Overview of the initial evaluation, diagnosis, and staging of patients with suspected lung cancer

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INTRODUCTION

Lung cancer is the leading cause of cancer deaths worldwide in both men and women [1]. Non-small cell lung cancer (NSCLC) accounts for the majority (approximately 85 percent) of lung cancers with the remainder as mostly small cell lung cancer (SCLC). Most patients present for diagnostic evaluation because of symptoms suspicious for lung cancer or an incidental finding on chest imaging. The goal of the initial evaluation is to obtain sufficient clinical and radiologic information to guide diagnostic tissue biopsy, staging, and treatment.

This review will provide a general overview of the initial evaluation, diagnosis, and staging of patients with suspected lung cancer. Typically, the approach for those with suspected NSCLC is the same for those with suspected SCLC, although most of the data is derived from patients with suspected NSCLC. Thus, throughout the text of this topic the term NSCLC is frequently cited. The approach to a patient and modalities used for tissue biopsy and treatment of patients with NSCLC are reviewed elsewhere. (See "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer" and "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer" and "Management of stage I and stage II non-small cell lung cancer" and "Management of stage III non-small cell lung cancer" and "Overview of the initial treatment of advanced non-small cell lung cancer" and "Personalized, genotype-directed therapy for advanced non-small cell lung cancer".)

GENERAL GOALS AND TIMING OF EVALUATION

For each patient with suspected lung cancer the overall goal is a timely diagnosis and accurate staging so appropriate therapy can be administered. The general approach should be tailored to the individual values and preferences of the patient, the clinical presentation, as well as the technical expertise at the practicing institution. Our approach to the initial evaluation and radiologic staging of patients with suspected lung cancer is concordant with the guidelines issued by the American College of Chest Physicians (ACCP), the National Comprehensive Cancer Network (NCCN), and the National Institute for Health and Care Excellence (NICE) guidelines [2-4]. The role of multidisciplinary teams in the timely evaluation of patients with suspected lung cancer is discussed in detail separately. (See "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer", section on 'Role of multidisciplinary teams'.)

Goals — The major goals of the initial evaluation of a patient with suspected lung cancer are to assess the following (figure 1):

- Clinical extent and stage of disease

- Optimal target site and modality for the first tissue biopsy
- Specific histological subtype
- Presence of comorbidities, secondary complications, and paraneoplastic syndromes that influence treatment options and outcome
- Patient values and preferences that influence diagnostic and therapeutic choices

The preferred approach uses imaging as a road map and invasive biopsy as a tool to confirm both the histopathological diagnosis and the stage of disease. When feasible, diagnosis and staging should be established concurrently by targeting for invasive biopsy the abnormality that would yield the most advanced stage. However, some patients will require multiple imaging studies and/or invasive procedures for tissue sampling. Although imaging and sampling procedures are often described separately, in practice, the pathways to diagnosis and staging are often synchronous. As an example, thoracentesis with cytology examination of fluid or transbronchial needle aspiration biopsy of mediastinal lymphadenopathy may provide both diagnosis and staging data.

No single diagnostic algorithm sufficiently addresses the complexity and variation in disease patterns of lung cancer. The local expertise and resources, as well as institution and health system factors, may influence the approach taken. Multi-disciplinary teams may help facilitate an investigative plan so that therapy can be implemented in a timely fashion. The selection of a biopsy modality, the role of multidisciplinary teams, and the procedures used to obtain tissue are discussed in detail separately. (See "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer" and "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer", section on 'Role of multidisciplinary teams' and "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer".)

Timeliness of the evaluation — Despite conflicting data, there is consensus that the initial evaluation of patients with suspected lung cancer be performed in a timely and efficient manner [4]. Most patients can be investigated in an outpatient setting. However, patient factors including comorbidities (eg, respiratory failure, hemoptysis, debilitating metastases to the brain or bone) may lead clinicians to conduct the work-up in a hospital setting. Expedient diagnosis is especially important when there is concern for small cell carcinoma, such as in patients with large, central tumors or evidence of bulky mediastinal disease. (See 'Differential diagnosis' below.)

While some observational series show improved time to therapy with system-driven interventions (eg, multidisciplinary clinic and tumor board, healthcare and hospital associated rapid investigation systems), few studies report improved patient-relevant outcomes due to the intervention [5-7]. We prefer that patients with tolerable symptoms and no evidence of complications complete the initial evaluation within six weeks [4]. While most cases of non-small cell lung cancer (NSCLC) are slow growing with a typical doubling time of 90 to 180 days, some cases are rapidly growing and can progress during the evaluation period. One case series reported disease progression in 13, 31, and 46 percent of patients at 4, 8, and 16 weeks, respectively, with distant metastasis newly evident in 3, 13, and 13 percent of cases [8]. These data suggest that it may be helpful to reevaluate disease stage with imaging in some patients who have a delay in completion of evaluation by eight weeks or more.

Patient values and preferences — It is critical that the initial evaluation of patients with suspected lung cancer establish good communication that adequately assesses patient goals [9]. Patient preferences vary significantly along a spectrum from aggressive investigation aimed at cure to minimal or no investigation and symptom-directed treatment only. Establishing patient preferences early facilitates shared decision-making for future diagnostic and therapeutic choices.

CLINICAL MANIFESTATIONS

Signs and symptoms — The majority of patients who present with clinical signs or symptoms due to lung cancer have advanced disease [10]. The most common presenting manifestations are the following [11-14]:

- Cough – 50 to 75 percent
- Hemoptysis – 25 to 50 percent
- Dyspnea – 25 percent
- Chest pain – 20 percent

Less common manifestations include the signs and symptoms or laboratory abnormalities of distant metastases or paraneoplastic syndromes. When any of these manifestations are present in a patient with suspected lung cancer, they should prompt additional testing. (See 'Laboratory' below and 'Radiographic staging' below.)

Lung cancer should always be suspected in a current or former smoker with new onset of cough or hemoptysis. Both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) can present with similar symptoms, and few clinical features reliably distinguish them from each other. Features that suggest SCLC include rapidly progressive symptoms and the presence of paraneoplastic syndromes (eg, syndrome of inappropriate antidiuretic hormone), bulky multi-station mediastinal metastasis, superior vena cava syndrome, and bone and brain metastases. In contrast, Pancoast's syndrome and hypercalcemia are more frequently encountered in patients with NSCLC.

The spectrum of clinical signs and symptoms including paraneoplastic syndromes that can be seen in patients with lung cancer are discussed in detail separately. (See "Clinical manifestations of lung cancer".)

Initial imaging — Asymptomatic patients may come to clinical attention during screening or following the incidental detection of imaging abnormalities. Patients with symptoms suggestive of primary or metastatic lung cancer should undergo initial imaging with chest radiograph. Every attempt should be made to obtain and review any prior chest imaging studies to determine the age and growth pattern of identified abnormalities. Solid-appearing lesions on chest computed tomography (CT) that are stable in size for at least two years are highly unlikely to represent lung carcinoma [15]. Malignant non-solid and part-solid nodules often grow more slowly, so a longer period of stability is needed to exclude malignancy. (See "Diagnostic evaluation of the incidental pulmonary nodule".)

Findings suggestive of cancer or cancer-related complications on chest radiograph should be further evaluated with contrast-enhanced CT chest. (See 'Radiographic staging' below.)

The following features should prompt further evaluation for lung cancer, regardless of symptoms:

- Chest radiograph demonstrating a new or enlarging focal lesion, a pleural effusion, pleural nodularity, enlarged hilar or paratracheal nodes, endobronchial lesion, post-obstructive pneumonia or segmental or lobar atelectasis. (See "Diagnostic evaluation of the incidental pulmonary nodule", section on 'Computed tomography'.)

- CT findings suggestive of malignancy in a patient with a solitary pulmonary nodule include large lesion size (eg, >15 mm), irregular or spiculated borders, upper lobe location, thick-walled cavitation, presence or development of a solid component within a ground glass lesion, and detection of growth by follow-up imaging. The finding of multiple nodules in a patient with a known or suspected extrathoracic malignancy strongly suggests pulmonary metastasis.

Estimation of cancer probability — The probability of lung cancer may be estimated by using clinical data (eg, patient's age, sex, family history, and presence of emphysema) as well as the radiographic features of the nodule (calculator 1). If lung cancer is suspected based upon symptoms, CT findings, or probability calculations, formal CT staging focused on the primary tumor (T-factor in **T**umor **N**ode **M**etastasis staging) and lymph nodes (N) should be obtained, if not already performed. Estimating the probability of cancer for solitary pulmonary nodules, the approach to initial radiographic staging, and modalities used for imaging patients with suspected NSCLC are discussed in detail separately. (See

'Radiographic staging' below and "Diagnostic evaluation of the incidental pulmonary nodule", section on 'Assessing the risk of malignancy'.)

