Cost-Effective Diagnosis and Staging Strategies for Lung Cancer

Bharat Bhandari, MD, David E. Ost, MD*

KEYWORDS

• Lung cancer • Lung cancer diagnosis and staging • Lung cancer diagnosis • Bronchoscopy • Robotic bronchoscopy

KEY POINTS

- In patients with peripherally located tumors with clinical-radiographic stage T1N0M0 disease, who are good surgical candidates, and who prefer surgery, a strategy of either computed tomography-guided biopsy or convex endobronchial ultrasound (cEBUS) with rapid onsite pathologic evaluation (ROSE) and peripheral bronchoscopic biopsy is best.
- In patients with peripherally located tumors with clinical-radiographic stage T1N0M0 disease who are good surgical candidates and who prefer surgery, bronchoscopic strategies are more expensive than CT-guided biopsy strategies, but they are associated with fewer complications.
- In patients with centrally located tumors, in those with tumors greater than 3 cm in size and in those with evidence of possible lymph node involvement by PET-CT, a strategy of cEBUS with ROSE and peripheral biopsy as needed is best, resulting in lower costs and fewer complications.
- Improvements in bronchoscopic sensitivity are likely to provide the greatest net monetary benefit in patients with stage I/II disease.

INTRODUCTION

Globally, lung cancer continues to exhibit the highest mortality rate among all cancers, and remains the single highest cause of cancer-related deaths, accounting for 18% of all cancer deaths.[1] The incidence of lung cancer is nearly on par with its mortality, with approximately 2.20 million new cases and over 1.79 million associated deaths occurring annually worldwide.[2] However, the optimal diagnostic and staging strategy for patients with suspected lung cancer remains imprecisely defined. While different guidelines have been developed to inform diagnostic testing strategy,[3,4] there is significant variation in clinical practice.[5] Guideline-inconsistent diagnosis and staging has been associated with an increase in number of invasive tests, increased complications from those tests, and delays in treatment.[6]

An ideal diagnostic and staging strategy for lung cancer should provide all the necessary information so that the best treatment options can be identified. This needs to be done in a timely and cost-effective manner while minimizing complications. In this article we will examine the existing evidence and guidelines on lung cancer diagnosis and staging and update them with data on new technologies such as robotic bronchoscopy that may be able to improve lung cancer diagnosis and staging. To do this in a systematic manner, we will first review the performance characteristics of tests for lung cancer. This will include both tests for diagnosis as well

Department of Pulmonary Medicine, The University of Texas MD Anderson Cancer Center Houston, TX 77030, USA
* Corresponding author.
E-mail address: dost@mdanderson.org

Clin Chest Med 46 (2025) 289–300
https://doi.org/10.1016/j.ccm.2025.02.007

Abbreviations

ACCP	The American College of Chest Physicians
cEBUS	convex endobronchial ultrasound
CTLB	computed tomography guided lung biopsy
EMN	electromagnetic navigation
HAL	Help with the Assessment of Adenopathy in Lung Cancer
HOMER	Help with Oncologic Mediastinal Evaluation for Radiation
ICCR	incremental cost complication ratio
ICER	incremental cost-effectiveness ratio
NCCN	National Comprehensive Cancer Network
NPV	negative predictive value
NSCLC	nonsmall cell lung cancer
PET-CT	PET-computed tomography
pN2	probability of mediastinal metastasis
QALY	quality-adjusted life year
RB	robotic bronchoscopy
rEBUS	radial endobronchial ultrasound
ROSE	rapid onsite pathologic evaluation
RTCT	real-time computed tomography
SPN	solitary pulmonary nodule
VATS	video-assisted thoracoscopic surgery
WTP	willingness of pay

as tests that facilitate staging. In each instance we will describe the sensitivity, specificity, and complications of the tests. We will then integrate this evidence with decision theory, cost-effectiveness analysis, and treatment considerations to arrive at a straightforward algorithmic approach for lung cancer.

PERFORMANCE CHARACTERISTICS OF TESTS FOR LUNG CANCER

Diagnostic modalities for peripheral lesions encompass a range of techniques, each with distinct applications and performance characteristics. These techniques can be broadly classified as radiographic imaging, mediastinal staging, and peripheral biopsy modalities. They include mediastinoscopy, surgical lung biopsy/video-assisted thoracoscopic surgery (VATS), convex endobronchial ultrasound (cEBUS) with rapid onsite pathologic evaluation (ROSE), peripheral biopsy with electromagnetic navigation (EMN) and radial endobronchial ultrasound (rEBUS), peripheral biopsy with robot and computed tomography guided lung biopsy (CTLB). Crucial to note is that test sensitivity can vary for a given test depending on the clinical context. Because of this, decisions regarding the selection and sequencing of diagnostic tests hinge upon factors such as lesion attributes, anatomic location, and the overall health status of the patient.

Radiographic Imaging

PET-computed tomography (PET-CT) has become standard of care for radiographic initial staging of lung cancer. The American college of Chest Physicians guidelines recommend PET-CT over conventional chest CT for mediastinal nodal staging.[7] In a large meta-analysis, PET-CT was found to be superior to conventional chest CT for mediastinal staging in nonsmall cell lung cancer (NSCLC). PET-CT had a pooled sensitivity and specificity of 0.79 and 0.91, respectively. Conventional CT had a pooled sensitivity and specificity of 0.60 and 0.77.[8] In another meta-analysis comparing PET-CT and conventional chest CT for detecting mediastinal lymph node metastases in NSCLC, PET-CT showed a significantly higher diagnostic accuracy with a Q value of 0.90 (95% CI, 0.86–0.95) compared to CT's Q value of 0.70 (95% CI, 0.65–0.75).[9] The Q value is a statistical measure from the summary receiver operating characteristic curve, indicating the overall accuracy of a diagnostic test by combining sensitivity and specificity. A higher Q value (closer to 1) reflects greater diagnostic accuracy. In another study the diagnostic accuracy and sensitivity of the staging regimen in predicting operability were assessed, with the assumption that none of the patients classified as having inoperable disease after staging should have undergone surgery (specificity, 100%). In the PET-CT group, the diagnostic accuracy was 79% (95% CI, 69–86) and sensitivity was 64% (95% CI, 52–75). In the conventional staging group/mediastinoscopy group, accuracy was 60% (95% CI, 50–70) and sensitivity was 32% (95% CI, 21–45).[10] PET-CT has also been used for patients with limited-disease small cell lung cancer undergoing concurrent chemoradiotherapy, resulting in significant treatment field modifications.[11]

PET-CT is useful for mediastinal staging but should not be relied upon as the sole tool for this purpose.[12] PET-CT has a significant rate of false negatives in stage I NSCLC ~ 11% (7.6% in noncentral and 14.8% in central cancers).[13] Some studies even predicted up to 26% false negative N2 disease.[14] Thus, PET-CT, while useful, is not sufficient by itself to stage NSCLC.[15] These results underscore the importance of comprehensive evaluation methods to minimize diagnostic errors and enhance clinical decision-making when staging lung cancer.

