Chapter

1

The Diagnosis and Staging of Lung Cancer

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Lung cancer is the leading cause of cancer-related mortality in the United States. Swift diagnosis, simultaneous staging, and performing mutation analyses when indicated permits rapid initiation of appropriate treatment which is the objective of the evaluation of every patient with a suspected or known lung cancer. A multi-disciplinary diagnostic thoracic tumor board evaluation guiding the use of combined positron emission tomography-computed tomography, endobronchial ultrasound guided fine needle aspiration, endoscopic ultrasound guided fine needle aspiration, electromagnetic navigational bronchoscopy, mediastinoscopy, thoracentesis, video-assisted thoracoscopic surgery, and or computed tomography or ultrasound guided fine needle aspiration is critical in our opinion to achieve this goal.

Introduction

Lung cancer remains the leading cause of cancer-related mortality in the United States despite advances in chemotherapeutic options and surgical technique. 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, stereotactic radiotherapy, 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.

In this article, I 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[1] published in 2010 continues with the pre-existing method of assessing tumor size and its affect 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). The TNM classification system is then used to derive a stage of NSCLC which ranges from localized disease (stage IA) to wide-spread disease (stage IV) providing information on expected prognosis and survival.

Diagnostic and Staging Modalities

Combined PET-CT

PET is an imaging technique that captures the level of metabolic activity of different tissues. Patients are given an intravenous 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[2] as well as for staging evaluation.[3] A study by Gould (2001) reports that PET fails to detect lung cancer in 3.2% of cases but 22.2% of the time it falsely suggests the presence of cancer.[4] More recently, Fischer (2009) 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.[5] An earlier trial found similar benefits with PET imaging alone.[6]

Delayed PET imaging is also of interest. Cancer continues to increase FDG uptake over 1.5 to 5 hours.[7] Thus, an increase in the SUV of nodules, masses, or lymph nodes over time may suggest a cancerous etiology.[8] However, a more recent retrospective study of 47 patients with non-small cell lung cancer found that dual time point imaging did not improve the accuracy of lymph node staging.[9]

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 while 97 untreated patients with lung cancer had a mean SUV of 5.29 $\pm$ 2.72.[10] This emphasizes the importance of obtaining 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.[11] In

addition, some lung cancers such as bronchioloalveolar carcinomas and carcinoid tumors have been reported to have negative PET imaging results.[12] 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.[13] In addition, the change in activity with chemotherapy correlates with histopathologic response.[14]

Endobronchial Ultrasound Guided Fine Needle Aspiration (EBUS-FNA)

Prior to the development of EBUS-FNA, patients who were candidates for surgical resection of suspected or diagnosed lung cancer often required a staging mediastinoscopy to evaluate for potential spread of cancer to lymph nodes in the mediastinum, the area within the chest located between the two lungs that contains the trachea, esophagus, heart, and the great vessels. However, mediastinoscopy is associated with a complication rate of as high as 2-3%, and more importantly is unable to sample certain lymph nodes such as hilar (station 10, 11, 12), para-aortic (station 6), or aortopulmonary window (station 5) lymph nodes. Consequently, subsequent thoracotomy has been reported to result in no tumor resection in up to 10% of patients because of detection of advanced stage lung cancer at the time of surgery.[15] 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 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 lesions under general anesthesia.[15] These investigators reported accurate sampling of lymph nodes from stations 1, 2, 4, 7, and 10, with 9 diagnoses of malignancy and 2 diagnoses of benign disease. Yasufuku (2004) reported their experience with 70 patients who underwent EBUS-FNA of mediastinal (stations 2, 3, 4, and 7) and hilar (stations 10 and 11) adenopathy under local anesthesia, reporting a sensitivity and specificity for malignancy of 95.7% and 100%, respectively.[16] Five of the sampled lymph nodes were described as 1 cm or less in diameter with the 2 false-negative biopsies occurring in lesions between 1.1 and 2.0 cm. Yasufuku (2005) published additional EBUS-FNA experience with 105 patients reporting a sensitivity and specificity for malignancy of 94.6% and 100%, respectively.[17] Additional studies report sensitivities and specificities for malignancy of 88.9% - 94% and 96.4% - 100%, respectively.[18] A recent retrospective study out of Australia demonstrated that EBUS alone can achieve a false negative rate for mediastinal lymph node sampling of only 4.9%.[19] 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, excluding one, have demonstrated sensitivities and specificities for malignancy of 87% - 96% and 100%, respectively which is comparable to EBUS-FNA.[20] However, one study reported a lower sensitivity and specificity of 86% and 83%, respectively.[21] 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. A recent advance in bronchoscopy called electromagnetic navigational bronchoscopy (ENB) is now able to overcome this limitation for select lesions that are more than 1 to 1.5cm 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. The guidance catheter is made up of a flexible inner wire which emits electromagnetic pulses inside of a plastic sheath which is then left in place once the catheter has been successfully maneuvered to the lung nodule. However, the actual biopsy is performed assuming the catheter position is accurate and in close proximity to the lung nodule. 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 that the actual biopsy is not performed under real-time visualization of the target. This final limitation is significant because the position of the catheter relative to the target nodule may change as the patient is breathing and the catheter may be dislodged when biopsy tools are inserted into the sheath leading to the nodule. Consequently, the diagnostic accuracy of this biopsy modality for peripheral nodules ranges between 69-74%.[22]

