



Milton Rochman. *Hopes and Dreams*. Acrylic on board, 36" × 48".
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*Newer techniques are improving
the accuracy of mediastinal
staging of non-small-cell
lung cancer.*

Mediastinal Staging of Non-Small-Cell Lung Cancer

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Background: *The goal of preoperative staging of non-small-cell lung cancer (NSCLC) is to identify patients who will benefit from surgical resection. Various imaging and less invasive modalities are now available to improve therapy decision making.*

Methods: *The available staging methods are reviewed, including conventional methods, surgical staging, and less invasive means of pathologic staging.*

Results: *Computed tomography alone is not sufficiently accurate to stage the mediastinum, and further definitive testing is usually indicated. Positron emission tomography, along with mediastinal biopsy techniques using transbronchial needle aspiration or endoscopic ultrasound, has the potential to improve the accuracy of pretreatment staging.*

Conclusions: *Every effort should be made to accurately discriminate between benign and malignant mediastinal disease. With further research on the proper roles of these new imaging modalities, they will become more widely used and will improve the accuracy of pretreatment staging of NSCLC.*

Introduction

Bronchogenic carcinoma is the leading cause of cancer death in both men and women. In 2001, it is estimated that more than 169,000 people in the United States will be diagnosed with lung cancer and

157,000 people will die of the disease.¹ Non-small-cell lung carcinoma (NSCLC) accounts for approximately 80% of all bronchogenic carcinomas, with small-cell lung carcinoma (SCLC) accounting for the remainder. After primary pathologic diagnosis of lung cancer, staging becomes the most important task. The staging process begins by evaluating the position and size of the primary tumor. Next, extent of spread to thoracic structures, including mediastinal lymphatics, and to extrathoracic organs is assessed in order to distinguish resectable from unresectable disease.

With better understanding of prognosis and new advances in treatment, the staging of lung cancer is a constantly evolving process. In 1997, the staging sys-

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tem of NSCLC was changed to provide greater specificity for identifying patients with similar prognosis and treatment options.² TNM staging as defined by this consensus is beyond the scope of this article but is reported elsewhere.^{2,3}

In general, stage I-II disease is treated with surgery alone. Mediastinal involvement is an ominous sign for prognosis and is important for determining resectability. Stage III (locoregional disease) has historically been treated with chemotherapy and radiotherapy. Recent studies^{4,6} suggest that surgery may be added to the chemotherapy and radiotherapy for certain subgroups of patients. Stage IIIB disease with contralateral mediastinal involvement is a contraindication to surgery. Finally, chemotherapy or supportive care is preferred for most stage IV disease. In rare instances, surgery has been offered for resection of a primary lung tumor with concomitant resection of an isolated brain metastasis.

The first step in mediastinal staging involves radiographic imaging with contrasted computed tomography (CT). Lymph nodes are defined as pathologic based solely on short axis size greater than 1 cm.⁷ However, CT is not sufficiently accurate to solely stage the mediastinum, and further definitive testing is usually indicated. If there is evidence of mediastinal adenopathy, imaging is then followed by mediastinal sampling, usually through mediastinoscopy. If there is no evidence of mediastinal adenopathy on CT, some thoracic surgeons sample the mediastinal lymph nodes at the time of thoracotomy. The goal of preoperative staging is to identify patients who would not benefit from surgical resection, thus avoiding the morbidity and mortality associated with major thoracic surgery. These patients often have significant pulmonary and cardiovascular comorbidity secondary to age and tobacco use. This review examines the methods used to stage NSCLC, including newer staging techniques (positron emission tomography imaging), less invasive means of pathologic staging (transbronchial lymph node sampling, percutaneous transthoracic needle aspiration, and endoscopic ultrasound-guided fine-needle aspiration of the mediastinum), as well as the more conventional techniques.