Mediastinoscopy: Cervical and Anterior Mediastinoscopy

Historically mediastinoscopy was the standard of care for mediastinal staging until the advent of

EBUS. It allows biopsy of lymph node stations 2R, 2L, 4R, 4L, 7, 10R, and 10L. With extended mediastinoscopy dissection between the anterior aspect of left innominate vein and the sternum over the aortic arch, it gives access to lymph node stations 5 and 6. Alternative approaches to biopsy stations 5 and 6 include the Chamberlain procedure, CT-guided biopsy, or a left thoracoscopic approach. Transcervical extended mediastinal lymphadenectomy and video-assisted mediastinal lymphadenectomy offer extensive bimanual dissection of lymph nodes, with a sensitivity of 0.96 and a negative predictive value (NPV) of 0.99. Nevertheless, these techniques come with an elevated risk of recurrent laryngeal nerve injury.[16,17] Two large metanalyses compared the sensitivity of cEBUS to mediastinoscopy for mediastinal staging of NSCLC, the reported pooled sensitivity of mediastinoscopy was found to be 81% (95% CI, 75%-86%) and of 81.8% (95% CI, 69.1%-90.9%) for video-assisted cervical mediastinoscopy respectively.[18,19]

The complication rates reported for mediastinoscopy vary, generally ranging from approximately 1% to 6%. According to a retrospective review of 2145 consecutive mediastinoscopies, the overall complication rate was 1.07%, with specific complications including hemorrhage (0.33%), vocal cord dysfunction (0.55%), tracheal injury (0.09%), and pneumothorax (0.09%).[20] A meta-analysis of 8 studies involving 1245 patients found a complication rate of 6.0%, with laryngeal recurrent nerve palsy accounting for 2.8%.[21] Surgeons should exercise caution in situations where mediastinoscopy presents increased risks, such as redo procedures and mediastinal fibrosis resulting from prior radiation therapy.[22]

Surgical Lung Biopsy/Video-Assisted Thoracoscopic Surgery

Surgical lung biopsy is a more invasive procedure for mediastinal staging. VATS provides access to lymph node stations 5, 6, 7, 8 and 9. However only ipsilateral mediastinal nodes are accessible and station 2L and 4L are technically challenging to biopsy.[23] In addition, VATS also provides visualization of the pleural space and facilitates assessment of possible chest wall invasion as well as an opportunity to do wedge biopsies of peripheral lung nodules.

Robust data regarding performance characteristics of surgical lung biopsy for mediastinal staging of lung cancer are not available. A retrospective analysis found the sensitivity of diagnosing lung cancer by surgical biopsy to be 164/165 (99.4%).[24] Another retrospective study of 366 patients reported sensitivity of VATS for metastases to be 99%.[25] According to a propensity-matched analysis from the Society of Thoracic Surgeons (STS) database, the operative mortality for wedge resection is 1.21%, which is significantly lower than the 1.93% observed for anatomic resection ($P = .01$). Major morbidity occurs in 4.53% of patients undergoing wedge resection, compared to 8.97% for anatomic resection ($P<.0001$).[26] Common complications include postoperative pain and persistent air leak.

Convex Endobronchial Ultrasound and Rapid on Site Evaluation

The American College of Chest Physicians (ACCP) recommends cEBUS as the initial test for invasive nodal staging in most patients due to its minimally invasive nature, high sensitivity and specificity, and low complication rate.[3] In contrast to mediastinoscopy, cEBUS offers the advantage of accessing and sampling bilateral mediastinal and hilar lymph nodes. Specifically, cEBUS can sample lymph nodes, including stations 2 (upper para-tracheal), 4 (lower para-tracheal), 7 (subcarinal), and 10 (hilar). Additionally, unlike mediastinoscopy and VATS, cEBUS can sample the hilar lymph node stations 11 (interlobar) and 12 (lobar) bilaterally. Rarely, some nodal stations may require EUS, such as the inferior mediastinal lymph node stations 8 (para-esophageal) and 9 (pulmonary ligament), which are beyond the reach of cEBUS.[27] This comprehensive access allows for a more thorough evaluation and staging of lung cancer.

Performance characteristics for cEBUS have been studied extensively. A large meta-analysis encompassing 14 prospective studies with 1658 patients found that cEBUS demonstrated a pooled sensitivity of 92% (95% CI, 0.91–0.93) and a pooled specificity of 100% (95% CI, 0.90–1.00).[28] Another trial compared cEBUS and mediastinoscopy for staging lung cancer and found comparable sensitivity and accuracy for both mediastinoscopy (79% and 93%, respectively) and cEBUS (81% and 93%, respectively). The cohort had a higher percentage of stage I cancers (59%) yielding a lower sensitivity for both cEBUS and mediastinoscopy.[29] The sensitivity of cEBUS is dependent on burden of disease in the involved lymph nodes. Thus, cEBUS sensitivity varies depending on PET-CT findings. Patients with PET-CT N2 or N3 disease that truly have lymph node metastasis have a higher burden of malignant cells in the PET avid lymph nodes than patients with PET-CT N0 disease that have occult malignant nodal involvement. Therefore, the sensitivity of cEBUS is higher in patients with PET-avid

nodal disease compared to patients with PET-negative occult nodal disease. A study of patients with radiographic N0 disease reported the sensitivity of cEBUS to be 36.7%.[30] In contrast, a study of patients with PET positive clinical-radiographic N2/N3 disease reported a sensitivity of 88.0%.[31] In a large systematic review and metanalysis, which included 16,181 patients, the overall rate of serious adverse events (mediastinitis, perforation, hemorrhage and pneumothorax) for cEBUS was 0.05%, with no reported mortality and minor adverse events reported at a rate of 0.22%.[32] cEBUS can be safely performed using either moderate sedation or general anesthesia with similar efficacy.[33]

ROSE is a cytologic diagnostic procedure that assesses the adequacy and accuracy of biopsy samples during various procedures including cEBUS through immediate microscopic examination of cytology smears. The primary benefits of ROSE include ensuring adequate and representative samples, reduced need for repeat procedures by confirming sample adequacy in real-time and immediate specimen triage for additional diagnostic tests crucial for personalized treatment planning. A retrospective study of 438 patients and 965 lymph nodes using ROSE and cEBUS reported a sensitivity of 96.5% and specificity of 100% for lymph node staging, and the concordance rate between ROSE and the final pathologic diagnosis was 94.3%, demonstrating high agreement.[34]