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 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 probe. This device can be inserted through a standard bronchoscope and then passed through the patient's airways to the lung nodule at which time ultrasound can be used to confirm the presence of the lesion either adjacent to or surrounding the probe. 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.[23-26]

Due to this limitation, some studies have examined the utility of employing an electromagnetic navigational system to maneuver a guidance catheter to the peripheral nodule and then passing the radial endobronchial ultrasound probe through the guidance catheter to confirm accurate localization of the lesion of interest. Eberhardt (2007) found that the diagnostic yield with rEBUS alone was 69% and with ENB alone was 59%. But using ENB to maneuver the catheter to the lesion of interest followed by rEBUS to confirm localization of the lesion prior to biopsy increased diagnostic yield to 88%.[22] Chee (2013) also found that the diagnostic yield from rEBUS alone was 43% which increased to 50% when ENB was combined with rEBUS.[26-27]

Cervical and Anterior Mediastinoscopy

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, introduced in 1994,[28] permits easier handling and visualization during the procedure as well as potential access to posterior subcarinal lymph nodes.[29]

A number of studies have evaluated the performance of mediastinoscopy. The largest was a retrospective review of all mediastinoscopies performed by the Cardiothoracic Surgery Division at Washington University School of Medicine between January 1988 and September 1998.[30] 1,745 patients underwent cervical mediastinoscopy with known or suspected lung cancer. 422 (24%) of these patients were found to have N2 or N3 disease. 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 thoracotomy. N2 nodal involvement was detected at the time of thoracotomy 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%[31] and 9%.[32] About half of the false negative results (42-57%) were due to lymph nodes that are not accessible by mediastinoscopy.[33]

The major limitations to performing mediastinoscopy are bleeding disorders, severe hyphosis, 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%[34] and 11%.[35] It is generally well tolerated and most patients can avoid an overnight hospital stay.[33]

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.[36] Additional complications include catheter insertion site pain, coughing, hemothorax, localized infection, intraabdominal 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.[37] The rate of detection is dependent upon the type of carcinoma, the number of pleural fluid specimens obtained, and the extent of pleural involvement.[38]

Video-assisted Thoracoscopic Surgery (VATS)

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%.[39] The most common complication was prolonged air leaks.