Computed Tomography/ Magnetic Resonance Imaging

Computed tomography is currently used to radiographically stage the mediastinum in patients with primary bronchogenic cancer. The accuracy of CT in staging the mediastinum has been controversial over the last 20 years largely due to variability of patient selection and study design. Mediastinal nodes larger

than 1 cm on short axis are defined as pathologic.⁷ One objective of CT is to identify patients who do not have mediastinal disease so they can proceed to resection without the need for further mediastinal staging. It has been reported that 3% to 16% of patients with mediastinal lymph nodes less than 1 cm on CT have tumor involvement at mediastinoscopy, thus rendering them unresectable.^{8,9} A goal of preoperative staging with CT is to spare patients with known mediastinal involvement the morbidity of surgical staging. This may not be possible as up to 30% of patients with enlarged nodes on CT do not have evidence of neoplastic disease at surgical exploration of the mediastinum.¹⁰ Put simply, if all lymph nodes greater than 1 cm were assumed to be cancerous, 30% of patients with otherwise resectable tumors would be denied potentially curative surgery.

Several factors affect the accuracy of CT for staging bronchogenic carcinoma. Accuracy is lessened by central tumors, obstructive pneumonia, and prior granulomatous disease. Peripheral tumors may increase the accuracy.⁸ A meta-analysis of CT accuracy for assessment of mediastinal lymph node involvement in bronchogenic carcinoma found an overall sensitivity and specificity of 79% and 78%, respectively.¹¹

Magnetic resonance imaging (MRI) is often helpful in evaluating direct invasion of tumor into mediastinal structures including the heart, superior vena cava, aorta, and subcarinal area. With respect to staging of mediastinal lymph nodes, MRI has been shown to be no better than conventional CT imaging. It suffers from limited spatial resolution and the inability to obtain images during held respiration. This can lead to blurring of separate lymph nodes into one large node. A thorough review of this modality is reported elsewhere.¹²

Positron Emission Tomography

Given the shortfalls of CT staging, a more accurate method of staging patients nonsurgically is needed. Positron emission tomography (PET) was introduced recently as an alternative or complementary means of staging disease. Cancer has enhanced metabolic activity and avidly utilizes glucose. Patients are injected with fluorine-18 fluorodeoxyglucose (FDG) and imaged using PET. To identify malignancy, PET depends on demonstrating metabolic differences between tumor and normal tissue. This is determined by tumor size and metabolic activity. Potential advantages of PET imaging include the identification of tumor foci in normal-sized lymph nodes, which could reduce the number of surgical procedures performed for unresectable disease.

To measure the ability of PET to detect metastases in mediastinal lymph nodes, Pieterman and colleagues¹³ prospectively compared PET imaging with a standard approach to staging. The sensitivity and specificity of PET were found to be 91% and 86%, respectively, while CT was 75% sensitive and 66% specific. The use of PET resulted in different clinical staging in 62 of 102 patients, with stage being lowered in 20 patients and raised in 42 patients. However, 17% of patients had false-positive “hot spots” in the mediastinum or at distant sites. The false-positive results were mainly due to inflammation, often from obstructing endobronchial tumors. Other studies have also noted the risk of false-positive results due to inflammatory processes.^{14,15} Valk and colleagues¹⁶ examined PET for whole-body staging as well as for mediastinal staging. Mediastinal PET and CT findings were compared with results of surgical staging in 76 patients. The sensitivity and specificity of PET for diagnosing mediastinal disease were 83% and 94%, respectively, while CT had a sensitivity of 63% and specificity of 73%. Overall, they found a 20% improvement in accuracy of PET over CT imaging for mediastinal staging of NSCLC. With respect to the size of mediastinal lymph nodes, a recent study by Gupta et al¹⁷ compared small nodes (less than 1 cm) and large nodes (greater than 1 cm) using CT, PET, and histologic sampling. PET was found to be reliable and accurate for detecting lymph nodes of less than 1 cm, with sensitivity and specificity of 97% and 82%, respectively.