INITIAL EVALUATION

For staging purposes, the eighth edition (table 1 and table 2) will be used in this topic.

Clinical — Every patient with suspected lung cancer should undergo a thorough history and physical exam. The presence of signs or symptoms typically indicates advanced disease and portends a poor prognosis [10]. The clinical evaluation should be symptom-directed with particular attention to non-pulmonary symptoms that might suggest metastases (table 3). For example:

- Hip pain may prompt plain radiographs of the hip (M1b disease)
- Horner's syndrome (ipsilateral ptosis, anhidrosis, and miosis) may prompt an MRI of the superior sulcus (T3 disease)
- Neurologic symptoms may prompt imaging of the brain or spinal cord (M1b disease)
- Hypotension with sinus tachycardia and pulsus paradoxus may prompt an echocardiogram to evaluate for malignant pericardial effusion (M1a disease) (see 'Imaging metastatic disease' below)

We prefer symptom-directed evaluation because it prompts appropriate imaging and laboratory testing for the identification of nodal or metastatic disease and paraneoplastic syndromes. A meta-analysis of 25 studies that examined the role of the clinical evaluation for the detection of metastatic disease reported a high negative predictive value of an expanded clinical exam for brain (95 percent), abdominal (94 percent), and bone (89 percent) metastases [16]. Symptoms can also be prognostic. In a cohort of 1266 patients with lung cancer, asymptomatic patients or patients with symptoms due to the primary tumor had a better prognosis than patients with signs and symptoms suggestive of metastatic disease [10].

Laboratory — We perform the following laboratory studies when chest imaging is suspicious for lung cancer [4,17]:

- Complete blood count
- Electrolytes
- Calcium
- Alkaline phosphatase
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total bilirubin
- Creatinine
- Albumin and lactate dehydrogenase (not essential)

A detailed clinical exam together with laboratory testing can predict the likelihood of metastases in patients with lung cancer, especially non-small cell lung cancer (NSCLC) [16]. Abnormal testing in these circumstances can prompt additional imaging that guides the clinician in their diagnostic and staging work-up. For example:

- Liver function test abnormalities possibly due to liver metastasis should prompt evaluation of the liver with liver-directed imaging. (See 'Imaging metastatic disease' below.)

- Calcium elevation should prompt additional imaging for bone metastasis and/or a work up for a paraneoplastic manifestation of the primary tumor. (See "Hypercalcemia of malignancy: Mechanisms".)

- Elevation of the alkaline phosphatase could be due to liver or bone metastases and should prompt measurement of gamma glutamyl transpeptidase (GGT). When GGT is normal an evaluation for bone metastasis is indicated; when abnormal, an evaluation for liver metastases is indicated.

A prolonged diagnostic work-up can ultimately delay and complicate definitive cancer therapy [4]. Thus, in patients that present with signs or symptoms of paraneoplastic syndromes, an evaluation targeted at the paraneoplastic syndrome is warranted in parallel with the evaluation of NSCLC. The evaluation of patients with possible paraneoplastic syndromes is discussed in the following sections:

- Paraneoplastic syndromes of muscle, nerve, and bone (see "Overview of paraneoplastic syndromes of the nervous system" and "Clinical manifestations of dermatomyositis and polymyositis in adults", section on 'Association with malignancy')
- Endocrine paraneoplastic syndromes (see "Diagnostic evaluation of adults with hyponatremia" and "Establishing the diagnosis of Cushing's syndrome" and "Diagnostic approach to hypercalcemia")

Serum tumor markers have not been shown to have broad clinical utility in patients with NSCLC and their routine use is not recommended. (See "Overview of the initial treatment and prognosis of lung cancer", section on 'Prognosis of NSCLC'.)

Radiographic staging

Overview — The clinical staging of patients with suspected lung cancer, in particular NSCLC, starts with radiographic imaging [2-4]. Determining the highest radiographic stage prior to biopsy facilitates the selection of a modality that optimizes tissue sampling for diagnosis. We and others agree that every patient with suspected NSCLC should undergo the following [2,18]:

- Imaging of the chest with contrast-enhanced computed tomography (CT) scan
- Imaging of the upper abdomen including liver and adrenal glands, usually by extension of the chest CT through this region (see 'CT scan of the chest' below)
- Imaging directed at sites of potential metastasis when symptoms or focal findings are present or when chest CT shows evidence of advanced disease (see 'Imaging metastatic disease' below)

There are conflicting data regarding the harms and benefits (improved survival or reduction in futile thoracotomy) of routinely performing whole body positron emission tomography (PET) or integrated PET/CT in every patient with suspected NSCLC [19-22]. Until large randomized trials provide more convincing data demonstrating improved survival or a clear reduction in thoracotomies with routine PET or PET/CT, we prefer an approach that is symptom and/or CT-directed. (See 'Whole body PET' below and 'Integrated PET/CT' below.)

CT and (in some cases) PET provide a non-invasive assessment of tumor size (T), mediastinal node enlargement (N), and potential intra- or extra-thoracic metastases (M) [2,18]. Although confirmation by tissue biopsy must be pursued, these imaging tests provide the basis for the initial assessment of the TNM stage of disease (table 1 and table 2) and help guide the clinician in choosing the optimal site(s) for tissue sampling. (See "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer", section on 'Approach to the patient'.)

There is no perfect threshold for what is considered metastatic lymphadenopathy by CT or PET. Small lymph nodes can harbor occult malignancy and some lesions that are not highly fluorodeoxyglucose (FDG)-avid are malignant. However, cut-offs worrisome for metastasis to mediastinal lymph nodes are:

- Size >1 cm by short-axis diameter on transverse CT scan and/or
- FDG uptake greater than that of mediastinal blood pool on PET imaging [23]

The major limitation of CT and PET is that neither can stage NSCLC with a high degree of accuracy. The prevalence of granulomatous disease such as tuberculosis or histoplasmosis in the local patient population is an important factor in

interpretation of PET results [24]. Consequently, with the possible exception of bulky and confluent mediastinal disease (group A (table 4)), the identification of suspicious mediastinal metastases by CT or PET does not bypass the need for histologic assessment of mediastinal lymph nodes for accurate staging and exclusion of alternative diagnoses [25]. (See 'CT scan of the chest' below.)

The relatively low sensitivity and specificity of CT (55 and 81 percent) and PET (80 and 88 percent) can miss occult cancer (false negatives) and result in missed opportunities for potentially curative thoracotomy (false positives) [2,20]. Thus, the major use of CT and PET as staging tools is to facilitate the optimal approach to biopsy so that patients can be accurately staged histologically and futile surgery avoided. The accuracy of CT and PET and the approach to tissue biopsy are discussed separately. (See "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer" and 'CT scan of the chest' below and 'Whole body PET' below.)

Routine extrathoracic imaging aimed at detecting metastases is not necessary in all patients and should be directed at symptoms and abnormal physical examination findings. Because of the higher prevalence of occult brain metastasis in patients with stage III or IV NSCLC, some experts believe that routine brain imaging is warranted, although there is little evidence that early detection and treatment of occult metastasis improves outcomes [2]. Brain CT scan should be used when MRI is not available. The poor sensitivity of PET for brain metastases limits this modality in the detection of brain NSCLC. (See 'Imaging metastatic disease' below.)

CT scan of the chest — Every patient with suspected lung cancer should undergo CT scan of the chest. Intravenous (IV) contrast enhancement is preferable as it may distinguish mediastinal invasion of the primary tumor or metastatic lymph nodes from vascular structures. Images of the liver and adrenal glands should also be included. In most patients, CT scan assesses the anatomic location and size of the tumor (T), nodal (N), and metastatic disease of the pleura, liver, and adrenal glands (M). With the possible exception of those with bulky mediastinal tumor (group A, see below), most patients with mediastinal node involvement by CT will need tissue biopsy of the mediastinum (ie, mediastinal staging) to confirm suspected mediastinal nodal disease. The role of CT in the evaluation and staging of patients suspected to have NSCLC is discussed here. The value of CT in the evaluation of a solitary pulmonary nodule is discussed separately. (See "Diagnostic evaluation of the incidental pulmonary nodule", section on 'Computed tomography'.)

The major advantage of CT is that it provides accurate anatomic definition of the tumor within the thorax, which consequently directs tissue biopsy for histopathologic diagnosis and staging. For example, CT frequently permits the accurate identification of T3 or T4 lesions (ie, larger tumors that invade surrounding bony or mediastinal structures) and identifies high-yield targets for biopsy including N1-3 lymph nodes (table 1 and table 2). CT also identifies tumor-related atelectasis or post-obstructive pneumonitis (T2 disease) and intra-thoracic and extra-thoracic metastatic disease that can prompt additional testing (eg, MRI for brachial plexus or bone involvement), as well as co-existing lung disease (eg, emphysema) that may affect biopsy choice or operability. (See "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer", section on 'Assessing patient risk'.)