A systematic review and meta-analysis assessed the impact of ROSE on the diagnostic yield of cEBUS found that the use of ROSE resulted in significantly fewer needle passes (mean difference [95% CI], −1.1 [-2.2 to −0.005]; $P<.001$) and decreased overall procedural time; however, no difference in diagnostic yield was noted.[35] However, ROSE also offers the significant advantage of reducing the necessity for additional bronchoscopic procedures, such as peripheral bronchoscopy. If ROSE identifies malignant cells on cEBUS, peripheral biopsy can be avoided, since the diagnosis has already been made. By avoiding unneeded peripheral biopsies in select cases, ROSE decreases costs and complications.[36]

Peripheral Biopsy with Electromagnetic Navigation and Radial Endobronchial Ultrasound

Initial advanced diagnostic bronchoscopy systems used EMN platforms. A systematic review and meta-analysis found the pooled sensitivity of EMN for malignancy to be 77% (95% CI, 72%-82%).[37] The NAVIGATE trial of EMN systems found a sensitivity for malignancy of 69% and a specificity of 100%. Subsequently the multicenter AQuiRE registry reported sensitivity for lung cancer in patients with peripheral pulmonary lesions of 54% to 69% for EMN.[38–40] The complication rate of EMN is generally reported to be between 3% and 8.4%, with pneumothorax being the most frequent complication. A systematic review and meta-analysis encompassing 15 trials and 1033 lung nodules found a pneumothorax rate of 3.1%, with chest tube drainage required in 1.6% of these cases.[41]

Peripheral bronchoscopy using rEBUS as an adjunct with flexible bronchoscope improved lesion localization, but navigating to the site of the lesson still posed a challenge.[42] An updated meta-analysis found a pooled sensitivity of 72% (95% CI, 70%-75%) for rEBUS, with a pooled pneumothorax rate of 0.7% (95% CI, 0.3%-1.1%).[43]

Peripheral Biopsy with Robotic Bronchoscopy

The advent of robotic bronchoscopy (RB) represents a notable advancement in bronchoscopy, offering extended reach beyond traditional flexible bronchoscopy and distal bronchoscope control with stability to facilitate biopsies of peripheral nodules.[44] A metanalysis evaluating the diagnostic efficacy and safety of RB reported a pooled diagnostic yield of 81.9% and a pooled sensitivity for malignancy of 87.6%. Complication rates, notably pneumothorax (1.18%) and bleeding (0.04%), were low.[45] Another retrospective multicenter study compared the efficacy and diagnostic performance of RB to CTLB for diagnosing pulmonary nodules suspected of lung cancer. Overall diagnostic yield was similar between RB (87.6%) and CTLB (88.4%) and the complication rate was significantly lower for RB versus CTLB (4.4% vs 17%; $P=.002$).[46] Currently 3 robotic platforms are available in the market, which include the Monarch Platform (FDA 2018), Ion Endoluminal RB Platform (FDA 2019), and Galaxy System (FDA 2023).[47] The newer systems or the so called second generation of robots are integrated with real-time CT (RTCT) with improved lesion localization. One study reported a procedural sensitivity for malignancy of 84% when using RB combined with RTCT.[48] Another study involving shape-sensing robotic-assisted bronchoscopy (Ion system) with RTCT reported a sensitivity of 87.3% for malignancy.[49]

Percutaneous Computed Tomography Guided Lung Biopsy

According to a meta-analysis referenced by the British Thoracic Society, the overall sensitivity of CTLB for lung cancer is approximately 90.7% (95% CI 88.8% to 92.4%), and the specificity is

around 93.9% (95% CI 91.1% to 96.0%).[50] Pneumothorax represents the most common complication following CTLB with reported incidence rates ranging from 9% to 43%. When pneumothorax complications occur, the necessity for chest tube placement varies, required in approximately 7% of cases.[51–55]

DIAGNOSTIC/STAGING STRATEGY

While many guidelines and textbooks often consider lung cancer diagnosis and lung cancer staging separately,[36,56–58] it is important to recognize that diagnosis and staging occur simultaneously, and as such they are indivisible when assessing the efficacy of clinical strategies for the evaluation of patients with possible lung cancer. The cycle of care in this case begins immediately after a lung lesion is first recognized on imaging. The cycle of care ends in 1 of 2 ways. First, the strategy may rule out lung cancer, often by establishing an alternative diagnosis other than lung cancer (eg, infection or hamartoma). Second, the cycle of care ends when a diagnosis of lung cancer is made *and all other requisite information for proper treatment has been obtained.*

This concept of evaluating efficacy over the entire cycle of care as opposed to focusing solely on discreet steps within the cycle of care is important because it fundamentally alters the way we think about and measure the impact of diagnostic test selection and outcomes. It is the outcomes over the entire cycle of care that matter, not just the outcomes of the individual steps contained within the cycle. For example, in a patient with a 2.0 cm lung nodule with ipsilateral hilar lymphadenopathy by PET-CT and no evidence of distant metastatic disease, percutaneous CTLB will be more likely to establish the diagnosis than bronchoscopy with cEBUS guided transbronchial needle aspiration of the lymph nodes with ROSE and peripheral biopsy with rEBUS guidance if needed. If we were to evaluate alternatives strategies based solely on the outcome of this individual step in the process (ie, establish a diagnosis), we would choose CTLB. However, over the entire cycle of care, the cEBUS + ROSE/rEBUS strategy is superior. This is because even if the CTLB establishes a diagnosis, a second test will be required to stage the mediastinum. In contrast, the cEBUS + ROSE/rEBUS strategy can potentially both diagnose and stage the patient with 1 test, and it has fewer complications. Thus, even though CTLB has a higher diagnostic yield, in aggregate the costs and complications *over the entire cycle of care* will be higher with CTLB than with cEBUS + ROSE/rEBUS because of the downstream consequences.[36]

Using this conceptual framework for evaluating aggregate strategies, there are 2 main questions that must be resolved to determine optimal diagnostic/staging strategies (**Fig. 1**). The first question is what are the patient's comorbidities and health status, and based on these, if this is indeed cancer, what are the treatment options available? The second question is what is the clinical-radiographic stage at presentation? These questions must be asked and answered in parallel, rather than in series, right at the start of the process. Once these 2 questions are addressed, we can identify the most cost-effective strategies for any given patient consistent with their values and preferences (see **Fig. 1**).

