Review

Lung Cancer Staging—A Clinical Practice Review

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Abstract: Lung cancer is the leading cause of cancer-associated death globally. Staging provides classification of the anatomic extent of cancer that is used consistently worldwide. Lung cancer staging is necessary for prognostication, to inform treatment options, and to allow accurate representation in clinical trials. Staging also separates operable from inoperable disease. Since its introduction in the 1970s, the Tumor, Node and Metastasis (TNM) Staging System has undergone significant revisions, with the latest version, the eighth edition, being effective internationally since 2017. Advances in bronchoscopic and thoracoscopic technologies have expanded procedures to diagnose lung cancer and accurately define the anatomic stage. Understanding the advantages and disadvantages of available methods for staging lung cancer is critical to clinician decision making. In patients with lung cancer without distant metastases, the staging of mediastinal lymph nodes determines treatment options. To minimize the risk and cost, the most appropriate method of staging should identify the highest disease stage while carrying acceptable risk. Minimally invasive endoscopic needle techniques to stage the mediastinum are the first choice to assess for metastases in accessible lymph node stations. Surgical techniques are generally reserved for specific clinical situations, including following negative endoscopic needle techniques when suspicion for nodal involvement is high and to assess endoscopically inaccessible lymph nodes. This review provides a concise account of TNM staging of non-small cell lung cancer (NSCLC) and overview of procedures available for the staging of lung cancer.

Keywords: non-small cell lung cancer; endobronchial ultrasonography; transbronchial needle aspiration; video-assisted thoracoscopic surgery; pleuroscopy

1. Introduction

Lung cancer is the second most common cancer in men and women in the United States and the leading cause of cancer-related death in the world [1]. NSCLC accounts for 80–90% of lung cancer cases [1]. Accurate staging of lung cancer is crucial as it is the most important predictor of survival and determines treatment options. The stage at diagnosis directly correlates with mortality and determines candidacy for potentially curative surgical resection. A comprehensive literature search was performed to inform this review utilizing PubMed. Keywords utilized to identify articles included: lung cancer staging, non-small cell lung-cancer, endobronchial ultrasonography, and video-assisted thoracoscopic surgery with a focus on articles published after 2013, when the last iteration of the American College of Chest Physician clinical practice guidelines on staging of NSCLC was published.

The Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) are the official bodies that define the stage classification systems and ensure global consistency. The TNM Staging System was accepted by the UICC Committee on Tumour Nomenclature and Statistics in 1953 as the basis for anatomical staging. Following this, in 1996 the International Association for the Study of Lung Cancer (IASLC), a global organization dedicated to the study of lung cancer, developed an international database for external validity of future iterations of TNM. The UICC has determined that the IASLC is the primary source of recommendations for lung cancer staging [2]. Based on the IASLC's

collection and analysis of lung cancer data, the TNM staging has undergone substantial revisions. The current version is the eighth edition, which became the worldwide standard in January 2017.

The database for the eighth edition was collected between 1999 and 2010 from 16 different countries, and 77,156 patients were included in the study [3]. A major highlight of the latest edition is the re-classification and subclassification of the different stages of lung cancer based on the collected prognostic data. Subclassification of tumor size and extent of extrathoracic involvement are among the most important changes.

2. TNM Staging System

TNM staging is the description of the anatomic extent of cancer and includes tumor (T) to describe the magnitude of the primary tumor, nodal (N) to depict involvement of regional lymph nodes, and metastases (M) for distant metastases beyond regional lymph nodes (Table 1). Each of these components are divided further into subcategories. The T stage is determined by the size of the primary tumor and the extent of invasion of surrounding structures. Tumors should be measured using the single largest dimension measured in one of three standard planes (axial, coronal, sagittal) using thin, one-millimeter sections. Based on the analysis of patients in the most recent database, it was determined that with each centimeter increase in tumor size, there is a poorer prognosis, but no demonstrable difference in survival once a tumor exceeds six centimeters [3]. By size, tumors are categorized as Tis or carcinoma in situ if the tumor is found only in the top layers of cells lining the lung or bronchus and has not extended beyond this. T1 tumors have a maximum diameter of three centimeters, T2 tumors have a maximum diameter between three and five centimeters, T3 have a maximum diameter between five and seven centimeters, and T4 have a maximum diameter greater than 7 cm. T1 and T2 tumors are further subclassified in one-centimeter increments to provide better prognostic classification, as outlined in Table 1. Regarding involvement of adjacent structures, the involvement of the main bronchus aligns with the prognosis of a T2 stage. Similarly, obstructive atelectasis is staged as T2, regardless of the amount of lung involvement, as this is reflective of the prognostic value of endobronchial growth of the tumor [4]. Tumors that invade the visceral pleura are T2a, and those that invade the parietal pleura, pericardium, or chest wall are considered T3. Tumors that invade the diaphragm, heart or great vessels, esophagus, vertebrae, carina, and recurrent laryngeal nerve represent T4 disease. A satellite nodule in the same lobe as the primary nodule is classified as T3, but a nodule in a different lobe of the same lung is classified as T4. A separate nodule in the contralateral lung would be classified as M1a, as detailed below.

The eighth edition is the first to provide recommendations on the radiologic staging of subsolid nodules. Subsolid nodules are most often adenocarcinoma, and the solid component of a nodule usually correlates with the invasive component of the adenocarcinoma [5]. If the solid component of the part solid nodule is larger than 5 mm, the T staging is determined by the diameter of the solid component.

The N stage assesses tumor burden in the regional hilar and mediastinal nodes. The N-descriptor remained the same between the seventh edition and the eighth edition; thus, the nodal stations are as outlined in the IASLC nodal map developed in the seventh TNM edition. The nodal stage consistently separates patients into different prognostic groups.