Four major radiographic groups defined by CT findings, have been suggested to facilitate further diagnostic work-up and staging [2]. These groups include patients with the following findings on CT scan (table 4):

- A – Patients with bulky tumor encircling/invading mediastinal structures such that isolated lymph nodes cannot be distinguished from primary tumor (image 1)
- B – Patients with discrete lymph node enlargement >1 cm such that an isolated lymph node can be distinguished from the primary tumor (image 2 and image 3)
- C – Patients with central tumor and elevated risk of nodal disease despite normal sized nodes (ie, high risk for N2/3 disease) (image 4)
- D – Patients with low risk of N2/3 involvement or distant metastatic disease (ie, peripheral T1 tumors) (image 5 and image 6)

The allocation of patients to these categories helps guide the clinician in the selection of a targeted site for tissue biopsy. As an example, patients in group A are not candidates for surgical treatment. The focus of biopsy in this setting is on diagnosis of the tumor by the safest method and imaging may be used as the staging modality. In contrast, for all patients with discrete suspicious lymphadenopathy (group B), invasive sampling of the mediastinum and in particular, the targeted node, is critical for accurate staging. The selection of modality based upon the radiographic findings described above (A through D) and disease stage is discussed in detail separately. (See "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer", section on 'Approach to the patient'.)

The major limitation of CT is its low accuracy in the identification of mediastinal metastases [2,26]. A 2013 systematic review of 43 studies reported the accuracy of CT as a mediastinal staging tool in 7368 patients with suspected NSCLC, where a positive scan was defined as lymph nodes measuring >1 cm in short scanning diameter (prevalence of mediastinal metastasis was 30 percent) [2]. CT predicted mediastinal lymph node involvement with a sensitivity, specificity, positive predictive value and negative predictive value of 55, 81, 58, and 83 percent, respectively. Thus, due to its low sensitivity and specificity, CT scanning is not a reliable modality for accurately staging the mediastinum in patients with NSCLC. With the exception of bulky mediastinal disease, this necessitates tissue sampling in most cases to confirm suspected regional lymph node involvement. (See "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer" and "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer", section on 'Approach to the patient'.)

Whole body PET — Despite the widespread use of whole-body PET as a routine staging tool, there is no consensus regarding the value of this practice. [19-21]. Although whole-body PET is more accurate than CT in detecting occult disease, its use has not been shown to improve survival, and the evidence is conflicting on whether PET can reduce the risk of futile thoracotomy. Thus, the use of PET as a staging modality should be considered in the context of the risk of missing occult disease, patient preferences, and local expertise. We prefer the selective use of PET in potentially resectable patients with T2 or T3 lesions by CT stage (table 1 and table 2) to detect occult metastases, or those at high risk of surgical complications. When a PET scan is positive, with the exception of those with bulky mediastinal tumor (group A), it does not obviate the need for tissue biopsy to confirm suspected disease. The value of PET in mediastinal staging is discussed here. The role of PET in the evaluation of a solitary pulmonary nodule and in the evaluation of distant metastases associated with NSCLC is discussed separately. (See 'Modality' below and "Diagnostic evaluation of the incidental pulmonary nodule", section on 'Positron emission tomography/computed tomography'.)

PET scanning has limited anatomic resolution but does provide information on the metabolic activity of the primary tumor, mediastinal involvement, and potential distant metastases. There are no standardized criteria defining what constitutes a positive PET result and no ideal cut-off point for the standardized uptake value (SUV). However, lymph nodes with FDG uptake greater than that observed in the mediastinal blood pool are highly suspicious for metastatic disease [23].

PET is more accurate in the evaluation of mediastinal disease (N) when compared to contrast-enhanced chest CT and sometimes detects occult disease (eg, liver, adrenal, bone, and pleural metastases) outside the thoracic cavity (M) that is not radiologically evident by CT scanning. With respect to mediastinal staging by PET, one systematic review of 45 studies which included 4105 patients reported sensitivity, specificity, positive predictive value and negative predictive values of 80, 88, 75, and 91 percent, respectively [2]. Another meta-analysis of 39 studies reported increased sensitivity of PET (100 percent) when lymph nodes were also enlarged (>1 cm) on CT [26].

The rationale for the use of PET in operable patients with potentially resectable cancers is derived from randomized trials that included patients with radiographic (CT) **stage I, II, and IIIA NSCLC** (per The 7th edition of the TNM system (table 5)) that suggest a reduction in futile thoracotomy when PET is performed. However, trials evaluating the association between PET scanning and therapeutic outcome in this population have had conflicting results [20-22,27,28]. While two studies suggest a reduction in the rate of futile thoracotomies with the use of PET as a staging modality in this

population [20,22], three studies suggest no difference in the same population [21,27,28]. This conflict may be explained by the heterogeneity in scanning modality and population studied (high risk versus low risk metastatic disease). Our approach prioritizes the avoidance of unnecessary surgery.

The value of PET in radiographic **stage IA1-3 (T1a-cN0M0)** NSCLC is also controversial. In this population, the estimated prevalence of metastatic disease is very low (approximately 4 percent) [29]. Some argue that PET is unnecessary in this situation and proceed directly to either cervical mediastinoscopy or surgical resection of the primary tumor with mediastinal sampling at the time of surgery, while others believe that when used in this context, PET can further reduce the risk of unnecessary surgery [26,29-33]. While we favor surgical resection with mediastinal sampling, it is also reasonable to perform PET scanning pre-operatively in those at high surgical risk. Importantly, patients and clinicians must be aware that limiting preoperative staging to imaging alone without biopsy of radiographically positive lymph nodes sampling carries a risk of a false positive result that may result in a missed opportunity for surgical cure.

When staging the mediastinum, errors associated with PET that should be considered are the following :

- False positives can occur with benign FDG-avid lesions such as infections, inflammation, and granulomatous disease [34].
- False negatives typically occur when there are microscopic foci of metastasis, and in non-enlarged lymph nodes (<10 mm) [35-37]. As an example, although PET can be positive in small lesions, the detection of occult malignancy in normal sized lymph nodes for early stage cancer is lower than for enlarged nodes.

Integrated PET/CT — Despite its widespread use, there is no consensus regarding the routine use of integrated PET/CT as a staging modality for patients with suspected NSCLC [38]. Although randomized trials suggest that the use of integrated PET/CT reduced futile thoracotomies, and is probably superior to either modality alone, it has not been shown to improve survival. We prefer the routine use of CT together with the targeted use of dedicated PET OR PET/CT in patients with suspected NSCLC. In general, the indications for PET/CT are the same as for dedicated PET. In many centers, only PET/CT is available, in which case it is the de facto test of choice. As is true for dedicated PET, a suspicious finding for metastases on PET/CT should always prompt biopsy for histologic confirmation. The value of integrated PET/CT in mediastinal staging is discussed here. The role of integrated PET/CT in the evaluation of solitary pulmonary nodules is discussed separately.

One of the major limitations of whole-body PET alone is the poor anatomic definition of suspicious lesions. For example if metabolic activity is seen in the region of the mediastinum, its relation to vascular, hilar or endobronchial structures is unknown. The addition of coregistered CT to PET scanning adds correlative anatomic information, thereby combining the advantages of both imaging modalities [39,40]. However, one meta-analysis of 19 studies (2014 patients) of integrated PET/CT in patients suspected of having NSCLC reported a sensitivity, specificity, positive predictive value, and negative predictive value of 62, 90, 63, and 90 percent, respectively [2]. Although the sensitivity was lower than that reported in meta-analyses of CT or PET alone, it is not plausible that addition of information obtained from either modality would reduce sensitivity. The reasons for this lower sensitivity are unclear. Differences in methodology between the included studies may be responsible.

Two randomized trials showed that, by appropriately altering the disease stage, integrated PET/CT prevents unnecessary thoracotomies [20,22]. In a total of 526 patients suspected to have potentially resectable NSCLC, compared to conventional staging, integrated PET/CT prevented unnecessary thoracotomy in 7 to 17 percent of patients. Additionally, integrated PET/CT has been shown to detect unanticipated stage IV disease [39,41-47].

Imaging metastatic disease

Indications — Although most clinicians agree that routine imaging for distant metastases is not required for every case of suspected NSCLC, the practice varies widely among clinicians. Regardless of the imaging modality used, tissue confirmation of suspected metastases is indicated. We prefer imaging that is symptom-focused or CT-directed and typically image the following groups:

- Patients with focal symptoms, signs, or laboratory tests suggestive of metastatic disease. The modality used depends on the site of suspected metastases. (See "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Sampling metastatic disease'.)