In addition to staging the mediastinum, PET has shown promise for identifying distant metastasis. In the study by Valk et al,¹⁶ PET revealed extrathoracic

metastasis not suspected by conventional means in 11% of patients. Surprisingly, there were no reported false-positive results. In 19 of 99 patients, CT imaging suggested metastasis at distant sites and PET imaging did not. Follow-up in 14 of these patients remained negative with one false-negative result.

The brain and the genitourinary system are two organ systems where PET is less accurate for identifying malignancy. The brain takes up glucose, and the genitourinary system concentrates and excretes the radio-tracer. These areas avidly enhance, making it difficult to differentiate metastatic disease from normal activity.

In summary, PET appears to be more accurate than conventional CT scanning for staging the mediastinum (Table). Unlike CT, PET relies on increased metabolic activity rather than solely on the size of the lymph nodes. It can identify not only disease in nodes less than 1 cm, but also unsuspected extrathoracic metastasis. Disadvantages include difficulty with accurate anatomic placement of lesions as well as with extent of local tumor involvement, both necessary for staging. CT scanning is still needed in the majority of patients. Also, in two extrathoracic areas, the brain and the genitourinary system, PET is not as accurate for imaging. As the brain is one of the most common sites of distant metastasis, symptoms of spread to the brain need to be investigated with MRI or CT.

Although PET scanning is still in its infancy, it has been shown to be a cost-effective tool in staging lung

Computed Tomography vs Positron Emission Tomography in the Mediastinal Staging of NSCLC

| Author | Number of Patients | Malignant/Benign (Type of Evaluation) | PET Sensitivity (%) | PET Specificity (%) | CT Sensitivity (%) (Size Criteria) | CT Specificity (%) |
|-----------------------------------|--------------------|---------------------------------------|---------------------|---------------------|------------------------------------|--------------------|
| Pieterman et al ¹³ | 102 | 32/70 (patients) | 91 | 86 | 75 (1.0 cm) | 66 |
| Valk et al ¹⁶ | 74 | 24/52 (sides) | 83 | 94 | 63 (1.0 cm) | 73 |
| Chin et al ¹⁸ | 30 | 9/21 (patients) | 78 | 81 | 56 (1.5 cm) | 86 |
| Wahl et al ¹⁹ | 23 | 11/16 (sides) | 82 | 81 | 64 (1.0 cm) | 44 |
| Patz et al ²⁰ | 42 | 12/39 (stations) | 83 | 82 | 43 (1.0 cm) | 85 |
| Scott et al ²¹ | 62 | 10/65 (stations) | 100 | 98 | 60 (1.0 cm) | 93 |
| Sasaki et al ²² | 29 | 17/54 (stations) | 76 | 98 | 65 (1.0 cm) | 87 |
| Steinert et al ²³ | 47 | 58/133 (stations) | 93 | 99 | 72 (0.7-1.1 cm) | 94 |
| Sazon et al ²⁴ | 37 | 16/16 (patients) | 100 | 100 | 81 (1.0 cm) | 56 |
| Vansteenkiste et al ²⁵ | 50 | 14/36 (patients) | 67 93* | 97 97* | 67 (1.5 cm) | 63 |
| Guhlmann et al ²⁶ | 32 | 20/12 (patients) | 80 | 100 | 50 (1.0 cm) | 75 |
| Bury et al ²⁷ | 50 | 21/19 (patients) | 90 | 86 | 72 (1.0 cm) | 81 |

CT = computed tomography

PET = positron emission tomography

*PET plus CT

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cancer and is now covered by Medicare for the staging of lung cancer.²⁸ Currently, this technology is expensive and is generally performed only in tertiary care medical centers. It requires a special scanner, production of the radioactive isotope, and staff trained in nuclear medicine.

Surgical Staging

Surgical staging of the mediastinum is often performed prior to primary resection. Historically, this task has been performed by mediastinoscopy, anterior mediastinotomy, and ultimately thoracotomy. Percutaneous transthoracic needle biopsy using CT guidance has been steadily improving with advances in scanning techniques. Transbronchial needle aspiration and endoscopic ultrasound with fine-needle aspiration are

less invasive techniques that may also be used to stage the mediastinum prior to surgical resection.