Lymph node metastasis to the ipsilateral hilum is classified as N1. Lymph node metastasis to the ipsilateral mediastinum or subcarinal lymph node is categorized as N2. Based on the analysis for the upcoming ninth TNM edition, it is proposed that the N2 category be divided into subgroups N2a and N2b, representing single-station and multi-station involvement, respectively, based on distinctly different prognoses [6]. Lymph node metastasis to the contralateral mediastinal or hilar lymph nodes, as well as ipsilateral or contralateral scalene and supraclavicular lymph nodes, are considered N3. Assigning lymph nodes to the correct lymph node station based on location is necessary. As such, it is important to differentiate between ipsilateral and contralateral, or right versus left lymph

node stations. For example, the border between the right and left paratracheal lymph nodes is the left lateral wall of the trachea [7]. Similarly, the border between the lower paratracheal lymph nodes and the hilar lymph nodes is an important distinction; the inferior border of the paratracheal lymph nodes is defined by the superior aspect of the pulmonary artery on the left and the inferior border of the azygous vein on the right. The determination of nodal disease includes a combination of anatomic and metabolic imaging; transbronchial and transesophageal needle aspiration; and mediastinoscopy and thoracoscopy, which are discussed below.

Table 1. TNM classification of lung cancer per the eighth edition.

Category	Definition
Tis	Carcinoma in situ
T1a	Tumor $\leq$ 1 cm (cm)
T1b	Tumor > 1 cm to $\leq$2 cm
T1c	Tumor > 2 cm to $\leq$3 cm
T2a	Tumor > 3 cm to $\leq$4 cm; or any size involving the main bronchus or visceral pleura, or leading to obstructive atelectasis
T2b	Tumor > 4 cm to $\leq$5 cm
T3	Tumor > 5 cm to $\leq$7 cm; or any size involving the parietal pleura, parietal pericardium, chest wall, T1–T2 nerve roots, phrenic nerve; or satellite tumor in same lobe as primary tumor
T4	Tumor > 7 cm; or any size invading the mediastinum, diaphragm, trachea, main carina, recurrent laryngeal nerve, esophagus, visceral pericardium, vertebral body, great vessels, heart, cervical nerve roots; or satellite tumor in separate lobe of ipsilateral lung
N0	No reginal lymph nodes involved
N1	Ipsilateral peribronchial, hilar, and intrapulmonary nodes
N2	Ipsilateral mediastinal and subcarinal nodes
N3	Contralateral mediastinal, hilar, or any scale or supraclavicular node
M1a	Separate tumor nodule in contralateral lung, pleural, or pericardial involvement
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases

The M stage is defined by the presence of distant metastasis beyond regional lymph nodes. Lung metastases can be intra- or extra-thoracic. Patients with single extra-thoracic metastasis have better prognosis than those with several metastatic sites; thus, M1 is divided into a, b, and c to represent thoracic metastatic disease (separate tumor nodule in the contralateral lobe, pleural nodules or malignant pleural/pericardial effusion), single extrathoracic metastasis, and multiple extrathoracic metastases, respectively. If pulmonary metastases are not verified histologically, this may lead to over-staging, as most pulmonary nodules detected in patients with lung cancer are benign [8]. It is also necessary to distinguish intrapulmonary metastases from a synchronous primary lung cancer, as secondary primary lung cancers should be staged separately. Comprehensive histologic and molecular characterization of the tumors may be required to determine this difference. The final stage is based on the combination of the T, N, and M categories.

3. Neuroendocrine Tumors

Neuroendocrine tumors (NETs) of the lung include carcinoids (typical and atypical), large cell neuroendocrine cancer, and small cell lung cancer (SCLC). NETs of the lungs are staged using the AJCC TNM system described above, with the exception of SCLC. SCLC is a unique entity characterized by early metastatic spread and has been staged

using the Veterans' Administration Lung Study Group (VALSG) two-stage system since the late 1950s [9], which determines curative versus noncurative treatment options. The VASLG system includes limited stage (LS) and extensive stage (ES). LS includes disease confined to one hemithorax that is able to be encompassed in a single, safe radiotherapy port. This includes hilar, mediastinal, and ipsilateral supraclavicular lymph nodes but no extra-thoracic metastases. ES is defined as any disease beyond that defined by LS.

4. Imaging Techniques for Staging

Computed tomography (CT) of the chest is routinely used for the initial staging of tumor size and mediastinal involvement in patients with lung cancer, given its low cost, wide availability, and use in detection of the primary tumor; however, it has limited accuracy for the detection of lymph node metastases. A lymph node must measure greater than one centimeter in short axis to be radiographically defined as lymphadenopathy. Benign, inflammatory, or reactive lymph nodes often exceed the one-centimeter threshold, so using the size criterion alone is of low diagnostic value. The pooled sensitivity of the CT size criterion in isolation is 55% with a specificity of 81% [10,11]. By using size on CT alone, 42% of lymph nodes greater than 1 cm would be over-staged, as they are benign, and 17% of metastases to lymph nodes smaller than 1 cm would be missed [11].

In patients with a normal clinical evaluation and no suspicious extrathoracic abnormalities on chest CT who are considered for curative-intent treatment, fludeoxyglucose positron emission tomography (FDG PET) is recommended for the evaluation of metastases [10]. Common extrathoracic metastatic sites that can be evaluated via PET are the adrenal glands, liver, and skeletal system. The standardized uptake value (SUV) is a measure of metabolic activity detected by FDG PET, and a cut-off SUV of 2.5 and greater is generally applied to distinguish neoplastic from benign tissue. By using FDG PET/CT for NSCLC, the sensitivity is increased to 77–90% with a specificity of 86–95% in lesions greater than one centimeter [10,12,13]. FDG PET also carries the risk of false positives, as non-neoplastic lesions such as granulomatous disorders or infections may generate metabolic activity, so enlarged FDG-positive lymph nodes must be histologically confirmed via tissue biopsy to verify metastatic involvement [12]. Despite limited sensitivity, PET remains important for staging and is recommended to detect occult metastatic disease in order to avoid noncurative surgical resection [10]. In patients with an imaging finding (CT or PET) suggestive of extra thoracic metastases, tissue biopsy of the abnormality is recommended to pathologically confirm the clinical stage [10].