Comorbidities and Treatment Options

Comorbidities and treatment options are fundamental to determining any diagnostic strategy. It is the potential benefit of treatment in those patients that have disease as compared to the potential harm of unnecessary treatment in those without disease that determines the treatment threshold.[59] The treatment threshold is the probability of disease at which the benefits of treating a patient with disease and the potential harms of accidently treating a patient without disease are equal. If the probability of disease is greater than the treatment threshold, then if no additional diagnostic tests are available, empiric treatment will be warranted. Conversely, if the probability is less than the treatment threshold, and all diagnostic avenues have been exhausted, then conservative management and observation will be warranted.

This has been best studied for the case of the solitary pulmonary nodule (SPN), which is just a special subset of all patients being evaluated for possible lung cancer. SPNs can be thought of as patients with a clinical-radiographic stage of T1, N0, and M0 disease by PET-CT. The important question to ask up front is what the patient's comorbidities are, and do they impact the treatment alternatives available? A patient with a 2-cm SPN and end-stage COPD on home oxygen with concurrent cardiac issues is not likely to be a candidate for lobectomy but may be a candidate for stereotactic body radiation therapy (SBRT). Biopsy and mediastinal sampling to rule out lymph node involvement will be useful in such patients, since any nodal disease will alter the treatment plan and preclude SBRT. Conversely, a patient with the same 2-cm SPN that is a good surgical candidate with high functional status and good lung function with a PET-CT showing no lymph node involvement and no distant metastasis may be able to go straight to surgery after a positive

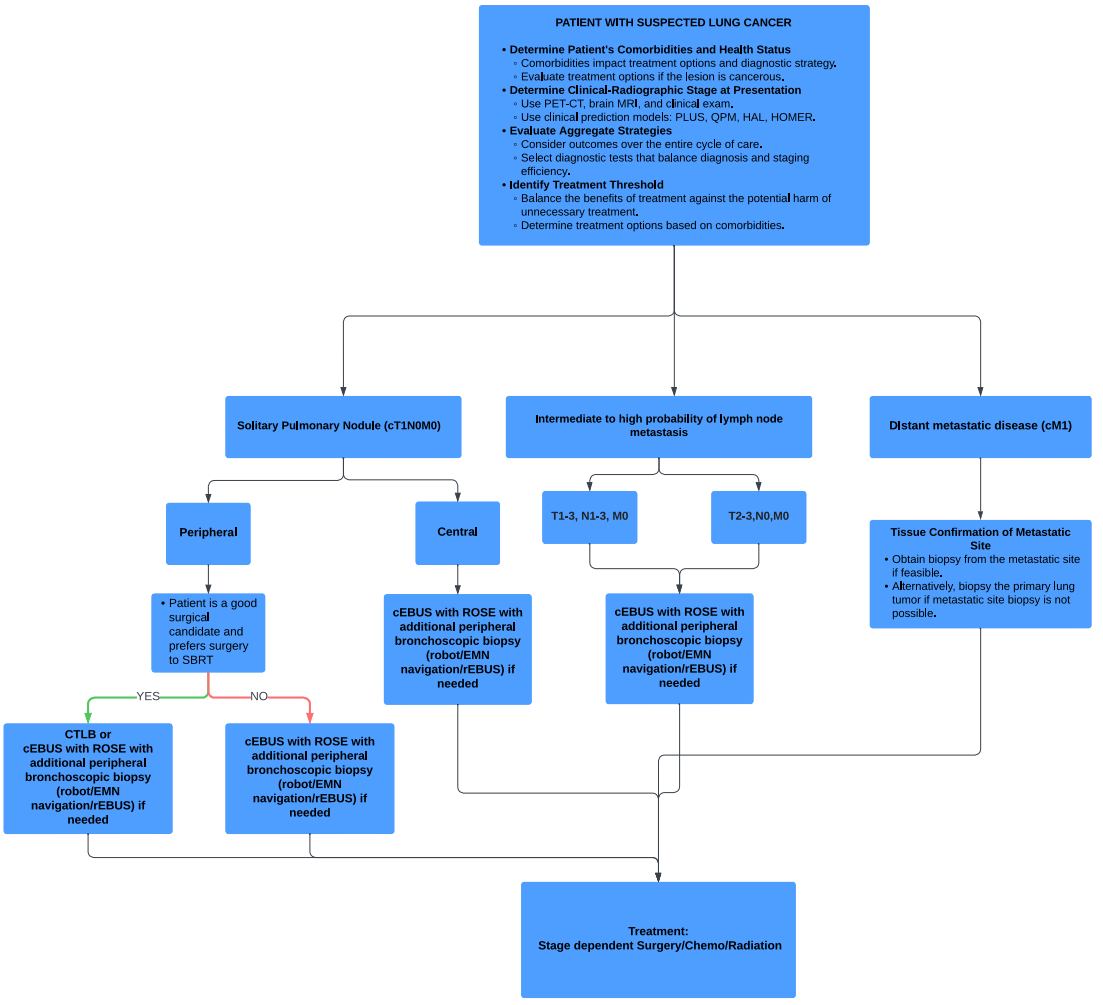

Fig. 1. Algorithm for developing a complete diagnosis and staging strategy for suspected lung cancer.

biopsy in select cases.[3,56,60] The diagnostic approach is different even though the lung nodule itself and the probability of cancer are identical. What differ are the comorbidities, which impact treatment choices, which in turn impact the potential for benefit and harm, which changes the treatment threshold, and which in turn impacts optimal diagnostic strategy. So as a rule of thumb, it is useful to ask up front before the diagnostic testing process begins: what does the end-game look like in term of treatment options should this prove to be cancer, given that individual patient's comorbidities and expressed preferences? By knowing the end, it is easier to plan the beginning.