Mediastinoscopy

If mediastinal adenopathy on CT is present, a surgical mediastinal procedure is often performed prior to thoracotomy. Mediastinoscopy is the historic gold standard for staging the mediastinum. Mediastinoscopy is most often used to sample lymphatics in the paratracheal (station 4) and anterior subcarinal (station 7) region (Fig 1). The subcarinal area is more difficult to sample and has a lower yield. The aortopulmonary (station 5) region is accessible by extended cervical mediastinoscopy. Finally, anterior mediastinotomy is needed to sample lymphatics in the subaortic and lateral aortic region.²⁹ Overall, mediastinoscopy has a reported sensitivity of 87% and specificity of 100%.³⁰ In addition to

this superior sensitivity and specificity, mediastinoscopy may be able to differentiate between stage IIIA and IIIB mediastinal involvement. As more is learned about lung cancer treatment, this will be important for prognosis and for potential therapy.

As with any surgical procedure, mediastinoscopy has risks and limitations. It requires general anesthesia and has a morbidity of 1% and a mortality of 0.2%. The procedure adds considerable expense to the staging workup. The estimated current cost is \$1,700 for the procedure alone and \$7,500 for a mediastinoscopy with a 2-day hospital stay.^{29,31}

Percutaneous Transthoracic Needle Aspiration

Percutaneous transthoracic needle aspiration (PCNA) can be used to sample mediastinal lesions. A biopsy of every region of the mediastinum can be obtained with this technique. Lesions in the left mediastinum, including the