Contrast-enhanced MRI has a higher sensitivity for the detection of brain metastases compared to CT and PET due to the small size of most brain metastases and background brain FDG uptake. MRI brain is recommended in all patients with stage III or IV NSCLC and anyone with neurological symptoms on clinical evaluation [10]. MRI brain is recommended in all patients diagnosed with SCLC [14]. MRI will detect brain metastases in 10–15% of asymptomatic patients with SCLC, including 12% of patients who would otherwise be staged as LS [14].

5. Invasive Techniques to Stage the Mediastinum

5.1. Endoscopic Staging

In patients with lung cancer with mediastinal lymph node enlargement without distant metastases, with or without PET avidity, invasive staging of the mediastinum is recommended over imaging alone [10,15]. For patients with a peripheral stage IA tumor by negative PET/CT who are surgical candidates, it has been suggested that invasive pre-operative evaluation of the mediastinal nodes is not required [10]. Prior studies report that a negative PET without distant or nodal metastases in patients with tumors under three centimeters in the outer one-third of the lung virtually excludes lymph node metastases and therefore would suggest invasive staging is unnecessary prior to surgical resection [10,13,15]. Conversely, occult lymph node metastases (OLM) are often found during surgical resection; in a more recent study of surgically treated patients with NSCLC,

OLM was found in 23.1% of all pre-operative clinical N0-staged patients, and one-half of these patients had tumors under three centimeters [16]. Similarly, in another study, which compared lobar to sublobar resection, the rate of OLM was found to be approximately 6.4% in those with pre-operative clinical stage IA (N0) [17]. This study concluded that in patients with peripheral NSCLC with tumor size of 2 cm or less and pathologically confirmed node-negative disease, sublobar resection was not inferior to lobectomy with respect to disease-free survival [17]. These data suggest that despite current lung cancer staging guidelines, endoscopic staging should be considered in all patients considered for wedge resection or radiation therapy in which concomitant lymph node dissection will not be performed. These data are increasingly more relevant as expanded lung cancer screening is implemented and the proportion of patients with early stage lung cancer increases.

In patients with central tumors $\geq$ 3 cm, a negative PET does not exclude lymph node metastases, and guidelines suggest invasive staging of the mediastinum should be performed [15,18]. Interestingly, there is no consensus definition for central location, and in one study looking at participants from the National Lung Screening Trial, there was no difference in the rate of lymph node metastasis based on location or tumor size [19]. This would again suggest that patients with small, peripheral lung cancers may also benefit from mediastinal staging. There are multiple invasive strategies to stage the mediastinum, and the optimal strategy is based on local availability, physician expertise, and the anatomic location of the suspected nodal metastases.

Conventional flexible bronchoscopy can determine the endobronchial extension of the primary tumor or detect radio-occult endobronchial lesions [5]. Blind transbronchial needle aspiration (TBNA) can be performed during initial flexible bronchoscopy if pathologically enlarged mediastinal lymph nodes have been identified on CT of the chest. This process is most accurate for enlarged lymph nodes in the subcarinal station (7) but can also be utilized for the lower paratracheal stations (4R and 4L) and hilar lymph nodes [20]. A meta-analysis of data involving patients who underwent blind TBNA showed this technique had a pooled sensitivity of 39% to detect nodal metastases with a false-negative rate of 28% [21,22]. Based on low diagnostic yield and significant advancements in mediastinal staging with the advent of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), blind TBNA is rarely utilized.

Endobronchial ultrasonography (EBUS) allows for the real-time visualization of structures adjacent to airways via a curvilinear ultrasound transducer at the tip of the bronchoscope in addition to direct airway visualization. The ultrasound transducer guides the TBNA of lymph nodes and parabronchial masses (Figure 1). In the mediastinal staging of lung cancer, EBUS-TBNA has an overall median sensitivity of 89% and a median negative predictive value of 91% [10]. All FDG-PET-positive lymph nodes and any lymph node $\geq$ 5 mm in the short axis measured by ultrasound should be biopsied. The optimal number of nodal aspirations per station for histopathological staging has been reported to be three, particularly in the absence of rapid on-site evaluation (ROSE) [23–25]. The current data suggest that ROSE reduces the number of needed aspirations as well as the number of additional procedures required, and this may be beneficial in determining the quantity of malignant cells available for molecular analysis [25]. The American College of Chest Physicians' (CHEST) guidelines regarding EBUS-TBNA suggest that additional samples beyond those needed for diagnosis be obtained for molecular analysis [26]. To avoid contamination, the order of sampling should begin with the N3 stations followed by N2 and finally the N1 stations. There are 19-, 21-, 22-, and 25-gauge needles commercially available for use with EBUS. Controversy remains regarding the effect of needle size on diagnostic yield of EBUS-TBNA; a prospective randomized clinical trial comparing the 19-gauge EBUS needle to the 21-gauge needle revealed that the diagnostic yield was similar (89.4% vs. 88.7%, p = 0.71); however, in malignant lymph nodes, the 19-gauge showed higher smear cellularity (32.6% vs. 13.0%, p = 0.05) and rapid on-site evaluation adequacy (84.8% vs. 63.0%, p = 0.004) [26].

Figure 1. EBUS image of lymph node station 7.