Clinical-Radiographic Stage at Presentation

The second key element is clinical-radiographic stage. Clinical-radiographic stage is determined by the patient's PET-CT, other available imaging (eg, brain MRI), and clinical examination. As described above, PET-CT has many limitations and is not sufficiently accurate to determine stage by itself. However, PET-CT is informative regarding the probability of nodal metastasis and can be combined with other clinical factors such as age, histology, and central location to arrive at quantitative estimates of the probability of metastatic hilar and mediastinal lymph node involvement. Examples of clinical prediction models that do this include the PLUS Prediction Model, Quebec Prediction Model, Help with the Assessment of Adenopathy in Lung Cancer (HAL) model, and Help with Oncologic Mediastinal Evaluation for Radiation (HOMER) model.[61–64]

While all 4 models provide estimates of the probability of hilar and mediastinal lymph node involvement, some are more granular than others. While PLUS, HAL, and the Quebec model are suitable for patients that are good surgical candidates,

they do not distinguish between N0 and N1 disease, which makes them less useful for patient that are considering SBRT. For patients receiving SBRT, knowing how likely the patient is to have N1 disease matters. HOMER is the only available model that provides probabilities for N0, N1, and N2|3 nodal involvement. A web-based calculator using HOMER is available (https://biostatistics.mdanderson.org/shinyapps/HOMER/). Notably, the same variables are used in all 4 models. Factors associated with a higher probability of metastatic nodal involvement include central location, higher N stage by PET-CT, younger age, and adenocarcinoma histology.[61–64]

It is the prediction of the probability of nodal and distant metastasis that make PET-CT clinical-radiographic stage useful. Using PET-CT clinical-radiographic stage and clinical prediction rules, as well as information on comorbidities, allows us to select more optimal diagnostic/staging strategies. Patients will fall into one of 3 main groups, as determined by clinical-radiographic stage. First are patients with an SPN with a low probability of lymph node metastasis (cT1N0M0), second are patients with an intermediate to high probability of lymph node metastasis but without evidence of distant metastatic disease (T1-3, N1-3, M0, and those with central lesions), and finally are patients with evidence of distant metastatic disease (M1) at presentation.

Solitary pulmonary nodules (T1, N0, M0)

The classification of T1N0M0 lung tumors (Stage I) exhibit distinct prognostic and staging considerations depending on whether they are centrally or peripherally located. Central tumors in the inner one-third of the hemithorax, delineated by concentric lines arising from the midline. Central tumors are defined differently by the European Society for Therapeutic Radiology and Oncology and other European societies as being inner two-third and peripheral being outer one-third.[65] Regardless, central tumors are close to the mediastinum and major airways, and are associated with a higher rate of nodal metastasis.[60,61,66] Thus, patients with centrally located clinical-radiographic T1N0M0 tumor should usually undergo cEBUS with ROSE and peripheral bronchoscopic biopsy if required as their first diagnostic test (see **Fig. 1**).

The diagnostic and staging approach for patients with peripheral clinical-radiographic T1N0M0 tumors depends on whether the patient is a good candidate for lobectomy and the patient's treatment preferences. Peripheral lung tumors are lesions located in the outer one-third or by some societies outer two-third of the lung parenchyma.[67] In contrast to central lung cancer, which involves tumors located near the hilum or main bronchi, peripheral lung cancer is generally found in the outer regions of the lung parenchyma.[66] For patients with peripheral T1N0M0 tumors who are good surgical candidates and who prefer surgery to SBRT for treatment, a strategy of peripheral biopsy using CTLB or bronchoscopy is sufficient, and the patient can be referred for lobectomy without invasive mediastinal staging before surgery, as the risk of occult lymph node metastasis is minimal, and at the time of surgery lymph node dissection and sampling can be performed (see **Fig. 1**). Straight surgical resection, specifically lobectomy, has traditionally been the gold standard for peripheral T1 lung cancer. However, recent evidence suggests that sublobar resection, including segmentectomy and wedge resection, may be a viable alternative for select patients with peripheral T1 lung cancer.[68] However, not biopsying a peripheral T1 lung cancer lesion before surgical resection has significant drawbacks, including the risk of misdiagnosing benign lesions, as shown in the CALGB 140503 trial where 16% of suspected malignant lesions were benign, leading to unnecessary surgeries. Additionally, 7% of patients were understaged, with undetected nodal metastases impacting treatment decisions.[68] Intraoperative diagnoses also reduce the likelihood of comprehensive lymph node sampling, potentially affecting adjuvant therapy. Furthermore, preoperative biopsies enhance diagnostic accuracy, decreasing the incidence of nontherapeutic procedures and, despite some debate, may mitigate the theoretic risk of tumor dissemination during surgery. Overall, obtaining a tissue diagnosis is associated with improved guideline-concordant care, as it increases rates of lymph node harvest and upstaging, ultimately benefiting patient management.

The incremental cost-effectiveness ratio (ICER) is a statistical used in cost-effectiveness analysis to evaluate the cost per additional unit of benefit provided by one health care intervention compared to another. It is calculated by dividing the difference in costs between the 2 interventions by the difference in their effectiveness. The incremental cost complication ratio (ICCR) is similar to ICER except that the effectiveness is conveyed in terms of avoiding complication. Both ICER and ICCR provide a quantitative measure of the additional cost associated with achieving an additional unit of effect, such as a quality-adjusted life year (QALY) gained depending on the willingness of pay (WTP), making it a critical tool in health economics for decision-making about health care resource allocation. A decision analysis showed that CTLB is the least costly strategy for diagnosis

in T1N0M0 peripheral tumors who are good surgical candidates. However, CTLB was associated with more complications (risk difference of 14%), needing more time to complete evaluation (8 days) with a higher chance of undetected occult N2-N3 disease (risk difference 2.3%), and had a slightly increased risk of mortality (risk difference, 0.07%). The additional cost of cEBUS with or without peripheral bronchoscopy with rEBUS to avoid 1 complication related to CTLB (ICCR) was found to be $12,037. The ICCR was $22,436 higher for lesions less than 2 cm, but only $11,104 if bronchus sign was present. Thus, if the WTP was $13,000 or more cEBUS becomes more optimal than CTLB, conversely at a WTP of $10,000 CTLB is the most optimal choice.[36] Another cost-effectiveness analysis done by Kujawa and colleagues for already diagnosed stage I lung cancer found similar results.[69] In patients with N0 status on imaging, they found that foregoing mediastinal lymph node sampling and proceeding to surgery was the least effective strategy (QALY, 5.80) but was also the least expensive strategy ($11,863). Mediastinal sampling with cEBUS alone was cost-effective with an ICER of approximately $26,000 per QALY when the probability of mediastinal metastasis (pN2) exceeded 2.5%. cEBUS followed by mediastinoscopy was cost-effective only when probability of N2 disease exceeded 57%, with an ICER of around $79,000/QALY.[36,69]

For patients with peripheral T1N0M0 tumors who are not good surgical candidates, or who prefer SBRT over surgery, mediastinal sampling using cEBUS and ROSE with peripheral bronchoscopic biopsy is warranted to rule out occult nodal metastasis (see **Fig. 1**). As suggested by the HOMER model,[70] cEBUS will only identify occult nodal metastasis in about 5% of these patients. However, since these patients will be treated with SBRT, knowing the status of the N1 and N2 nodes will be impactful for radiation planning, and as suggested by Kujawa, the pN2 disease would still be sufficient to warrant mediastinal sampling first.[69]