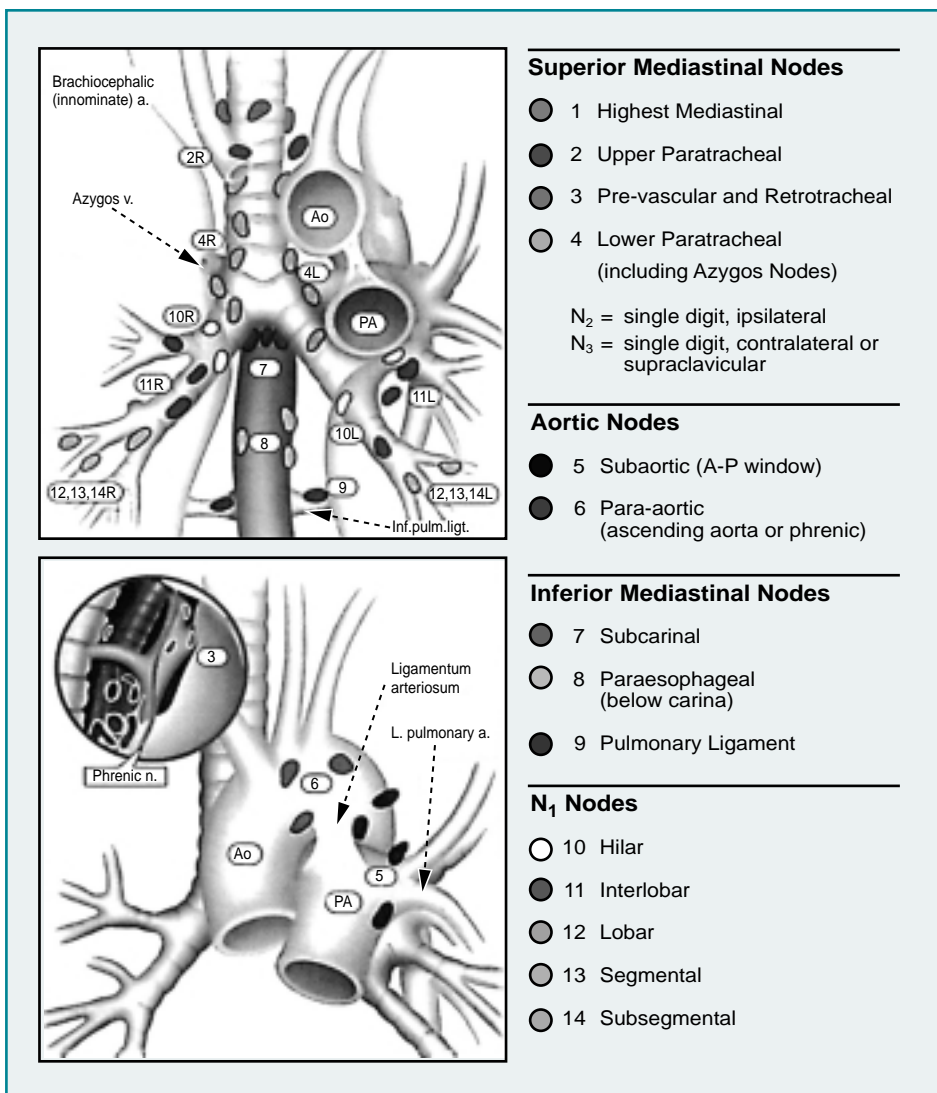


Fig 1. — Regional lymph node stations. Ao = aorta, PA = pulmonary artery. From Shields TW, LoCicero J III, Ponn RB, eds. *General Thoracic Surgery*. Philadelphia: Lippincott Williams & Wilkins; 2000:1302. Reprinted with permission.

para-aortic, as well as lesions in close proximity to the pulmonary artery can be sampled by PCNA. Although this may seem risky, biopsy under CT guidance is relatively safe in this region due to the relatively fixed anatomy and the direct visualization provided by CT.³² In addition, lesions in the anterior mediastinum inaccessible by transbronchial needle aspiration or endoscopic ultrasound can be easily biopsied using PCNA. Although less used than other modalities that provide more access, PCNA can be used to biopsy subcarinal and right paratracheal lesions.

The most significant complication with PCNA is major bleeding from an inadvertent puncture of a central vessel. For this reason, any bleeding diathesis is considered a contraindication for this procedure. Likewise, pulmonary hypertension is a relative contraindication to percutaneous biopsy of a central lesion. Pneumothorax is the most common complication from PCNA. Reports of pneumothorax noted in the literature vary widely, but most observe a frequency of 25% to 30%.³³ The risk of pneumothorax following percutaneous biopsy is influenced by the degree of concomitant pulmonary emphysema. Miller et al³⁴ found a 46% incidence of pneumothorax in patients with chronic obstructive pulmonary disease compared with a 7% incidence in normal patients as determined by spirometry and radiographs.

Transbronchial Needle Aspiration

Transbronchial needle aspiration (TBNA) was developed in the 1980s by Wang and Terry³⁵ as a method of sampling extrabronchial lesions through a flexible bronchoscope. TBNA requires the same preparation as bronchoscopy (ie, conscious sedation) and has a low risk of morbidity and mortality. TBNA can be performed at the same time as diagnostic bronchoscopy, thus avoiding a separate staging procedure. During the procedure, a needle is passed through the working channel of the bronchoscope and through the wall of the trachea or bronchus into the underlying lymph node. Needles are currently available for both cytology and histology. Accessible mediastinal nodes with a high diagnostic yield include 4R (paratracheal) and station 7 (subcarinal) lymph nodes. Although more difficult, biopsies using TBNA have been performed on 4L and station 5 (aortopulmonary window) nodes.

In a recent prospective study involving community hospitals and academic medical centers, Harrow et al³⁶ examined the overall sensitivity and specificity of TBNA in staging known bronchogenic carcinoma. Overall, the sensitivity was found to be more than 57% for lymph nodes greater than 10 mm, and the specificity

was 99%. TBNA precluded additional surgery in 29% of patients studied. In this study, right-sided tumors and right paratracheal and subcarinal adenopathy were predictive of a positive TBNA biopsy. Overall, the sensitivity of TBNA for staging NSCLC is between 40% and 80%.^{35,37-39} The presence of a cytopathologist can help to ensure that an adequate lymph node sampling is obtained. At this time, a factor limiting the widespread use of TBNA is training. TBNA is a relatively new procedure and is the most operator-dependent of the bronchoscopic procedures. With more formal training in this procedure, the yield should increase.