EBUS allows for the sampling of mediastinal lymph node stations 2R (right superior paratracheal), 2L (left superior paratracheal), 4R (right inferior paratracheal), 4L (left inferior paratracheal), and 7 (subcarinal), as well as hilar lymph node stations 10R, 10L, 11R, and 11L. EBUS cannot access lymph node stations 3 (prevascular and retrotracheal), 5 (subaortic), or 6 (para-aortic), nor 8 (para-esophageal) or 9 (pulmonary ligament). Lymph node stations 2L, 4L, 5, 7, 8, and 9 can be accessed via the esophagus with endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA). During EUS, aspiration is performed through the esophagus under direct vision, and linear ultrasound guides a needle into the lymph node. EUS has a sensitivity of approximately 89%, and when combined with EBUS, the sensitivity increases to approximately 91% [10] and provides access to the entire mediastinum with the exception of lymph node station 6. EUS and EBUS can be performed under conscious sedation or general anesthesia. EBUS with TBNA has a complication rate of 1–2% and mortality of 0.01% and is therefore considered a safe procedure [26]. In clinical N0 tumors following PET and CT, the risk of mediastinal nodal involvement has been reported as less than 20%, and the sensitivity for EBUS-TBNA to detect metastatic nodal disease drops to 17–41% [27–30]. Conversely, a significant proportion of patients with clinical N0 or N1 disease by PET/CT had pathologic N2 disease, and EBUS-TBNA identified 40% of these, thus improving diagnostic accuracy compared with PET/CT alone [30]. In patients with high or intermediate suspicion of N2 or N3 involvement and no evidence of distant metastases, invasive staging of the mediastinum is recommended over staging by imaging alone, and a needle technique is recommended over surgical staging [10]. In this setting, negative results obtained by minimally invasive endoscopic techniques should be surgically confirmed via the methods presented below.

5.2. Surgical Staging

Mediastinoscopy is performed by surgeons in the operating room under general anesthesia and allows for the exploration of the superior and middle mediastinum. Video-assisted mediastinoscopy (VAM) is preferred to mediastinoscopy due to increased visualization and sampling of more lymph node stations [13]. The procedure involves one incision just above the suprasternal notch, insertion of a mediastinoscope alongside the trachea, and

biopsy of mediastinal nodes. Mediastinoscopy affords access to right and left superior and inferior paratracheal lymph node stations (2R, 2L, 4R, 4L) and anterior subcarinal nodes (7), as well as right and left para-esophageal stations (8R, 8L) and right and left hilar (10R, 10L) stations, depending on the technique. Extended cervical mediastinoscopy provides access to subaortic (5) and para-aortic (6) lymph node stations. Given incomplete access to the mediastinum, this technique has a sensitivity of 78%, specificity of 100%, and a false-negative rate of 10% [20]. Newer techniques such as video mediastinoscopy increases the sensitivity to 89% [10]. Rates of morbidity and mortality are as low as 2% and 0.08%, respectively [10]. Mediastinoscopy is recommended if suspicion remains high for lymph node involvement following a negative EBUS with sufficient samples obtained [10].

Video-assisted thoracoscopic surgery (VATS) is performed by surgeons in the operating room under general anesthesia and usually with one lung ventilation. This procedure involves the creation of three port holes in the hemithorax and use of a video thoracoscope that is used to access the pleural space, lung, and mediastinum via the ports. VATS allows for the assessment of T, N, and M stages and thus has the ability to diagnose synchronous primary lung cancers versus make the distinction between T3 and T4 disease. The suspicion of pleural or pericardial effusion can be confirmed by this technique as well allowing for the diagnosis of M1a disease. VATS for the staging of the mediastinum affords access to ipsilateral lymph nodes. VATS has a median sensitivity of 99% and false-negative rate of 4% [31]. VATS can also be utilized to confirm the T stage as suggested radiographically, particularly in relation to T4 disease in which the invasion of the mediastinum or diaphragm precludes resection. In three studies, radiographically suggested T4 disease was excluded in 38% of patients by VATS among three studies [32–34]. The average complication rate of VATS performed for mediastinal staging is 2%, with no reported mortality [35]. A proposed algorithm for invasive staging of NSCLC is detailed below in Figure 2.
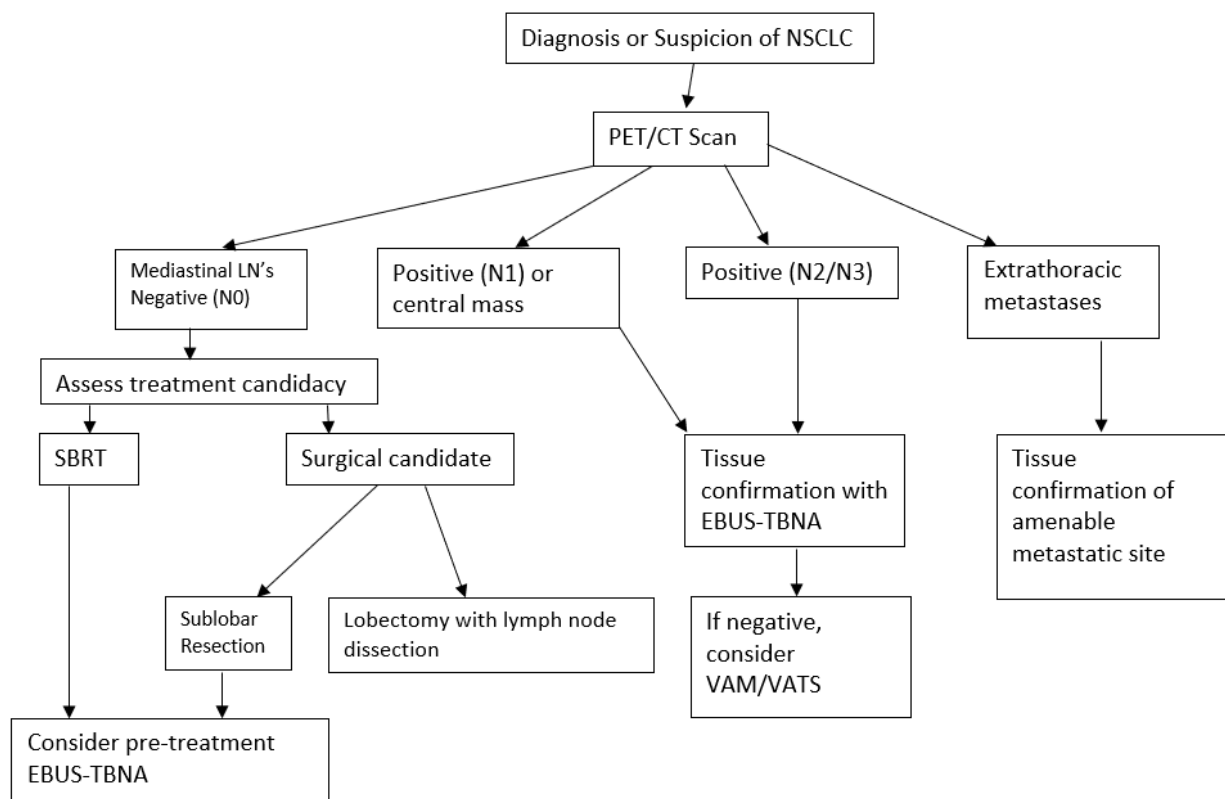