The evolution of bronchoscopy techniques, particularly the introduction of RB, has brought significant advancements in diagnostic accuracy and patient outcomes, although specific guidelines for its use remain underdeveloped. All the above-mentioned guidelines were written in 2013 before the advent of RB. The decision analyses above also predate the robotic era. Although the latest National Comprehensive Cancer Network (NCCN) guidelines 2024 include RB as an alternative diagnostic tool, it does not give specific recommendations for when RB should be employed. The integration of RB into clinical practice marks a significant advancement, offering high diagnostic sensitivity with low complication rates and the ability to perform concurrent staging.[45] As noted above, a previous decision analysis suggested that in good surgical candidates who preferred surgery over SBRT, a strategy of CTLB was cheaper than a strategy of cEBUS with rEBUS, but the bronchoscopic strategy resulted in fewer complications and decreased the number of patients with occult N2-3 disease that received futile surgery, with an ICCR of $12,037(36). It is likely, but currently unproven, that RB could further improve on this, lowering the ICCR of bronchoscopic strategies. A decision analysis estimated that a 10% improvement in bronchoscopy sensitivity results in a net monetary benefit of $19,805 in stage I/II patients, assuming a WTP of $100,000/QALY.[71]

Intermediate to high probability of nodal metastasis (cT1-3,N1-3, M0)

Major thoracic and oncological society guidelines emphasize the use of cEBUS for mediastinal staging in patients with suspected N2 or N3 involvement, recommending systematic invasive staging over imaging alone. The ACCP, the European Society of Thoracic Surgeons, and the NCCN, recommend the use of cEBUS and or endoscopic ultrasound (EUS) for staging for patients with high suspicion of N2 or N3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no distant metastases).[72] If there is a high probability of nodal disease by PET-CT (eg, PET avid N2 and N3 nodes), but cEBUS is negative for malignancy, more invasive techniques such as mediastinoscopy or surgery may be warranted to confirm that the nodes are truly negative.[58]

A cost-effective analysis for staging of cT1-3N1-3M0 lung cancer, showed that a strategy combining cEBUS with ROSE with peripheral bronchoscopy with rEBUS was most optimal and cost-effective, compared to other alternative approaches.[36] Using EMN with rEBUS was safer; however, it was more expensive, with an ICCR of $36,600.

Distant metastatic disease (cM1)

For patients with a suspicious solitary extra thoracic metastasis, obtaining tissue confirmation from the metastatic site guidelines advise fine needle aspiration or biopsy, provided it is feasible and minimally invasive (Grade 1C).[58] In patients with multiple bone metastases and overwhelming evidence of stage IV disease, biopsy of the most feasible and safest site is recommended. The selected site should permit the assessment of

molecular markers. Thus, bone biopsy is often not the best choice, as assessment of molecular marker from bone biopsies is not always possible due to specimen handling issues.[73] If obtaining a biopsy from the metastatic site is not possible due to accessibility or other factors, then a biopsy of the primary lung tumor is advised as an alternative.[73]

SUMMARY

In conclusion, cost-effective diagnosis and staging in lung cancer requires a comprehensive and tailored approach. Optimal strategies should integrate various diagnostic tests, such as PET-CT, cEBUS, ROSE, CTLB, and mediastinoscopy, to maximize diagnostic accuracy and minimize complications and costs. The optimal sequence depends on clinical-radiographic stage, comorbidities, and patient preferences. While PET-CT provides valuable initial staging information, it is not sufficient by itself to stage patients. In patients with T1N0M0, CTLB or advanced diagnostic bronchoscopic approaches are reasonable, depending on whether the patient is a good surgical candidate and whether they desire SBRT. In patients with central lesions and in those with nodal disease on PET-CT without distant metastasis, strategies that use cEBUS with ROSE with advanced diagnostic bronchoscopy techniques if required are best. By focusing on personalized diagnostic pathways that consider lesion characteristics, patient health status, and the likelihood of nodal involvement, clinicians can improve patient outcomes and deliver cost-effective lung cancer care.

CLINICS CARE POINTS

Pearls

- Diagnosis and staging should be integrated into a unified strategy to optimize patient management, rather than treating them as separate steps.
- Percutaneous computed tomography-guided lung biopsy (CTLB) has a high sensitivity and specificity for lung cancer, but carries a higher pneumothorax complication rate compared to bronchoscopy techniques.
- Robotic bronchoscopy (RB) offers a high diagnostic yield and sensitivity for malignancy with significantly lower complication rate and presents as an advancement to the previous electromagnetic navigation and radial endobronchial ultrasound systems.
- The combination of RB with real-time CT improves diagnostic sensitivity for malignancy, enhancing lesion localization and diagnostic accuracy.
- Rapid onsite evaluation by pathology demonstrates high sensitivity and specificity for lymph node staging during bronchoscopic procedures, reducing the needle passes, procedure time and need for repeat procedures.

Pitfalls

- Despite promising results, the efficacy and cost-effectiveness of RB are not yet fully established, and guidelines for its specific use in various scenarios remain underdeveloped.
- Models like PLUS, HAL, and Quebec do not distinguish between N0 and N1 disease, which can be a limitation for patients considering stereotactic body radiation therapy.
- PET-CT, while useful, has limitations in accurately staging nodal involvement on its own, often necessitating additional invasive procedures for confirmation.
- All diagnostic tests have inherent risks of false negatives. Even with advanced techniques like RB and convex endobronchial ultrasound, there remains a possibility of undetected malignancy, which can result in delayed diagnosis and treatment.

DISCLOSURE

D.E. Ost is a consultant for Intuitive Surgical, Becton Dickensen, and Johnson and Johnson. B. Bhandari has no COI to declare.

REFERENCES

1. R S. Mapping of global, regional and national incidence, mortality and mortality-to-incidence ratio of lung cancer in 2020 and 2050. Int J Clin Oncol 2022;27(4).
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 Countries. Ca - Cancer J Clin 2021;71(3).
3. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl).
4. Ettinger DS, Wood DE, Aisner DL, et al. NCCN guidelines insights: non-small cell lung cancer, version 2.2021. J Natl Compr Cancer Netw : J Natl Compr Cancer Netw 2021;19(3).
5. Ost DE, Niu J, Zhao H, et al. Quality gaps and comparative effectiveness in lung cancer staging and diagnosis. Chest 2020;157(5):1322–45.