- Patients with clinical stage III or IV disease have an increased risk of occult intracranial metastasis and may benefit from routine imaging of the brain with magnetic resonance imaging (MRI) or CT if MRI is not available. The rationale for routine brain imaging is the high risk of distant disease in this population, especially metastases to the brain. In this setting, an MRI of the brain may be performed for the early detection of brain metastases so that early treatment can be administered before development of neurologic deficits or seizures.

- In patients with clinical stage I/II disease who are candidates for curative resection, there is consensus that routine **brain** imaging with MRI is **not** indicated.

In contrast, some experts believe that PET or PET/CT is indicated to identify occult metastasis in patients with clinical stage IB/II disease. Both modalities have been shown in small prospective observational studies to result in the avoidance of unnecessary thoracotomy in patients with solid tumors [41,48-50]. It is less clear whether PET is useful to identify occult metastasis among patients with clinical stage IA NSCLC in whom the risk of occult metastasis is very low or among patients with clinical stage IIIA/B disease in whom the risk of occult stage IV disease may be high but of uncertain benefit to detect.

Patients may require repeat imaging during staging and evaluation when new symptoms arise or if there is a significant delay in initiation of therapy. The optimal timing for repeat imaging is not standardized and should be tailored to the individual patient. For example, patients with early stage disease who develop new onset headache or bone pain do require modification of the original evaluation plan to investigate those symptoms. A critical objective in the staging evaluation is timeliness. However, re-imaging is reasonable in select circumstances prior to biopsy when unavoidable, prolonged delays occur (eg, rapidly progressive disease or new symptoms) if there is a delay by eight weeks or more [2,4]. (See 'Timeliness of the evaluation' above.)

Modality — With the exception of brain metastases, whole body PET or PET/CT scanning is more accurate than conventional scanning (abdominal CT, bone scan) for the detection of unsuspected pleural and extrathoracic metastases [39,41-47]. When evaluating patients for brain metastases, gadolinium-enhanced MRI of the brain is usually preferred because it is more sensitive than non-enhanced MRI or CT. When PET, PET/CT or MRI is not available, conventional staging with abdominal CT, bone scintigraphy, and CT scan of the brain should be performed when indicated. The detection of occult metastases by any of these modalities is not associated with a proven survival benefit, although it is desirable to prevent an unnecessary surgical procedure. With the exception of brain, histologic confirmation of suspected metastatic disease by any of these modalities is indicated, unless there is convincing evidence of widespread metastasis by noninvasive imaging. Imaging directed at specific sites suspected to be involved with metastases is discussed separately. (See 'Site-specific imaging' below.)

Small randomized studies and case series of PET or PET/CT suggest that, when used as staging modalities for NSCLC, unsuspected metastases are discovered between 6 and 36 percent of cases [51-54]. Additionally, their discovery can result in stage migration (up-stage or down-stage) and changes in management in 19 to 22 percent of patients [41,46-48,53,55,56]. However, improved survival due to the discovery of occult metastases has not been reported, and most

cases of upstaging by PET should be confirmed by tissue sampling so as not to result in a missed opportunity for surgical cure.

Brain metastases can be hyper- or hypo-metabolic, thereby limiting the utility of PET for the detection of NSCLC in the brain [57]. Gadolinium-enhanced MRI of the brain is more sensitive than non-enhanced MRI or CT due to the increased detection of small cerebral lesions [58,59]. In addition, MRI improves detection when added to PET-CT and can be used in conjunction with this modality for the evaluation of suspected brain metastases [60,61].

Site-specific imaging — When imaging is indicated and PET or PET/CT is not available or is inconclusive, other modalities should be used to evaluate patients with suspected NSCLC for distant disease. The choice of imaging modality is determined by the anatomic location or suspected organ involved by metastatic disease. Organs that are frequently involved by metastatic NSCLC that may require imaging include the following:

- **Brain, spine, and nerve** – Gadolinium-enhanced MRI detects spinal bone lesions and brain lesions and differentiates metastases from other central nervous system lesions with greater sensitivity than nonenhanced MRI [2,62]. (See "Magnetic resonance imaging of the thorax" and "Epidemiology, clinical manifestations, and diagnosis of brain metastases", section on 'Imaging studies'.)

- **Adrenal gland** – Adrenal gland nodules or masses may be found by CT in 3 to 4 percent of patients during the initial work-up [63-65]. In patients with NSCLC, most adrenal nodules are benign. However, all adrenal anomalies in patients with suspected NSCLC require directed evaluation to distinguish benign lesions from malignant metastases. Those with imaging characteristics suggestive of malignancy should be considered for biopsy. (See "Evaluation and management of the adrenal incidentaloma", section on 'Typical imaging features' and "Evaluation and management of the adrenal incidentaloma", section on 'Adrenal metastases'.)

  PET scanning is a sensitive modality for the detection of adrenal metastases in patients with NSCLC. In a series of 94 patients with 113 adrenal masses, the sensitivity, specificity, and accuracy of PET imaging for detection of metastatic disease was 93, 90, and 92 percent, respectively [66]. Although PET scans are accurate for the detection of adrenal metastases, small lesions may be missed (<1.5 cm) [67-71]. Positive findings should be confirmed histologically.

  Conventional CT lacks a high sensitivity or specificity for the diagnosis of adrenal metastases [72]. CT scans that use specific adrenal imaging protocols significantly improve the sensitivity and specificity of CT for characterizing adrenal lesions. As an example, in two studies of 363 patients with 279 adrenal masses, CT identified adrenal adenomas with a high sensitivity (98 to 100 percent) and specificity (92 to 95 percent) [73,74].

  MRI also lacks sensitivity but may be helpful in distinguishing benign, fat-containing adrenal adenomas from adrenal metastases [75,76].

  Percutaneous biopsy and, rarely, adrenalectomy are considered for isolated lesions involving the adrenal gland. In the setting of overwhelming metastatic disease tissue, confirmation may not be necessary. (See "Evaluation and management of the adrenal incidentaloma", section on 'Fine-needle aspiration biopsy' and "Evaluation and management of the adrenal incidentaloma", section on 'Adrenalectomy'.)

- **Liver** – The liver is rarely (3 percent) the sole site of metastases and most liver lesions in patients with NSCLC are benign cysts or hemangiomas [77]. However, all liver abnormalities in patients with suspected NSCLC require directed evaluation to distinguish benign lesions from malignant metastases. Those with imaging (usually on CT, ultrasound, and/or radionuclide imaging) characteristics suggestive of malignancy should be considered for biopsy particularly if this is the only suspected metastatic site. (See "Approach to the adult patient with an incidental solid liver lesion", section on 'Malignant lesions' and "Approach to the adult patient with an incidental solid liver lesion".)

Limited data suggest that PET scanning can detect liver metastases with an accuracy of 92 to 100 percent [67,78,79]. Although subgroup analysis in observational case series suggest that PET may be superior to CT for the detection of liver metastases, false positive and false negative findings were also reported [67,80]. In the absence of overwhelming evidence of systemic metastasis such as multiple other sites with imaging consistent with tumor metastasis, isolated hepatic lesions require careful evaluation and biopsy to achieve accurate staging. Isolated PET-positive liver lesions in an otherwise early-stage patient should not be used as the basis for determination of metastatic tumor stage without confirmatory biopsy. (See "Approach to liver biopsy".)

- **Bone** – Although data are limited in NSCLC, PET scanning appears to be superior to radionuclide bone scintigraphy for the detection of bony metastases [67,81-85]. Two studies of 158 patients with biopsy-proven bony metastases from NSCLC reported that, compared to bone scintigraphy, PET scanning had similar sensitivity (93 percent) but greater specificity (93 to 96 versus 66 to 73 percent) for the detection of metastases [81,82]. However false positive and false negative findings on PET scan have been reported [67,71,86].

  Bone scintigraphy can be used when PET or PET/CT is not available or is inconclusive. The known caveat of bone scintigraphy is that the false positive rate is high due to the common prevalence of degenerative and traumatic skeletal disease in the general population. One meta-analysis of eight studies suggested that, compared to PET, bone scintigraphy has a comparable negative predictive value of >90 percent [2].

  MRI has comparable accuracy to bone scintigraphy for the diagnosis of bony metastases. In practice it can be used as a supplementary tool, especially when a suspected lesion crosses tissue planes to involve multiple structures [85,87,88]. For example, apical lesions that invade through the chest wall can involve the shoulder as well as the brachial plexus, and lesions of the posterior mediastinum can involve the vertebra and spinal canal. In these settings, MRI can be used in conjunction with other imaging modalities to distinguish true bony metastases from T3 lesions that are potentially resectable [89].