Figure 2. Proposed algorithm for staging the mediastinum in setting of NSCLC. PET: positron emission tomography, CT: computed tomography, LN: lymph node, SBRT: stereotactic body radiation therapy, EBUS-TBNA: endobronchial ultrasound–transbronchial needle aspiration, VAM: video-assisted mediastinoscopy, VATS: video-assisted thoracic surgery.

6. Supraclavicular Lymph Node Biopsy

The presence of ipsilateral or contralateral supraclavicular lymph node involvement designates N3 disease according to the TNM classification. To evaluate for supraclavicular lymphadenopathy, CT of the chest or neck or ultrasound can be utilized. If enlarged lymph nodes are identified in this region, histopathologic evaluation should be pursued through either percutaneous needle aspiration or excisional biopsy. Ultrasound guided percutaneous needle aspiration of a supraclavicular lymph node is shown in Figure 3. Suspicious lymph nodes can be identified using point-of-care ultrasound with a linear transducer. Ultrasound identifies up to 50% of non-palpable supraclavicular lymph nodes [36]. Lymph nodes appear as echo dense structures surrounded by a clearly defined hyperechoic capsule [36]. Lymph nodes do not collapse like surrounding vasculature, and a fatty central hilum may be identified. Ultrasound with fine needle aspiration cytology (FNAC) is utilized for head and neck cancer with a sensitivity and specificity over 90% [37]. Prior literature has suggested that ultrasound-guided FNAC is an effective way of sampling occult supraclavicular nodes in people with lung cancer, and this simultaneously excludes surgical resection [38,39]. In one study, further invasive diagnostic procedures were prevented in 11 of 117 patients following FNAC. Importantly, FNAC can be performed by trained pulmonologists utilizing local anesthesia and offers the ability to obtain core needle biopsies [40].
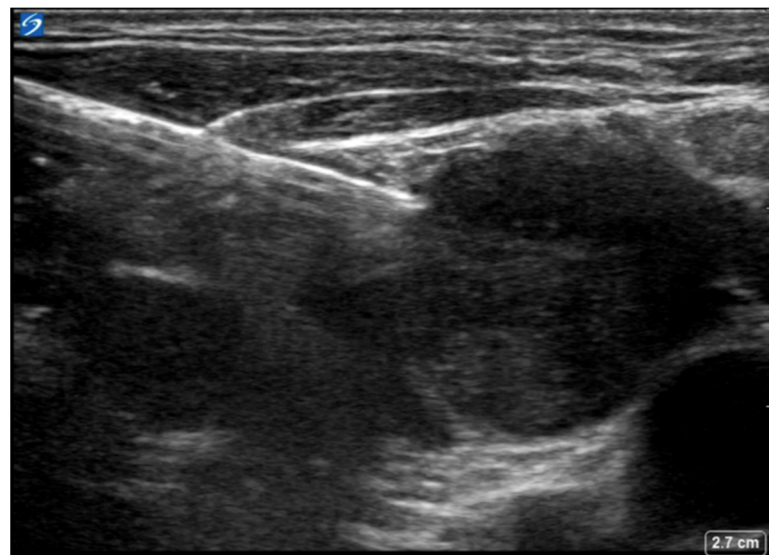

Figure 3. Soft tissue ultrasound image showing an enlarged right supraclavicular lymph node with the entire length of the needle visible entering from the left side of the screen.

7. Needle Aspiration Versus Core Biopsy

Specimens obtained via EBUS-TBNA or EUS-FNA are cytologic aspirates with limited cellular material and may lack architecture [41]. Cytologic specimens can be processed in multiple ways including direct smears, touch-preparation of tissue biopsies, alcohol-fixed liquid-based concentration methods, or by the creation of a tissue cell block. Core needle biopsies obtained via the transbronchial, endobronchial, or transthoracic route are larger and provide tissue architecture [41]. These are generally formalin fixed. Both biopsies and cytologic needle aspirations provide histopathologic diagnoses and are fit for molecular testing. Studies comparing these methods report a molecular testing success rate for biopsy specimens of 55–100% and for FNA or EBUS-TBNA cell block specimens of 46–95% [41–43]. Programmed death-ligand 1 (PD-L1) expression is an important therapeutic biomarker for NSCLC. A study looking at the adequacy of EBUS-TBNA samples for PD-L1 testing in particular found that there was no significant difference in sampling adequacy between EBUS-TBNA and other methods of tissue acquisition [44]. Advances in

diagnostic and molecular testing have allowed cytologic needle aspirations to be used to accurately diagnose and molecularly characterize lung cancer.

