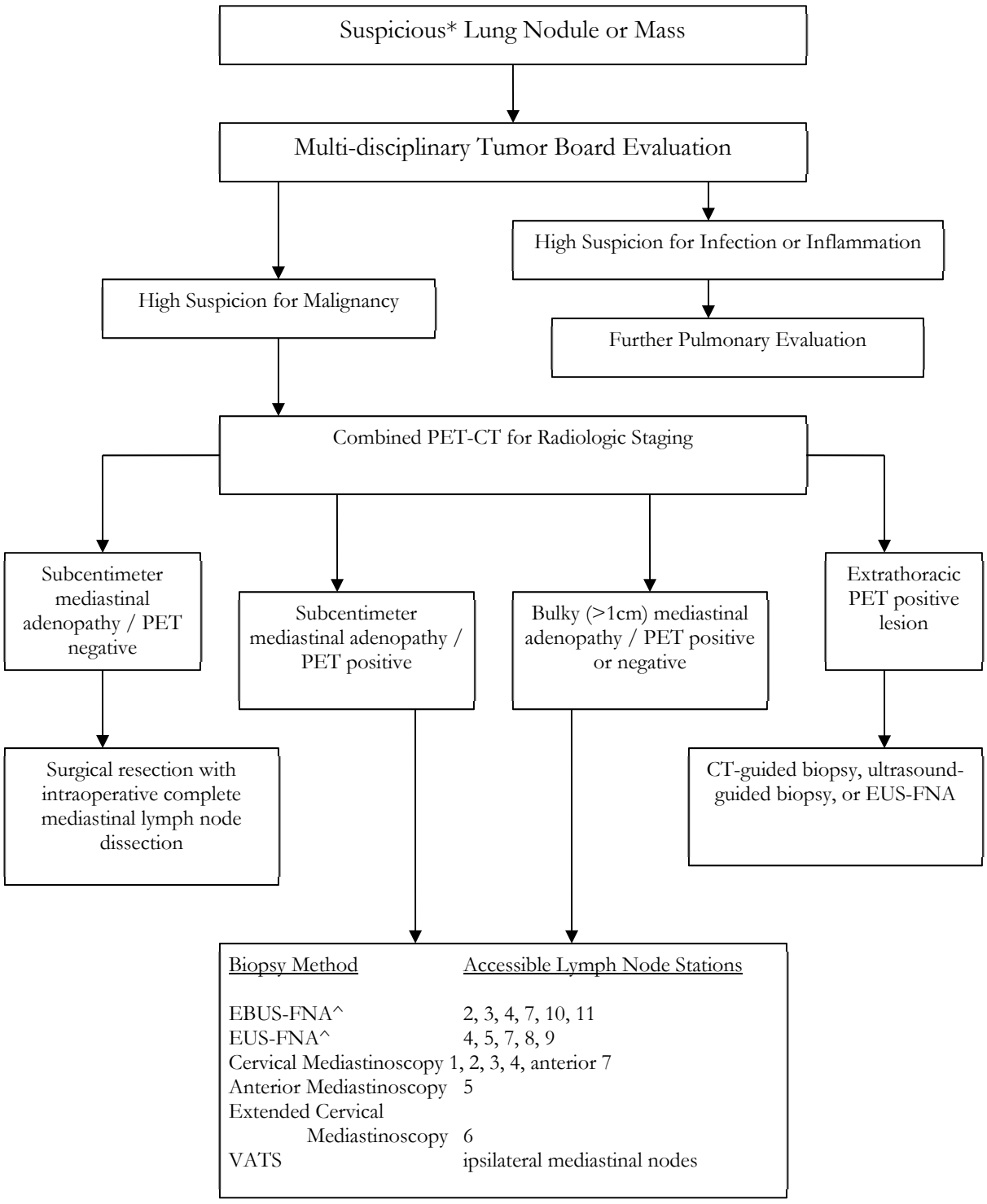
- What type of cancer do I have?
- What is the stage of my cancer?
- Has it spread to other areas of my body?
- Will I need more tests before treatment begins? Which ones?
- Will you help me find a doctor to give me another opinion on the best treatment plan for me?
- How serious is my cancer?
- What are my chances of survival?
- Who can I contact with any questions or problems I may experience?
- Should a family member or friend come with me to my treatment sessions?

"Though you feel like you're not where you're suppose to be, you shouldn't worry because the next turn you take, it will lead you to where you wanna go.

- Ellen

Figure 2.

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 should undergo surgical lymph node sampling for confirmation

Notes

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