- **Pleura** – Two common clinical presentations of pleural disease are: metastases associated with pleural effusion or multiple pleural-based nodules, and direct extension of the primary tumor to the pleura or chest wall. Complete evaluation of pleural disease may require multiple imaging modalities (PET, CT, ultrasound, and/or MRI) as well as invasive testing (thoracentesis, thoracoscopy, or pleural biopsy). While imaging is important in the detection of suspected pleural metastases, it should not obviate the need to sample the pleural disease for histological confirmation. (See "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Suspected pleural metastases' and "Imaging of pleural plaques, thickening, and tumors".)

  Careful review of CT imaging is particularly important in the evaluation of tumors with direct extension into extrapleural fat, visceral pleura, or parietal pleura. Such lesions are operable and need to be distinguished from metastatic disease of the pleural space (M1a) which is inoperable (table 1 and table 2) [90]. When imaging is insufficient to make this distinction, direct vision at the time of thoracotomy may be required.

  Retrospective studies have shown PET to be an accurate modality in the detection of pleural metastases from NSCLC [91,92]. In one retrospective study of patients with an established diagnosis of NSCLC, the sensitivity, negative predictive value, and accuracy of PET for detecting pleural metastases was 95, 67, and 92 percent. However, the prevalence of pleural metastases in this study may have falsely lowered the negative predictive value [91]. PET imaging, in another study, correctly detected the presence of malignant pleural involvement in 16 of 18 patients with NSCLC and more importantly excluded a malignant effusion in 16 of 17 patients with a sensitivity and accuracy of 88 and 91 percent, respectively [92]. PET is not useful in examining the extent of invasion across tissues planes.

  CT is important for the anatomic delineation of tumor involvement of all components of the pleural space, extrapleural fat, visceral and parietal pleura. Apart from obvious pleural masses, thickening and effusions, subtle

beading, and pleural puckering visible on CT are also highly suspicious for pleural metastases. The detection of metastatic pleural involvement by CT has been shown to have important implications for prognosis of patients with NSCLC. As an example, in one retrospective study of 98 patients with NSCLC, compared to wet pleural dissemination (pleural fluid), dry pleural dissemination (nodularity without pleural fluid) was associated with better median survival (38 versus 13 months) [93].

Ultrasound can also be used to evaluate the pleural space. In a small prospective case series, when distinguishing benign from malignant disease, the sensitivity of ultrasound was comparable to CT at 79 percent [94]. Pleural thickening >1 cm, pleural nodularity, and diaphragmatic thickening >7 mm were highly suggestive of malignant metastases [94].

MRI may be useful when evaluating the extent of tumor invasion through muscle, nerve, and bone but has not been formally studied as a staging tool pleural involvement in NSCLC.

DIAGNOSIS

A diagnosis of lung cancer should not be made without definitive pathology. At a minimum, this involves selecting a biopsy site and obtaining an adequate sample for microscopic examination. Additional consideration needs to be given to obtaining a large enough sample for supplemental immunohistochemical and genetic analysis.

Tissue biopsy — Acquiring tissue for microscopic examination is necessary for the diagnosis and staging of patients with suspected lung cancer. Most data are derived from studies of patients with non-small cell lung cancer (NSCLC). Although not absolute, for patients with higher disease stage, minimally invasive modalities (eg, endoscopic procedures) are typically preferred over more invasive modalities (eg, video-assisted thoracic surgery and mediastinoscopy) for the initial biopsy. Conversely, for patients with peripheral early stage disease, surgical biopsy is sometimes preferred because diagnosis and curative resection may be achieved simultaneously. (See "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer" and "Diagnostic evaluation of the incidental pulmonary nodule", section on 'Surgical biopsy'.)

Modality — The selection of a biopsy modality must take into consideration its yield for a target lesion in the context of safety and expediency, as well as the patient's preferences and values. Bronchoscopy with endobronchial ultrasound (EBUS)-directed biopsy has emerged as the most common modality used for diagnosis and staging of suspected NSCLC due to its high diagnostic accuracy for accessing central primary tumors and most mediastinal lymph nodes. Furthermore, EBUS-directed biopsy in patients with mediastinal adenopathy on computed tomography (CT) scan may be performed quickly and reduce the time to establishing of treatment decisions [95]. If initial tissue sampling provides inconclusive results or is insufficient for essential immunohistochemical or molecular characterization, a second biopsy procedure is required. The selection of a second biopsy procedure should favor modalities with a higher tissue volume (eg, surgical sampling). The selection of modality and procedures used for tissue biopsy of NSCLC are discussed separately. Although genetic and molecular microarray techniques of both tissue and peripheral blood have been studied as potential diagnostic tools designed to enhance the sensitivity of bronchoscopy for the diagnosis of lung cancer, further study is required before they can be recommended for routine use [96,97]. (See "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer" and "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer".)

Specimen type — A pathologic diagnosis can be made on cytopathologic or histopathologic (tissue biopsy) samples. In general, if both types of specimens can be obtained with similar feasibility and risks, a tissue biopsy is preferable to a cytologic specimen. This preference is based upon the ability to differentiate with greater accuracy adenocarcinoma features from squamous cell carcinoma as well as the importance of obtaining sufficient material for

immunohistochemical and genetic analysis of the tumor. (See "Pathology of lung malignancies" and "Personalized, genotype-directed therapy for advanced non-small cell lung cancer".)

Cytologic specimens can be obtained from the following sites:

- Lung – Sputum, transthoracic needle aspirates, and bronchoscopic washings, brushings, or needle aspirates (see "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Sputum cytology' and "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Endoscopic and image-guided procedures')
- Lymph node – Transthoracic, transbronchial, and transesophageal aspirates (see "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Endoscopic and image-guided procedures')
- Distant metastasis – Pleural fluid, needle aspirates of metastatic tissue (eg, liver) (see "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Sampling metastatic disease')

Core or biopsy tissue can be obtained from the following:

- Lung – Endobronchial biopsy (forceps), transbronchial biopsy (forceps or needle), transthoracic (needle) biopsy, surgical biopsy (see "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Endoscopic and image-guided procedures' and "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Video-assisted thoracic surgery')
- Lymph node – Bronchoscopic and transthoracic needle core biopsy, surgical biopsy (see "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Endoscopic and image-guided procedures' and "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Surgical staging procedures')
- Distant metastasis – Core needle aspirates of metastatic tissue (eg liver, bone, adrenal) (see "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Sampling metastatic disease')

The modalities used to obtain tissue in patients with suspected NSCLC are discussed in detail separately. (See "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer".)

Histopathology — Distinguishing among the different histologic subtypes of NSCLC is increasingly important to guide subsequent testing for specific mutations and to guide treatment selection, including the identification of patients who are more likely to respond to newer targeted therapies. Adenocarcinoma, squamous carcinoma, adenosquamous carcinoma, and large cell carcinoma are the four major histological subtypes of NSCLC. The four subtypes of NSCLC are histologically characterized by the absence of the pathologic features of small cell lung cancer (SCLC; eg, small cell size, nuclear molding, "salt and pepper" chromatin pattern, and nuclear crush artifact) together with the following:

- Adenocarcinoma – Neoplastic gland formation or intracytoplasmic mucin (picture 1 and picture 2) (see "Pathology of lung malignancies", section on 'Adenocarcinoma')
- Squamous cell carcinoma – The presence of keratin production by tumor cells and/or intercellular desmosomes ("intercellular bridges") (picture 3 and picture 4) (see "Pathology of lung malignancies", section on 'Squamous cell carcinoma')
- Adenosquamous carcinoma – Greater than 10 percent malignant glandular and squamous components (see "Pathology of lung malignancies", section on 'Adenosquamous carcinoma')

- Large cell carcinoma – The absence of glandular or squamous differentiation features (ie, poorly differentiated NSCLC)

Panels of **immunohistochemical** (IHC) stains are typically used to classify NSCLC (eg, adenocarcinoma, squamous cell carcinoma) and to distinguish NSCLC from other cancers involving the lung (eg, primary lung cancer from secondary metastases). The major IHC stains that are commonly used are the following:

- Adenocarcinoma is typically positive for thyroid transcription factor (TTF-1), mucin, napsin-A, surf-A, surf-B, PAS-D, and CK 7.
- Squamous cell carcinoma is typically positive for p40, p63, and cytokeratin 5/6 (CK5/6), and usually negative for CK 7.
- Adenosquamous or large cell carcinoma may have a combination of IHC staining patterns characteristic of both adenocarcinoma and squamous cell carcinoma.
- Poorly differentiated cancers and metastases from distant sites may need to be distinguished from primary NSCLC. As examples, stains that are classically negative in NSCLC are CK 20 (typically positive in adenocarcinoma of the colon) and estrogen and progesterone receptor (typically positive in adenocarcinoma of the breast), thereby distinguishing the tissue of origin for adenocarcinoma found in the lung. Other common staining patterns used to determine the tissue of origin for poorly differentiated neoplasms are described in the table (table 6). The stains (eg, chromogranin) that are used to distinguish NSCLC from SCLC are described separately. (See 'Differential diagnosis' below.)