An important application of VATS is to directly visualize tumors that are radiographically staged T4. Eggeling (2002) found that thoracoscopy upstaged 4 patients after discovering cancerous fluid collections while down staging 6 patients thought to have mediastinal invasion on computed tomography (CT).[40] The authors report a sensitivity and specificity for the accurate prediction of pathologic T4 lesions using CT to be 64.7% and 69%, respectively. This and additional publications[41] support the use of VATS to confirm T4 lesions designated by CT prior to categorizing the cancer as unresectable. 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 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 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 or immunomodulatory targets 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 so it is absolutely critical that the proceduralist is aware of the need to obtain an adequate amount of diagnostic tissue to accomplish these 3 goals. Currently, this is possible but as the number of targeted mutations increases, we may reach a point where a separate diagnostic procedure is needed to obtain enough tissue for all of the testing needed to determine the most appropriate first line treatment. An exciting and promising area of investigation is the use of a blood sample or a "liquid biopsy" to assess for multiple mutations but this is beyond the scope of this chapter to review.

Epidermal Growth Factor Reception (EGFR)

The most prevalent targetable mutation is epidermal growth factor receptor (EGFR). This particular mutation is most frequently found in lung adenocarcinomas and is more frequent in women, never smokers, and patients of East-Asian origin. The FDA has approved multiple treatment options targeting EGFR.

Anaplastic Lymphoma Kinase (ALK) – Rearrangements

ALK rearrangements are primarily found as fusions to echinoderm microtubule-like protein 4 (EML4) and have been detected in 4%[42] to 7% of NSCLCs.[43] Patients with an EML4-Alk mutation are more likely to have lung adenocarcinoma, more likely to be light to never smokers, more likely to be men, and tend to be younger.[44] There are FDA approved treatments directed against this mutation.

Kirsten Rat Sarcoma Virus (KRAS)

While rare (1 to 2% of NSCLCs), mutations of ROS1 are more likely to be found in patients with lung adenocarcinomas who were never smokers and are younger in age. The FDA has approved treatments directed against this mutation.

C-ros Oncogene 1 (ROS1)

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Programmed death 1 (PD-1) / Programmed death ligand 1 (PD-L1)

Some tumor cells are able to persist by evading the immune system by expressing on their cell surface PD-L1 which then interacts with T-cell surface receptor PD-1. This interaction then down-regulates the T-cell which allows the tumor cell to escape clearance by the immune system. Therapies targeting PD-1 or PD-L1 aim to prevent this T-cell - tumor cell interaction thereby restoring the anti-tumor function of the native immune system. This area of oncology treatment, immunotherapy, represents an exciting new treatment option for patients with non-small cell lung cancer who have had recurrent disease following primary treatment.

Additional Mutations

With the identification of multiple potential cancer driving mutation targets, many oncologists are approaching lung cancer as a chronic disease in which serial assessment for targetable mutations may identify additional salvage therapy options over time. A detailed review of these potential treatments and their application is beyond the scope of this chapter.

Who should undergo mutation analyses?

Currently, all patients with pathologically confirmed advanced-stage non-small cell lung cancer should have biopsy specimens sent for mutation analyses as directed by the medical

oncologist to assist in their treatment planning regardless of gender, ethnicity, or smoking history. Interestingly, a recently published meta-analysis has revealed a discordance rate of 12% between the primary tumor and metastatic lymph node tissue for the presence of an EGFR activating mutation where the primary tumor is more likely to harbor the mutation.[45] The clinical significance of this finding is not yet clear.

The key point to emphasize is that the goal of the proceduralist performing the biopsy is to keep the 3 above-mentioned goals in mind - diagnosis, stage, and if appropriate tissue for mutation analyses. So, obtaining enough tissue to perform these 3 goals is critical to the evaluation and management of patients with advanced stage non-small cell lung cancer.

Thoracic Tumor Board Diagnostic and Staging Algorithm

Our center has established a Diagnostic Thoracic Tumor Board that brings together the knowledge and expertise of our pulmonologists, oncologists, radiologists, and thoracic surgeons to evaluate patients with suspected or confirmed lung cancer employing standardized protocols to assist in the decision to pursue invasive testing versus serial imaging studies.[46-49] 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.[5] 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.[6]

Diagnosis if not previously made and staging is achieved by biopsy of the PET-avid lesion that would achieve the most advanced pTMN 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.