8. Thoracentesis and Pleuroscopy

Pleural effusions or pleural nodules and thickening are radiographically evident in up to one-third of patients with NSCLC at presentation [45]. Patients with known or suspected lung cancer presenting with a pleural effusion should undergo thoracentesis with cytopathologic analysis, as the presence of malignant cells in the pleural space represents stage M1a and ultimately stage IV disease. The diagnostic yield depends on the type of cancer and ranges from 40 to 60%, and yield increases only slightly with a second sample [46]. If the cytologic analysis following serial thoracenteses is negative, pleural biopsy is recommended. Pleuroscopy, or medical thoracoscopy, is an approach utilized to simultaneously sample pleural fluid and biopsy the pleura with an approximate sensitivity of 95% for pleural malignancies [46]. Pleuroscopy is performed by interventional pulmonologists in the operating room under general anesthesia. It involves the passage of a thoracoscope through a single incision in the chest wall for direct visualization of the pleura. Pleuroscopy can additionally offer pleural palliation via talc pleurodesis or placement of an indwelling pleural catheter during the same procedure.

9. Conclusions

In known or suspected NSCLC, accurate staging is crucial as it is the most important predictor of survival and determines treatment options, including candidacy for potentially curative surgical resection. Staging of lung cancer requires a thoughtful combination of imaging and invasive methods. This often begins with CT scan of the chest given the wide availability and its use in identifying the primary tumor. Unfortunately, CT scans are inaccurate in determining benign from malignant lymph nodes in the mediastinum. PET provides functional information with increased sensitivity and specificity when compared to chest CT and allows for the identification of extrathoracic metastatic sites, excluding the brain. Despite this, positive findings on PET scans must be confirmed by tissue sampling. The confirmation of mediastinal lymph node involvement can be performed using multiple methods with a range of invasiveness and separate safety and efficacy profiles. Risk can be mitigated by proceeding with the least invasive method, which will allow for the highest staging and determine operative candidacy versus non-surgical treatment strategies.

10. Future Directions

With the evolution of image-guided and robotic-assisted bronchoscopy (RAB) techniques, which received FDA approval in 2018 and 2019, it is now possible to biopsy sub-centimeter and peripheral pulmonary nodules, which were previously considered outside of reach by bronchoscopic methods [47]. RAB utilizes a pre-procedural CT scan to generate navigational airway pathways to reach the primary lesion. With this technology, the operator can navigate through smaller airways under direct visualization. With image-guidance and the use of RAB, interventional pulmonologists are able to offer a single procedure in which they establish a primary diagnosis and simultaneously stage the mediastinum via EBUS [47]. In addition to improving diagnostic yield for previously unreachable peripheral pulmonary nodules, future developments will expand its application to include therapeutics as well.

References

1. Torre, L.A.; Siegel, R.L.; Jemal, A. Lung Cancer Statistics. *Adv. Exp. Med. Biol.* **2016**, *893*, 1–19. [CrossRef]
2. Rami-Porta, R.; Asamura, H.; Travis, W.D.; Rusch, V.W. Lung cancer—Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J. Clin.* **2017**, *67*, 138–155. [CrossRef]
3. Rami-Porta, R.; Bolejack, V.; Giroux, D.J.; Chansky, K.; Crowley, J.; Asamura, H.; Goldstraw, P. The IASLC lung cancer staging project: The new database to inform the eighth edition of the TNM classification of lung cancer. *J. Thorac. Oncol.* **2014**, *9*, 1618–1624. [CrossRef]
4. Rami-Porta, R.; Bolejack, V.; Crowley, J.; Ball, D.; Kim, J.; Lyons, G.; Rice, T.; Suzuki, K.; Thomas, C.F.; Travis, W.D.; et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. *J. Thorac. Oncol.* **2015**, *10*, 990–1003. [CrossRef]
5. Travis, W.D.; Asamura, H.; Bankier, A.A.; Beasley, M.B.; Detterbeck, F.; Flieder, D.B.; Goo, J.M.; MacMahon, H.; Naidich, D.; Nicholson, A.G.; et al. The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. *J. Thorac. Oncol.* **2016**, *11*, 1204–1223. [CrossRef]
6. Huang, J.; Osarogiagbon, R.U.; Giroux, D.J.; Nishimura, K.K.; Bille, A.; Cardillo, G.; Detterbeck, F.; Kernstine, K.; Kim, H.K.; Lievens, Y.; et al. The International Association for the Study of Lung Cancer Staging Project for Lung Cancer: Proposals for the Revision of the N Descriptors in the Forthcoming Ninth Edition of the TNM Classification for Lung Cancer. *J. Thorac. Oncol.* **2023**; *in press*. [CrossRef]
7. Rusch, V.W.; Asamura, H.; Watanabe, H.; Giroux, D.J.; Rami-Porta, R.; Goldstraw, P. The IASLC lung cancer staging project: A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J. Thorac. Oncol.* **2009**, *4*, 568–577. [CrossRef]
8. Detterbeck, F.C.; Nicholson, A.G.; Franklin, W.A.; Marom, E.M.; Travis, W.D.; Girard, N.; Arenberg, D.A.; Bolejack, V.; Donington, J.S.; Mazzone, P.J.; et al. The IASLC Lung Cancer Staging Project: Summary of Proposals for Revisions of the Classification of Lung Cancers with Multiple Pulmonary Sites of Involvement in the Forthcoming Eighth Edition of the TNM Classification. *J. Thorac. Oncol.* **2016**, *11*, 639–650. [CrossRef] [PubMed]
9. Zelen, M. Keynote address on biostatistics and data retrieval. *Cancer Chemother. Rep. 3* **1973**, *4*, 31–42. [PubMed]
10. Silvestri, G.A.; Gonzalez, A.V.; Jantz, M.A.; Margolis, M.L.; Gould, M.K.; Tanoue, L.T.; Harris, L.J.; Detterbeck, F.C. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* **2013**, *143* (Suppl. S5), e211S–e250S. [CrossRef] [PubMed]
11. Alongi, F.; Ragusa, P.; Montemaggi, P.; Bona, C.M. Combining independent studies of diagnostic fluorodeoxyglucose positron-emission tomography and computed tomography in mediastinal lymph node staging for non-small cell lung cancer. *Tumori* **2006**, *92*, 327–333. [CrossRef] [PubMed]
12. Schmidt-Hansen, M.; Baldwin, D.R.; Hasler, E.; Zamora, J.; Abraira, V.; Roqué i Figuls, M. PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer. *Cochrane Database Syst. Rev.* **2014**, *2014*, CD009519. [CrossRef] [PubMed]
13. De Leyn, P.; Dooms, C.; Kuzdzal, J.; Lardinois, D.; Passlick, B.; Rami-Porta, R.; Turna, A.; Schil, P.V.; Venuta, F.; Waller, D.; et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *Eur. J. Cardiothorac. Surg.* **2014**, *45*, 787–798. [CrossRef]
14. Hochstenbag, M.M.; Twijnstra, A.; Wilmink, J.T.; Wouters, E.F.; ten Velde, G.P. Asymptomatic brain metastases (BM) in small cell lung cancer (SCLC): MR-imaging is useful at initial diagnosis. *J. Neurooncol.* **2000**, *48*, 243–248. [CrossRef]
15. Novello, S.; Barlesi, F.; Califano, R.; Cufer, T.; Ekman, S.; Levra, M.G.; Kerr, K.; Popat, S.; Reck, M.; Senan, S.; et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **2016**, *27* (Suppl. S5), v1–v27. [CrossRef]
16. Beyaz, F.; Verhoeven, R.L.J.; Schuurbiers, O.C.J.; Verhagen, A.F.T.M.; van der Heijden, E.H.F.M. Occult lymph node metastases in clinical N0/N1 NSCLC; A single center in-depth analysis. *Lung Cancer* **2020**, *150*, 186–194. [CrossRef]
17. Altorki, N.; Wang, X.; Kozono, D.; Watt, C.; Landrenau, R.; Wigle, D.; Port, J.; Jones, D.R.; Conti, M.; Ashrafi, A.S.; et al. Lobar or Sublobar Resection for Peripheral Stage IA Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2023**, *388*, 489–498. [CrossRef]
18. Reck, M.; Rabe, K.F. Precision Diagnosis and Treatment for Advanced Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2017**, *377*, 849–861. [CrossRef]
19. DuComb, E.A.; Tonelli, B.A.; Tuo, Y.; Cole, B.F.; Mori, V.; Bates, J.H.; Washko, G.R.; Estépar, R.S.J.; Kinsey, C.M. Evidence for Expanding Invasive Mediastinal Staging for Peripheral T1 Lung Tumors. *Chest* **2020**, *158*, 2192–2199. [CrossRef]
20. Navani, N.; Spiro, S.G.; Janes, S.M. Mediastinal staging of NSCLC with endoscopic and endobronchial ultrasound. *Nat. Rev. Clin. Oncol.* **2009**, *6*, 278–286. [CrossRef]
21. Holty, J.E.; Kuschner, W.G.; Gould, M.K. Accuracy of transbronchial needle aspiration for mediastinal staging of non-small cell lung cancer: A meta-analysis. *Thorax* **2005**, *60*, 949–955. [CrossRef] [PubMed]
22. Fiorelli, A.; Santoriello, C.; Di Natale, D.; Cascone, R.; Musella, V.; Mastromarino, R.; Serra, N.; Vicidomini, G.; Polverino, M.; Santini, M. In the era of ultrasound technology, could conventional trans-bronchial needle aspiration still play a role in lung cancer mediastinal staging? *J. Thorac. Dis.* **2017**, *9* (Suppl. S5), S386–S394. [CrossRef]