The common **genetic mutations** with known targeted therapies include mutations in epithelial growth factor receptor (EGFR) and rearrangements of the anaplastic lymphoma kinase (ALK) gene. These and other driver mutations involved in the pathogenesis of NSCLC are discussed in detail separately. (See "Personalized, genotype-directed therapy for advanced non-small cell lung cancer".)

The pathology, immunohistochemistry, and genetic mutations associated with lung malignancies are discussed in detail separately. (See "Pathology of lung malignancies" and "Personalized, genotype-directed therapy for advanced non-small cell lung cancer", section on 'NSCLC genotypes'.)

Differential diagnosis — The differential diagnosis of NSCLC depends on the presenting symptoms and imaging findings. Biopsy is required to distinguish NSCLC from other cancers or benign lesions of the lung. Among the malignant etiologies, the major entity that needs to be distinguished from NSCLC is SCLC. This distinction is critical because the prognosis and treatment for NSCLC and SCLC are different. Although not always present, there are a number of clinical, radiologic, and pathologic features that can help the clinician make this distinction.

The clinical, radiologic, and pathologic manifestations that may help to distinguish NSCLC from SCLC are the following:

- **Rapid presentation** – Although the common symptoms of lung cancer, cough, dyspnea, hemoptysis, and chest pain, can be encountered in both NSCLC and SCLC, a more rapid presentation over weeks favors SCLC. This may be due to the faster doubling time associated with SCLC. As an example, a rapidly growing lesion on chest imaging (eg, a mass that grows over three to six weeks) is more suggestive of SCLC rather than NSCLC.
- **Pancoast's syndrome** – Benign and malignant lesions of the superior sulcus (ie, the thoracic inlet at the apex of the lung) can cause Pancoast's syndrome. Pancoast's syndrome is a constellation of one or more clinical signs (eg, weakness and atrophy of the muscles of the hand and/or ipsilateral ptosis, anhidrosis, and miosis [Horner's syndrome]) that are due to compression or involvement of the brachial plexus (nerves and vessel) and the cervical sympathetic nerves. Unlike superior vena cava (SVC) syndrome, Pancoast's syndrome is overwhelmingly more common in NSCLC and rarely due to SCLC or a benign lesion. Imaging findings of apical masses that have malignant

features should always prompt additional evaluation and biopsy for NSCLC involvement of the thoracic outlet. (See "Superior pulmonary sulcus (Pancoast) tumors".)

- **Paraneoplastic syndromes** – Paraneoplastic manifestations are more commonly observed in SCLC. They are discussed separately in the following sections:
  - Paraneoplastic syndromes of muscle, nerve, and bone (see "Paraneoplastic syndromes affecting spinal cord, peripheral nerve, and muscle" and "Clinical manifestations of dermatomyositis and polymyositis in adults")
  - Endocrine paraneoplastic syndromes (see "Pathophysiology and etiology of the syndrome of inappropriate antidiuretic hormone secretion (SIADH)", section on 'Etiology' and "Etiology of hypercalcemia" and "Epidemiology and clinical manifestations of Cushing's syndrome", section on 'Clinical manifestations')
- **Pathology -** The major histologic feature that distinguishes NSCLC from SCLC is cell size. Typically, the cells in SCLC are roughly twice the size of lymphocytes when subjectively assessed on light microscopy. Additional features that distinguish SCLC from NSCLC include hyperchromatic appearance, small amounts of cytoplasm (ie, high nuclear to cytoplasmic ratio), cohesive sheets of small "blue" cells with rosette formation, crush artifact with necrosis, and cell fragility. When classic features of SCLC are present, morphologic criteria alone are often diagnostic and support high interobserver reliability [98]. In contrast, the classic features of epithelial differentiation (eg, keratin pearls [squamous], gland formation [adenocarcinoma]) do not support the diagnosis of small cell carcinoma but are highly suggestive for non-small cell carcinoma. (See "Pathology of lung malignancies", section on 'Small cell carcinoma' and "Pathology of lung malignancies", section on 'Adenocarcinoma' and 'Histopathology' above.)
- **Immunohistochemical staining** – Select patterns of immunohistochemical staining are typically used to confirm the tissue of origin in NSCLC (eg, TTF-1, CK5/6, p63) (table 6). SCLC can be positive for TTF-1. However, as a neuroendocrine tumor, SCLC should have no other shared IHC staining patterns with NSCLC and is typically positive for synaptophysin, CD56, chromogranin, or neuron specific enolase (NSE), while NSCLC is negative for these stains. The immunohistochemical characteristics of NSCLC are discussed separately. (See 'Histopathology' above.)
- **Other** – Superior vena cava syndrome and metastatic disease were originally thought to be more common in SCLC but due to the higher prevalence of NSCLC, they are commonly encountered in both entities.
  - **Superior vena cava syndrome** – SVC syndrome is a manifestation of benign or malignant disease of the mediastinum. The three most common malignancies associated with SVC syndrome are NSCLC, SCLC, and lymphoma. Unilateral disease may favor SCLC and NSCLC over lymphoma which is more likely to involve the mediastinum symmetrically. Biopsy is required to distinguish all three entities. (See "Malignancy-related superior vena cava syndrome".)
  - **Metastatic disease** – Clinical manifestations of metastatic disease, particularly bone metastases, are commonly seen in both SCLC and NSCLC. (See "Approach to the adult patient with an incidental solid liver lesion" and "Evaluation and management of the adrenal incidentaloma" and "Epidemiology, clinical manifestations, and diagnosis of brain metastases" and "Bone tumors: Diagnosis and biopsy techniques".)

Importantly, if biopsy demonstrates NSCLC but the clinical presentation or course is more consistent with SCLC (eg, rapid growth, multiple metastases, paraneoplastic syndromes), a second pathologic opinion and, rarely, a repeat biopsy is indicated due to a concern for misdiagnosis.

STAGING

The 8th edition for staging non-small cell lung cancer (NSCLC) (table 1 and table 2) is in use. Staging NSCLC determines the appropriate therapy and, when combined with the patient's unique features, provides valuable prognostic information. Four types of staging can be designated in patients with NSCLC:

- The clinical-diagnostic stage is based upon all investigations (clinical, laboratory, radiologic, and pathologic) that are undertaken prior to surgical resection. It is assigned the prefix c (eg, cT3N2M0). A limitation of clinical-diagnostic staging is that the stage is related to the intensity of the preoperative evaluation. Thus, a less aggressively staged patient may be inaccurately down-staged or up-staged.
- The surgical-pathologic stage is based on the clinical-diagnostic stage plus histopathologic data from the resected tumor and lymph nodes. It provides confirmation of the T descriptor, N descriptor, and histologic type. In addition, it takes into account the histologic grade, resection margins, and presence or absence of lymphovascular invasion. The surgical-pathologic stage is assigned the prefix p (eg, pT3N2M0).
- A retreatment stage is assigned if there is recurrence of disease, new staging evaluations have been completed and a new treatment program is planned.
- An autopsy stage is based on a complete postmortem examination.

The TNM system for staging NSCLC and the selection of modality for clinical-diagnostic staging are discussed separately. (See "Tumor, Node, Metastasis (TNM) staging system for lung cancer" and "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer" and "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer".)

The staging for small cell lung cancer (limited versus extensive and TNM) is also discussed separately. (See "Pathobiology and staging of small cell carcinoma of the lung", section on 'Staging'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diagnosis and management of lung cancer" and "Society guideline links: Hemoptysis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Non-small cell lung cancer (The Basics)")

- Beyond the Basics topics (see "Patient education: Non-small cell lung cancer treatment; stage I to III cancer (Beyond the Basics)" and "Patient education: Non-small cell lung cancer treatment; stage IV cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- The initial approach to patients with suspected lung cancer is based largely upon data derived from patients with non-small cell lung cancer (NSCLC). NSCLC is a heterogeneous group of tumors (eg, adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, large cell carcinoma) that together account for the majority of lung cancers. The goal of the initial evaluation of a patient with suspected NSCLC is to obtain sufficient clinical and radiologic information to proceed with diagnostic tissue biopsy, staging, and treatment in a timely fashion. A second major goal of the initial evaluation is to identify patient values and preferences that will determine the context and choices for care. (See 'General goals and timing of evaluation' above.)