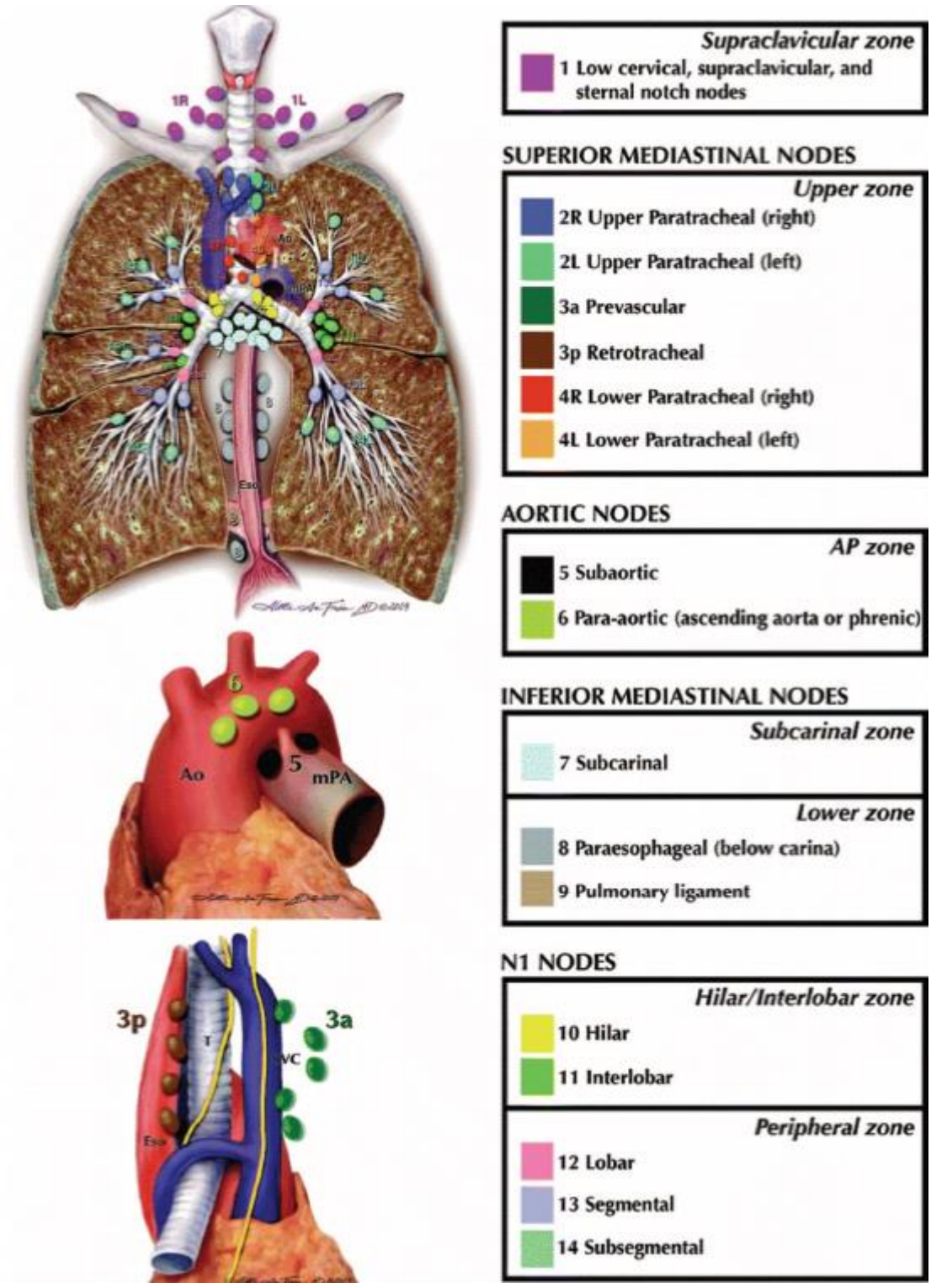
Conclusion

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. 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	5
Extended Cervical Mediastinoscopy	6
VATS	Ipsilateral hilar and mediastinal lymph nodes

Figure 1: Schematic of the lymph node stations within the chest – derived from Figure 4. of Chest. 2009;136:260-71.



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