Ongoing studies are examining the role of ultrasound-guided fiberoptic bronchoscopy. Ultrasound guidance is performed by first passing an ultrasound probe down the working channel of the bronchoscope to localize the lymph node. The probe is then withdrawn and transbronchial biopsies are performed in the standard fashion. In a prospective, randomized, controlled trial⁴⁰ that examined the role of ultrasound-guided TBNA vs standard TBNA, both techniques had a high sensitivity — 82% and 90%, respectively. Compared with standard TBNA, endobronchial ultrasound decreased the number of aspirates needed to achieve a diagnosis. However, there was no statistical difference in the diagnosis of malignancy. This may be due to the high sensitivity attained in this study using standard TBNA. Development of real-time endobronchial ultrasound techniques is ongoing. This would allow sampling under direct ultrasound visualization. Currently, ultrasound guidance with TBNA is available at only a few major medical centers.

Endoscopic Ultrasound-Guided Mediastinal Lymph Node Aspiration

One of the most exciting developments in the staging of the mediastinum has been the development of transesophageal endoscopic ultrasonographic guidance for fine-needle aspiration (EUS/FNA) of mediastinal lymph nodes. Initially developed to study echo features of gastrointestinal malignancies, EUS has become the study of choice for defining local tumor and lymph node staging of gastrointestinal tumors. Esophageal EUS provides accurate images of the entire posterior mediastinum, including lymph nodes in the subcarinal, aortopulmonary, and paraesophageal regions. This has led to studies of its diagnostic accuracy for mediastinal malignancy. In an early study⁴¹ examining mediastinal malignancies, EUS echo features had an accuracy of 84% compared with 49% for conventional CT. The development of echoendoscopes capable of imaging parallel to the long axis of the scope made EUS-guided intervention possible. Lymph nodes in the subcarinal,