- The most common clinical manifestations of NSCLC at presentation are cough, hemoptysis, and dyspnea. Asymptomatic patients may come to clinical attention during screening or following the incidental detection of imaging abnormalities. Symptoms, when present, often represent advanced disease. (See 'Signs and symptoms' above and 'Initial imaging' above.)

- The clinical evaluation should be symptom-directed. This approach relies upon the clinician maintaining a high index of suspicion for nodal or metastatic disease, which in turn allows appropriate imaging and invasive testing to confirm nodal or metastatic disease. (See 'Clinical' above and 'Laboratory' above.)

- Every patient with suspected NSCLC should undergo computed tomography (CT) scan of the chest and upper abdomen (usually contrast-enhanced) to evaluate the extent of the primary tumor and potential spread to the mediastinum, liver, and adrenal glands. Radiographic staging does not obviate the need for tissue biopsy. (See 'CT scan of the chest' above.)

- We do not perform positron emission tomographic scanning (PET) or integrated PET/CT in every patient with suspected NSCLC. For patients who have no symptoms or findings of metastatic disease and who also may be resection candidates, the role of preoperative PET or integrated PET/CT remains controversial. We prefer selective PET or PET/CT in patients who are resection candidates with larger primary lesions (eg, T2 or T3 by CT scan), or in those at high risk for surgical complications; in such cases the use of PET may reduce the incidence of futile thoracotomies, although false positive results are common and these require biopsy confirmation preoperatively. PET imaging in patients with clinical stage IA (T1N0M0) disease prior to curative surgery is also controversial; while we favor surgical resection with mediastinal sampling in this population, preoperative PET scanning in those at high surgical risk is appropriate. (See 'Whole body PET' above and 'Integrated PET/CT' above.)

- Routine imaging to screen for distant metastases is not required for every case of suspected NSCLC. Imaging for metastatic disease should be symptom-focused or CT-directed. Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain is used to evaluate symptomatic patients for brain metastases and to assess asymptomatic patients with clinical stage III or IV NSCLC. (See 'Imaging metastatic disease' above.)

- A diagnosis of NSCLC is made based upon the pathologic evaluation of cytologic (eg, pleural fluid) or histopathologic (eg, tissue biopsy) specimens. The initial radiographic staging optimizes the selection of a biopsy site and preferred modality to obtain a pathologic sample. Consideration should be given to obtaining a large enough sample to allow supplemental immunohistochemical and genetic analysis. (See 'Diagnosis' above and "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer".)

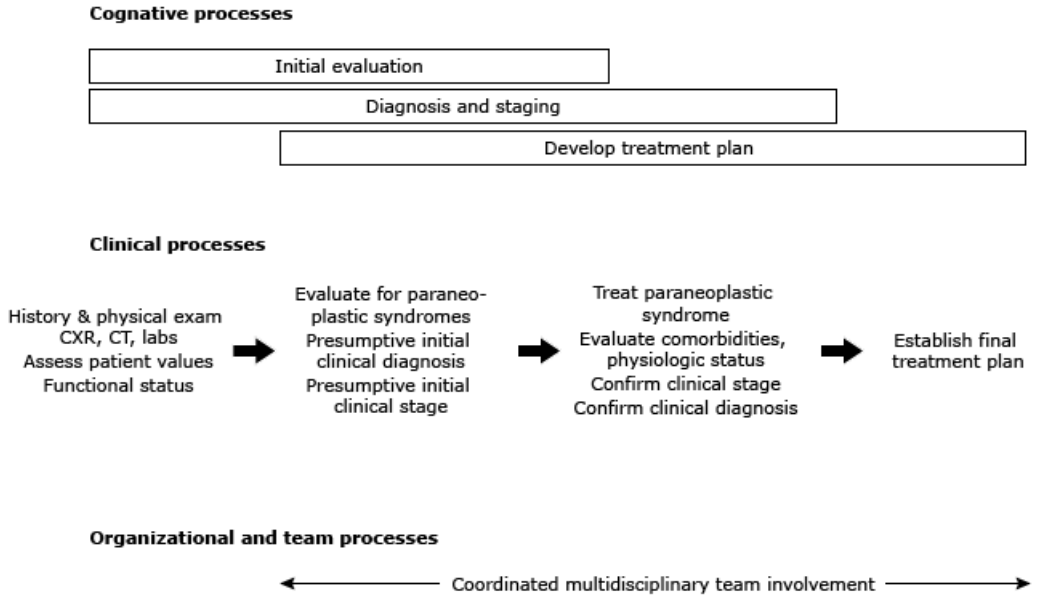
- Adenocarcinoma, squamous carcinoma, adenosquamous carcinoma, and large cell carcinoma are the four major histological subtypes of NSCLC. The main entity on the differential diagnosis of NSCLC is small cell lung cancer (SCLC). While clinical and imaging features can help the clinician distinguish NSCLC from SCLC, pathologic review of adequate biopsy specimens is required to make this distinction. (See 'Histopathology' above and 'Differential diagnosis' above.)

- The 8th edition of the Tumor Node Metastasis (TNM) (table 1 and table 2) is in use. The clinical-diagnostic stage is based upon investigations (clinical, laboratory, radiologic, and pathologic) that are undertaken prior to primary therapy. It is assigned the prefix c (eg, cT3N2M0). (See 'Staging' above.)

Topic 4632 Version 38.0

GRAPHICS

Overview of the initial evaluation and work up of patients with suspected non-small cell lung cancer



Overview of initial evaluation, diagnosis, staging, and treatment processes. There is significant overlap between cognitive processes. Developing a clinical diagnosis and assessment of the probable stage begins during the initial evaluation. This clinical assessment is subsequently refined on the basis of biopsy specimen findings that are part of formal staging and diagnosis. Similarly, information regarding the patient's functional status, comorbid conditions, and preferences may have an impact on treatment alternatives, and this in turn may have an impact on the type of diagnostic testing strategies chosen.

CXR: chest radiograph; CT: computed tomography.

Graphic 93835 Version 2.0

T, N, and M descriptors for the eighth edition of TNM classification for lung cancer

T: Primary tumor			
Tx	Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor ≤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)*		
T1a(mi)	**Minimally invasive adenocarcinoma**[¶]		
T1a	**Tumor ≤1 cm in greatest dimension***		
T1b	**Tumor >1 cm but ≤2 cm in greatest dimension***		
T1c	**Tumor >2 cm but ≤3 cm in greatest dimension***		
T2	Tumor >3 cm **but ≤5 cm** or tumor with any of the following features:[Δ] ▪ **Involves main bronchus regardless of distance from the carina but without involvement of the carina** ▪ Invades visceral pleura ▪ **Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung**		
T2a	**Tumor >3 cm but ≤4 cm in greatest dimension**		
T2b	**Tumor >4 cm but ≤5 cm in greatest dimension**		
T3	**Tumor >5 cm but ≤7 cm in greatest dimension** or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium		
T4	**Tumor >7 cm in greatest dimension** or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: **diaphragm**, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina		
N: Regional lymph node involvement			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension		
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)		
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)		
M: Distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis present		
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[◊]		
M1b	**Single extrathoracic metastasis**[§]		
M1c	**Multiple extrathoracic metastases in one or more organs**		
Stage groupings			
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	**T1a(mi)**	**N0**	**M0**
	T1a	**N0**	**M0**
Stage IA2	**T1b**	**N0**	**M0**
Stage IA3	**T1c**	**N0**	**M0**
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	**T1a to c**	**N1**	**M0**
	T2a	**N1**	**M0**
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	**T1a to c**	**N2**	**M0**
	T2a to b	N2	M0
	T3	N1	M0
	T4	N0	M0

	T4	N1	M0
Stage IIIB	**T1a to c**	**N3**	**M0**
	T2a to b	N3	M0
	T3	**N2**	**M0**
	T4	N2	M0
Stage IIIC	**T3**	**N3**	**M0**
	T4	**N3**	**M0**
Stage IVA	**Any T**	**Any N**	**M1a**
	Any T	**Any N**	**M1b**
Stage IVB	**Any T**	**Any N**	**M1c**

NOTE: Changes to the seventh edition are in bold.

TNM: tumor, node, metastasis; Tis: carcinoma in situ; T1a(mi): minimally invasive adenocarcinoma.
* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.
¶ Solitary adenocarcinoma, ≤3 cm with a predominately lepidic pattern and ≤5 mm invasion in any one focus.
Δ T2 tumors with these features are classified as T2a if ≤4 cm in greatest dimension or if size cannot be determined, and T2b if >4 cm but ≤5 cm in greatest dimension.
◊ Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor and the fluid is nonbloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
§ This includes involvement of a single distant (nonregional) lymph node.