6. CL W, Rayburn JR, Chang SC, et al. Not following the rules in guideline care for lung cancer diagnosis and staging has negative impact. Ann Thorac Surg 2020;110(5).
7. Silvestri GA, Tanoue LT, Margolis ML, et al. The noninvasive staging of non-small cell lung cancer: the guidelines. Chest 2003;123(1 Suppl).
8. Dwamena BA, Sonnad SS, Angobaldo JO, et al. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s–meta-analytic comparison of PET and CT. Radiology 1999;213(2).
9. Birim O, Kappetein AP, Stijnen T, et al. Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer. Ann Thorac Surg 2005;79(1).
10. Fischer B, Lassen U, Mortensen J, et al. Preoperative staging of lung cancer with combined PET-CT. N Engl J Med 2009;361(1).
11. van Loon J, Offermann C, Bosmans G, et al. 18FDG-PET based radiation planning of mediastinal lymph nodes in limited disease small cell lung cancer changes radiotherapy fields: a planning study. Radiother Oncol 2008;87(1).
12. G W, HB, Lopes de Figueiredo Pinto JA, Martínez-Mesa J, Zanini ML, et al. PET-CT has low specificity for mediastinal staging of non-small-cell lung cancer in an endemic area for tuberculosis: a diagnostic test study (LACOG 0114). BMC Cancer 2019;19(1).
13. Gómez-Caro A, Boada M, Cabañas M, et al. False-negative rate after positron emission tomography/computer tomography scan for mediastinal staging in cI stage non-small-cell lung cancer. Eur J Cardio Thorac Surg 2012;42(1).
14. Cerfolio RJ, Bryant AS, Ojha B, et al. Improving the inaccuracies of clinical staging of patients with NSCLC: a prospective trial. Ann Thorac Surg 2005;80(4).
15. Steinfort DP, Kothari G, Wallace N, et al. Systematic endoscopic staging of mediastinum to guide radiotherapy planning in patients with locally advanced non-small-cell lung cancer (SEISMIC): an international, multicentre, single-arm, clinical trial. Lancet Respir Med 2024;12(6).
16. M Z. Transcervical extended mediastinal lymphadenectomy: results of staging in two hundred fifty-six patients with non-small cell lung cancer. J Thorac Oncol 2007;2(4).
17. Call S, Obiols C, Rami-Porta R, et al. Video-assisted mediastinoscopic lymphadenectomy for staging non-small cell lung cancer. Ann Thorac Surg 2016;101(4).
18. Sehgal IS, Dhooria S, Aggarwal AN, et al. Endosonography versus mediastinoscopy in mediastinal staging of lung cancer: systematic review and meta-analysis. Ann Thorac Surg 2016;102(5).
19. Diebels I, Hendriks JMH, Van Meerbeeck JP, et al. Evaluation of mediastinoscopy in mediastinal lymph node staging for non-small-cell lung cancer. Interact Cardiovasc Thorac Surg 2021;32(2).
20. Lemaire A, Nikolic I, Petersen T, et al. Nine-year single center experience with cervical mediastinoscopy: complications and false negative rate. Ann Thorac Surg 2006;82(4).
21. Bousema JE, van Dorp M, Noyez VJJM, et al. Unforeseen N2 disease after negative endosonography findings with or without confirmatory mediastinoscopy in resectable non-small cell lung cancer: a systematic review and meta-analysis. J Thorac Oncol 2019;14(6).
22. Wei B, Bryant AS, Minnich DJ, et al. The safety and efficacy of mediastinoscopy when performed by general thoracic surgeons. Ann Thorac Surg 2014;97(6).
23. JA H. The role of VATS for staging and diagnosis in patients with non-small cell lung cancer. Semin Thorac Cardiovasc Surg 2007;19(3).
24. Ueda K, Tanaka T, Hayashi M, et al. Thoracoscopic coaxial cutting needle biopsy for clinically suspected lung cancer: technical details, diagnostic accuracy, and probable complications. Surg Endosc 2012;26(7).
25. Coutinho GF, Pancas R, Magalhães E, et al. Diagnostic value of surgical lung biopsy: comparison with clinical and radiological diagnosis. Eur J Cardio Thorac Surg 2008;33(5).
26. Linden PA, D'Amico TA, Perry Y, et al. Quantifying the safety benefits of wedge resection: a society of thoracic surgery database propensity-matched analysis. Ann Thorac Surg 2014;98(5).
27. Evison M, Edwards T, Balata H, et al. Prevalence of nodal metastases in lymph node stations 8 & 9 in a large UK lung cancer surgical centre without routine pre-operative EUS nodal staging. Lung cancer (Amsterdam, Netherlands) 2018;115.
28. Chandra S, Nehra M, Agarwal D, et al. Diagnostic accuracy of endobronchial ultrasound-guided transbronchial needle biopsy in mediastinal lymphadenopathy: a systematic review and meta-analysis. Respir Care 2012;57(3).
29. Yasufuku K, Pierre A, Darling G, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. J Thorac Cardiovasc Surg 2011;142(6).
30. Ong P, Grosu H, Eapen GA, 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 Thor Soc 2015;12(3).