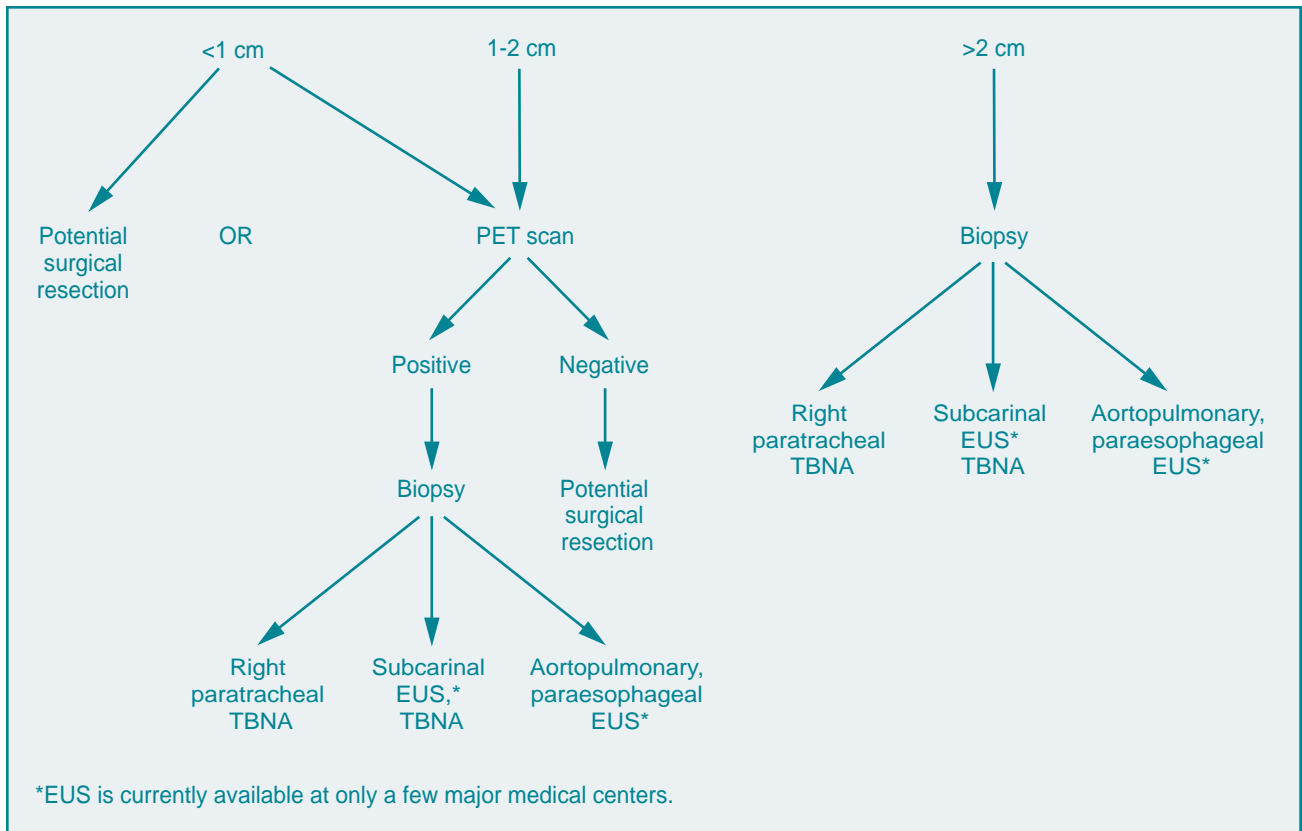


Fig 2. — Potential algorithm for nonsurgical mediastinal staging of NSCLC based on size and location of lymph nodes.

aortopulmonary, and paraesophageal regions and along the pulmonary ligament can be sampled.

Intense research currently is ongoing in this area. Silvestri and colleagues²⁹ used EUS to examine 27 patients with known or suspected lung cancer. Of these patients, 22 had enlarged lymph nodes on CT. Overall, 16 patients had positive findings on EUS with 15 positive fine-needle aspirates, and one patient had T4 disease not seen on CT. Of the 11 patients with negative biopsies, two had micrometastatic disease to the lymph node at surgery. In a study of patients who had unsuccessful bronchoscopic workup of presumed lung cancer, Fritscher-Ravens et al⁴² established a diagnosis of malignancy in 25 of 35 patients. The overall sensitivity of the procedure was 96%. In 7 patients, the punctured nodes were less than 1 cm, making them difficult to biopsy by other means. No complications were seen in this study.

Advantages of EUS over surgery include lower cost and lower morbidity. It can be performed under standard esophagogastroduodenoscopy (EGD) conditions, including conscious sedation. It can be used to biopsy lymph node levels that are inaccessible or difficult to access by mediastinoscopy, including the para-aortic and paraesophageal regions. Its advantages over conventional TBNA include the ability to visualize and biopsy nodes

less than 1 cm with seemingly good accuracy. Disadvantages include the inability to biopsy right paratracheal and pretracheal nodes due to the air-filled trachea, which blocks the ultrasound signal. Also, EUS is presently available in only a few major medical centers.

Conclusions

We have presented a brief look at the present state of mediastinal staging including PET imaging, FUS, and TBNA. Fig 2 is a potential algorithm for staging the mediastinum nonsurgically.

It appears the strength of PET imaging may lie in its strong negative predictive value. TBNA offers the advantage of being able to potentially stage the patient at the time of diagnosis. Sensitivity remains somewhat low, with the best results from right paratracheal or subcarinal lymph nodes. EUS offers the advantage of being able to sample lymph nodes smaller than 1 cm and can sample stations not easily accessible by TBNA or mediastinoscopy. These include paraesophageal and aortopulmonary lymphatics. In conclusion, the patient should never be denied potentially curative resection without tissue confirmation of malignant spread. These new modalities will undoubtedly improve the pretreatment staging of NSCLC.

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