23. Lee, H.S.; Lee, G.K.; Lee, H.-S.; Kim, M.S.; Lee, J.M.; Kim, H.Y.; Nam, B.-H.; Zo, J.I.; Hwangbo, B. Real-time endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal staging of non-small cell lung cancer: How many aspirations per target lymph node station? *Chest* **2008**, *134*, 368–374. [CrossRef]

24. Yasufuku, K.; Pierre, A.; Darling, G.; de Perrot, M.; Waddell, T.; Johnston, M.; Santos, G.d.C.; Geddie, W.; Boerner, S.; Le, L.W.; et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with medi-astinoscopy for mediastinal lymph node staging of lung cancer. *J. Thorac. Cardiovasc. Surg.* **2011**, *142*, 1393–1400.e1. [CrossRef] [PubMed]

25. Wahidi, M.M.; Herth, F.; Yasufuku, K.; Shepherd, R.W.; Yarmus, L.; Chawla, M.; Lamb, C.; Casey, K.R.; Patel, S.; Silvestri, G.A.; et al. Technical Aspects of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration: CHEST Guideline and Expert Panel Report. *Chest* **2016**, *149*, 816–835. [CrossRef]

26. Elmufdi, F.S.; Peterson, M.K.; Niccum, D.; Asche, S.; Ham, K. Evaluating Yield of 19 Versus 21 G EBUS-TBNA Needles: A Prospective Study. *J. Bronchol. Interv. Pulmonol.* **2021**, *28*, 29–33. [CrossRef]

27. von Bartheld, M.B.; van Breda, A.; Annema, J.T. Complication rate of endosonography (endobronchial and endoscopic ultrasound): A systematic review. *Respiration* **2014**, *87*, 343–351. [CrossRef]

28. Shingyoji, M.; Nakajima, T.; Yoshino, M.; Yoshida, Y.; Ashinuma, H.; Itakura, M.; Tatsumi, K.; Iizasa, T. Endobronchial ultrasonog-raphy for positron emission tomography and computed tomography-negative lymph node staging in non-small cell lung cancer. *Ann. Thorac. Surg.* **2014**, *98*, 1762–1767. [CrossRef]

29. Ong, P.; Grosu, H.; Eapen, G.A.; Rodriguez, M.; Lazarus, D.; Ost, D.; Jimenez, C.A.; Morice, R.; Bandi, V.; Tamara, L.; et al. Endobronchial ultrasound-guided transbronchial needle aspiration for systematic nodal staging of lung cancer in patients with N0 disease by computed tomography and integrated positron emission tomography-computed tomography. *Ann. Am. Thorac. Soc.* **2015**, *12*, 415–419. [CrossRef]