31. Um SW, Kim HK, Jung SH, et al. Endobronchial ultrasound versus mediastinoscopy for mediastinal nodal staging of non-small-cell lung cancer. J Thorac Oncol 2015;10(2).
32. von Bartheld MB, van Breda A, JT A. Complication rate of endosonography (endobronchial and endoscopic ultrasound): a systematic review. Respiration 2014;87(4).
33. Casal RF, Lazarus DR, Kuhl K, et al. Randomized trial of endobronchial ultrasound-guided transbronchial needle aspiration under general anesthesia versus moderate sedation. Am J Respir Crit Care Med 2015;191(7).
34. Nakajima T, Yasufuku K, Saegusa F, et al. Rapid on-site cytologic evaluation during endobronchial ultrasound-guided transbronchial needle aspiration for nodal staging in patients with lung cancer. Ann Thorac Surg 2013;95(5).
35. Sehgal IS, Dhooria S, Aggarwal AN RA. Impact of Rapid On-Site Cytological Evaluation (ROSE) on the diagnostic yield of transbronchial needle aspiration during mediastinal lymph node sampling: systematic review and meta-analysis. Chest 2018;153(4).
36. Vakil E, Jackson N, Sainz-Zunega PV, et al. Optimizing diagnostic and staging pathways for suspected lung cancer: a decision analysis. Chest 2021;160(6):2304–23.
37. Folch EE, Labarca G, Ospina-Delgado D, et al. Sensitivity and safety of electromagnetic navigation bronchoscopy for lung cancer diagnosis: systematic review and meta-analysis. Chest 2020;158(4).
38. Gildea TR, Mazzone PJ, Karnak D, et al. Electromagnetic navigation diagnostic bronchoscopy: a prospective study. Am J Respir Crit Care Med 2006;174(9).
39. Folch EE, Pritchett MA, Nead MA, et al. Electromagnetic navigation bronchoscopy for peripheral pulmonary lesions: one-year results of the prospective, multicenter NAVIGATE Study. J Thorac Oncol 2019;14(3).
40. Ost DE, Ernst A, Lei X, et al. Diagnostic yield and complications of bronchoscopy for peripheral lung lesions. results of the AQuIRE registry. Am J Respir Crit Care Med 2016;193(1).
41. Gex G, Pralong JA, Combescure C, et al. Diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules: a systematic review and meta-analysis. Respiration 2014;87(2).
42. Ali MS, Trick W, Mba BI, et al. Radial endobronchial ultrasound for the diagnosis of peripheral pulmonary lesions: a systematic review and meta-analysis. Respirology 2017;22(3).
43. Sainz Zuñiga PV, Vakil E, Molina S, et al. Sensitivity of radial endobronchial ultrasound-guided bronchoscopy for lung cancer in patients with peripheral pulmonary lesions: an updated meta-analysis. Chest 2020;157(4).
44. Chen AC, CT G. Robotic endoscopic airway challenge: REACH assessment. Ann Thorac Surg 2018;106(1).
45. Pyarali FF, Hakami-Majd N, Sabbahi W. G C. Robotic-assisted navigation bronchoscopy: a meta-analysis of diagnostic yield and complications. J Bronchology Interv Pulmonol 2024;31(1).
46. Yu Lee-Mateus A, Reisenauer J, Garcia-Saucedo JC, et al. Robotic-assisted bronchoscopy versus CT-guided transthoracic biopsy for diagnosis of pulmonary nodules. Respirology 2023;28(1).
47. Diddams MJ, HJ L. Robotic bronchoscopy: review of three systems. Life 2023;13(2).
48. Benn BS, Romero AO, Lum M. G K. Robotic-assisted navigation bronchoscopy as a paradigm shift in peripheral lung access. Lung 2021;199(2).
49. Styrvoky K, Schwalk A, Pham D, et al. Shape-sensing robotic-assisted bronchoscopy with concurrent use of radial endobronchial ultrasound and cone beam computed tomography in the evaluation of pulmonary lesions. Lung 2022;200(6).
50. Callister ME, Baldwin DR, Akram AR, et al. British thoracic society guidelines for the investigation and management of pulmonary nodules. Thorax 2015;70(Suppl 2).
51. Laspas F, Roussakis A, Efthimiadou R, et al. Percutaneous CT-guided fine-needle aspiration of pulmonary lesions: results and complications in 409 patients. J Med Imaging Radiat Oncol 2008;52(5).
52. Loh SE, Wu DD, Venkatesh SK, et al. CT-guided thoracic biopsy: evaluating diagnostic yield and complications. Ann Acad Med Singapore 2013;42(6).
53. Hiraki T, Mimura H, Gobara H, et al. CT fluoroscopy-guided biopsy of 1,000 pulmonary lesions performed with 20-gauge coaxial cutting needles: diagnostic yield and risk factors for diagnostic failure. Chest 2009;136(6).
54. Geraghty PR, Kee ST, McFarlane G, et al. CT-guided transthoracic needle aspiration biopsy of pulmonary nodules: needle size and pneumothorax rate. Radiology 2003;229(2).
55. Huo YR, Chan MV, Habib AR, et al. Pneumothorax rates in CT-Guided lung biopsies: a comprehensive systematic review and meta-analysis of risk factors. Br J Radiol 2020;93(1108).
56. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd edition American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e142S-e65S.
57. Ost DE, Jim Yeung SC, Tanoue LT, et al. Clinical and organizational factors in the initial evaluation of patients with lung cancer: diagnosis and management of lung cancer, 3rd edition American College of

Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e121S-e41S.
58. Detterbeck FC, Lewis SZ, Diekemper R, et al. Exece Summary: Diagnosis and management of lung cancer, 3rd edition American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl).
59. Ost DE, Gould MK. Decision making in patients with pulmonary nodules. Am J Respir Crit Care Med 2012;185(4):363–72.
60. Silvestri GA, Gonzalez AV, Jantz MA, et al. 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(5 Suppl). e211S-e50S.
61. Martinez-Zayas G, Almeida FA, Yarmus L, et al. Predicting lymph node metastasis in non-small cell lung cancer: prospective external and temporal validation of the HAL and HOMER Models. Chest 2021; 160(3).
62. Guinde J, Bourdages-Pageau E, Collin-Castonguay MM, et al. A prediction model to optimize invasive mediastinal staging procedures for non-small cell lung cancer in patients with a radiologically normal mediastinum: the quebec prediction model. Chest 2021;160(6).
63. O'Connell OJ, Almeida FA, Simoff MJ, et al. A prediction model to help with the assessment of adenopathy in lung cancer: HAL. Am J Respir Crit Care Med 2017;195(12).
64. Zhou J, Lu X, Chang W, et al. PLUS: predicting cancer metastasis potential based on positive and unlabeled learning. PLoS Comput Biol 2022;18(3).
65. Tekatli H, Spoelstra FOB, Palacios M, et al. S S. Stereotactic ablative radiotherapy (SABR) for early-stage central lung tumors: new insights and approaches. Lung cancer (Amsterdam, Netherlands) 2018;123.
66. Casal RF, Vial MR, Miller R, et al. What exactly is a centrally located lung tumor? results of an online survey. Ann Am Thor Soc 2017;14(1).
67. Chang JH, Poon I, Erler D, et al. The safety and effectiveness of stereotactic body radiotherapy for central versus ultracentral lung tumors. Radiother Oncol 2018;129(2).
68. Altorki N, Wang X, Kozono D, et al. Lobar or sublobar resection for peripheral stage ia non-small-cell lung cancer. N Engl J Med 2023;388(6).
69. Czarnecka-Kujawa K, Rochau U, Siebert U, et al. Cost-effectiveness of mediastinal lymph node staging in non-small cell lung cancer. J Thorac Cardiovasc Surg 2017;153(6).
70. Martinez-Zayas G, Almeida FA, Simoff MJ, et al. A prediction model to help with oncologic mediastinal evaluation for radiation: HOMER. Am J Respir Crit Care Med 2020;201(2).
71. Ost DE, Maldonado F, Shafrin J, et al. Economic value of bronchoscopy technologies that improves sensitivity for malignancy for peripheral pulmonary lesions. Ann Am Thorac Soc 2024;21(12):1759–69.
72. De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardio Thorac Surg 2014;45(5).
73. National Comprehensive Cancer Network. Non-small cell lung cancer. 2024 (version 4.2024). Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl_blocks.pdf.