30. Vial, M.R.; O'Connell, O.J.; Grosu, H.B.; Hernandez, M.; Noor, L.; Casal, R.F.; Stewart, J.; Sarkiss, M.; Jimenez, C.A.; Rice, D.; et al. Diagnostic performance of endobronchial ultrasound-guided mediastinal lymph node sampling in early stage non-small cell lung cancer: A prospective study. *Respirology* **2018**, *23*, 76–81. [CrossRef]

31. Rami-Porta, R.; Call, S.; Dooms, C.; Obiols, C.; Sánchez, M.; Travis, W.D.; Vollmer, I. Lung cancer staging: A concise update. *Eur. Respir. J.* **2018**, *51*, 1800190. [CrossRef]

32. Eggeling, S.; Martin, T.; Böttger, J.; Beinert, T.; Gellert, K. Invasive staging of non-small cell lung cancer—A prospective study. *Eur. J. Cardiothorac. Surg.* **2002**, *22*, 679–684. [CrossRef]

33. Sebastián-Quetglás, F.; Molins, L.; Baldó, X.; Buitrago, J.; Vidal, G.; Spanish Video-assisted Thoracic Surgery Study Group. Clinical value of video-assisted thoracoscopy for preoperative staging of non-small cell lung cancer. A prospective study of 105 patients. *Lung Cancer* **2003**, *42*, 297–301. [CrossRef]

34. Massone, P.P.; Lequaglie, C.; Magnani, B.; Ferro, F.; Cataldo, I. The real impact and usefulness of video-assisted thoracoscopic surgery in the diagnosis and therapy of clinical lymphadenopathies of the mediastinum. *Ann. Surg. Oncol.* **2003**, *10*, 1197–1202. [CrossRef]

35. De Giacomo, T.; Rendina, E.A.; Venuta, F.; Della Rocca, G.; Ricci, C. Thoracoscopic staging of IIIB non-small cell lung cancer before neoadjuvant therapy. *Ann. Thorac. Surg.* **1997**, *64*, 1409–1411. [CrossRef]

36. Kumaran, M.; Benamore, R.E.; Vaidhyanath, R.; Muller, S.; Richards, C.J.; Peake, M.D.; Entwisle, J.J. Ultrasound guided cytological aspiration of supraclavicular lymph nodes in patients with suspected lung cancer. *Thorax* **2005**, *60*, 229–233. [CrossRef]

37. Takashima, S.; Sone, S.; Nomura, N.; Tomiyama, N.; Kobayashi, T.; Nakamura, H. Nonpalpable lymph nodes of the neck: Assessment with US and US-guided fine-needle aspiration biopsy. *J. Clin. Ultrasound* **1997**, *25*, 283–292. [CrossRef]

38. Fultz, P.J.; Feins, R.H.; Strang, J.G.; Wandtke, J.C.; Johnstone, D.W.; Watson, T.J.; Gottlieb, R.H.; Voci, S.L.; Rubens, D.J. Detection and diagnosis of nonpalpable supraclavicular lymph nodes in lung cancer at CT and US. *Radiology* **2002**, *222*, 245–251. [CrossRef]

39. van Overhagen, H.; Brakel, K.; Heijenbrok, M.W.; van Kasteren, J.H.L.M.; van de Moosdijk, C.N.F.; Roldaan, A.C.; van Gils, A.P.; Hansen, B.E. Metastases in supraclavicular lymph nodes in lung cancer: Assessment with palpation, US, and CT. *Radiology* **2004**, *232*, 75–80. [CrossRef]

40. Ahmed, M.; Daneshvar, C.; Breen, D. Ultrasound-Guided Cervical Lymph Node Sampling Performed by Respiratory Physicians. *Biomed. Hub.* **2019**, *4*, 1–6. [CrossRef]

41. Folch, E.; Costa, D.B.; Wright, J.; VanderLaan, P.A. Lung cancer diagnosis and staging in the minimally invasive age with increasing demands for tissue analysis. *Transl. Lung Cancer Res.* **2015**, *4*, 392–403. [CrossRef]

42. Coley, S.M.; Crapanzano, J.P.; Saqi, A. FNA, core biopsy, or both for the diagnosis of lung carcinoma: Obtaining sufficient tissue for a specific diagnosis and molecular testing. *Cancer Cytopathol.* **2015**, *123*, 318–326. [CrossRef]

43. Schneider, F.; Smith, M.A.; Lane, M.C.; Pantanowitz, L.; Dacic, S.; Ohori, N.P. Adequacy of core needle biopsy specimens and fine-needle aspirates for molecular testing of lung adenocarcinomas. *Am. J. Clin. Pathol.* **2015**, *143*, 193–306. [CrossRef]

44. Perrotta, F.; Nankivell, M.; Adizie, J.B.; Maqsood, U.; Elshafi, M.; Jafri, S.; Lerner, A.D.; Woolhouse, I.; Munavvar, M.; Evison, M.; et al. Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for PD-L1 Testing in Non-small Cell Lung Cancer. *Chest* **2020**, *158*, 1230–1239. [CrossRef]

45. The American Thoracic Society; The European Respiratory Society. Pretreatment evaluation of non-small-cell lung cancer. *Am. J. Respir. Crit. Care Med.* **1997**, *156*, 320–332. [CrossRef]

46. Vial, M.R.; Eapen, G.A.; Casal, R.F.; Sarkiss, M.G.; Ost, D.E.; Vakil, E.; Grosu, H.B. Combined pleuroscopy and endobronchial ultrasound for diagnosis and staging of suspected lung cancer. *Respir. Med. Case Rep.* **2017**, *23*, 49–51. [CrossRef]

47. Diddams, M.J.; Lee, H.J. Robotic Bronchoscopy: Review of Three Systems. *Life* **2023**, *13*, 354. [CrossRef]