Graphic 109805 Version 1.0

Descriptors and T and M categories of the eighth edition with seventh edition for comparison*

Descriptor in 7th edition	Descriptor in 8th edition	**N categories: 8th edition** (7th edition)			
		Overall stage			
		N0	**N1**	**N2**	**N3**
T1 ≤1 cm	T1a	**IA1** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 >1 to 2 cm	T1b	**IA2** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 >2 to 3 cm	T1c	**IA3** (IA)	**IIB** (IIA)	IIIA	IIIB
T2 >3 to 4 cm	T2a	IB	**IIB** (IIA)	IIIA	IIIB
T2 >4 to 5 cm	T2b	**IIA** (IB)	**IIB** (IIA)	IIIA	IIIB
T2 >5 to 7 cm	T3	**IIB** (IIA)	**IIIA** (IIB)	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 structures	T3	IIB	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 >7 cm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 diaphragm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 endobronchial: location/atelectasis 3 to 4 cm	T2a	**IB** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T3 endobronchial: location/atelectasis 4 to 5 cm	T2b	**IIA** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	**IIIC** (IIIB)
M1a	M1a	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b single lesion	M1b	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1c multiple lesions	M1c	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)

* Where there is a change, the resultant stage groupings for the eighth edition are in bold, and the stage in the seventh edition is given in parenthesis.

Original figure modified for this publication. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016; 11:39. Table used with the permission of Elsevier Inc. All rights reserved.

Graphic 109806 Version 3.0

Clinical findings suggesting metastatic disease

Symptoms elicited in history
Constitutional - weight loss >10 pounds
Musculoskeletal - focal skeletal pain
Neurologic - headaches, syncope, seizures, extremity weakness, recent change in mental status
Signs found on physical exam
Lymphadenopathy (>1 cm)
Hoarseness, superior vena cava syndrome
Bone tenderness
Hepatomegaly (>13 cm span)
Focal neurologic signs, papilledema
Soft tissue mass
Routine laboratory tests
Hematocrit, <40% in males
Hematocrit, <35% in females
Elevated alkaline phosphatase, GGT, SGOT

GGT: gamma-glutamyltransferase; SGOT: serum glutamicoxalonacetic transaminase.

Graphic 93836 Version 1.0

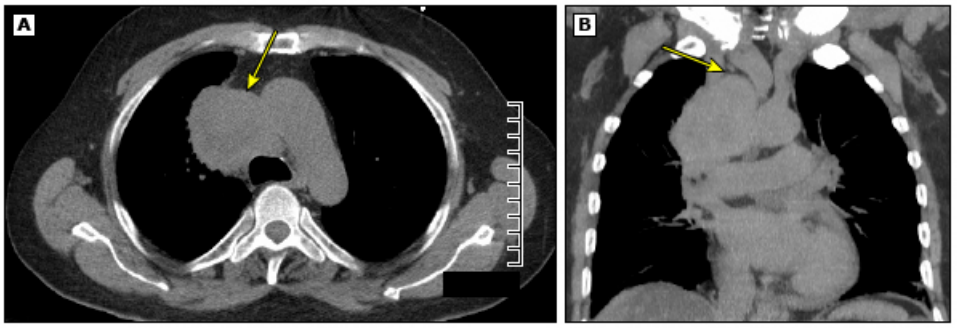
Computed tomographic-defined categories of lung cancer

Group	Description	Definition (by chest CT scan)
A	Mediastinal infiltration	Tumor mass within the mediastinum such that discrete lymph nodes cannot be distinguished or measured*
B	Enlarged discrete mediastinal nodes	Discrete mediastinal nodes ≥1 cm in short-axis diameter on a transverse CT image
C	Clinical stage II or central stage I tumor	Normal mediastinal nodes (<1 cm) but enlarged N1 nodes (≥1 cm) or a central tumor (within proximal one-third of the hemithorax)
D	Peripheral clinical stage I tumor	Normal mediastinal and N1 nodes (<1 cm) and a peripheral tumor (within outer two-thirds of hemithorax)

* This does not include a tumor mass within the lung that is abutting the mediastinum and tangentially involving the mediastinal pleura or fat (this situation pertains to the T stage of the primary tumor and not the N stage of the mediastinum).

Graphic 93837 Version 2.0

Invasion of lung cancer into the mediastinum on CT scan

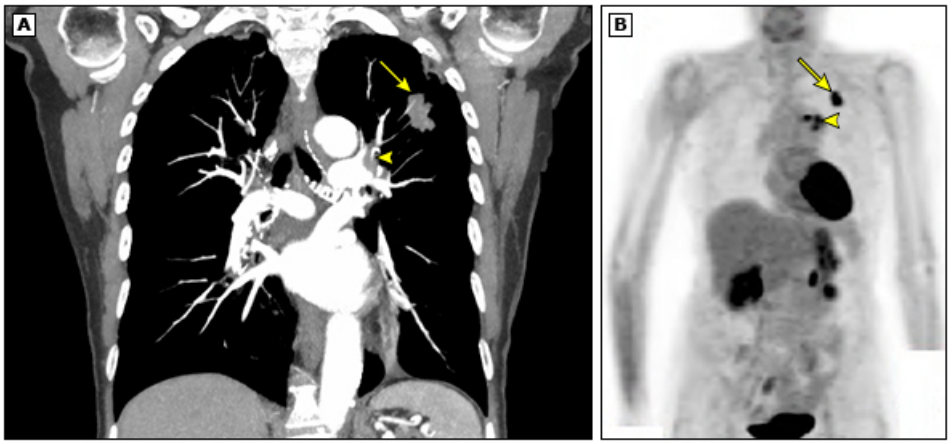


A non-contrast CT scan in axial projection (A) and with coronal reconstruction (B) shows a paramediastinal lung carcinoma invading the mediastinum (arrows). Contrast-enhanced CT scans are generally preferred for the evaluation of lung care; contrast is particularly helpful in assessing invasion of the mediastinum.

CT: computed tomography.

Graphic 91197 Version 2.0

T3N3M0 NSCLC on CT and PET

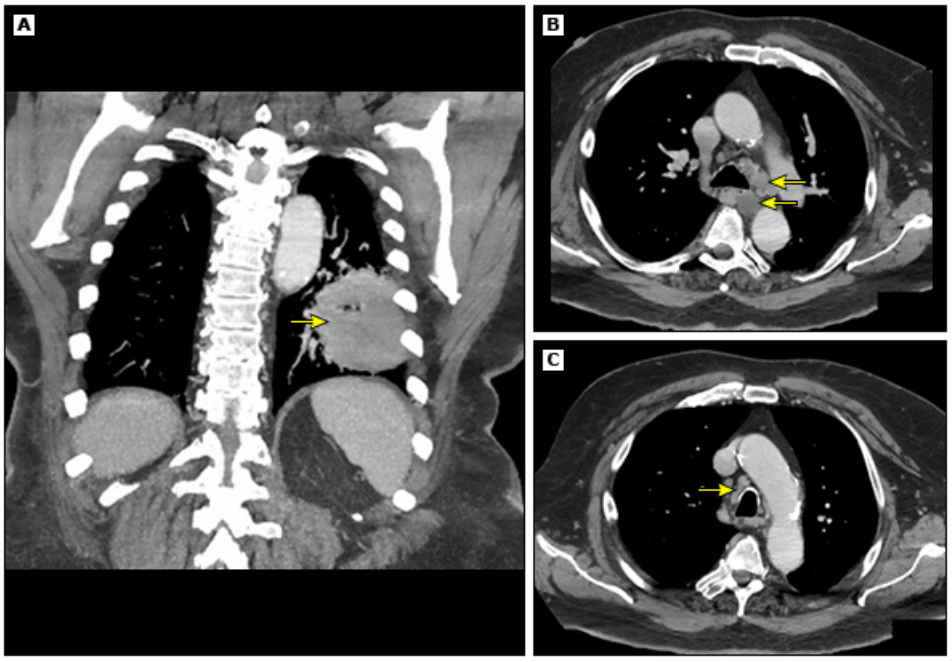


A coronal reconstruction of a chest CT scan (A) shows a 3 cm tumor in the left upper lobe (arrow) with small left hilar nodes (arrowhead). Image B shows an FDG avid nodule (arrow) with ipsilateral hilar and mediastinal disease (arrowhead).

NSCLC: non-small cell lung cancer; CT: computed tomography; PET: positron emission tomography; FDG: fluorodeoxyglucose.

Graphic 94802 Version 2.0

Stage T3N3M0 non-small cell lung cancer on CT

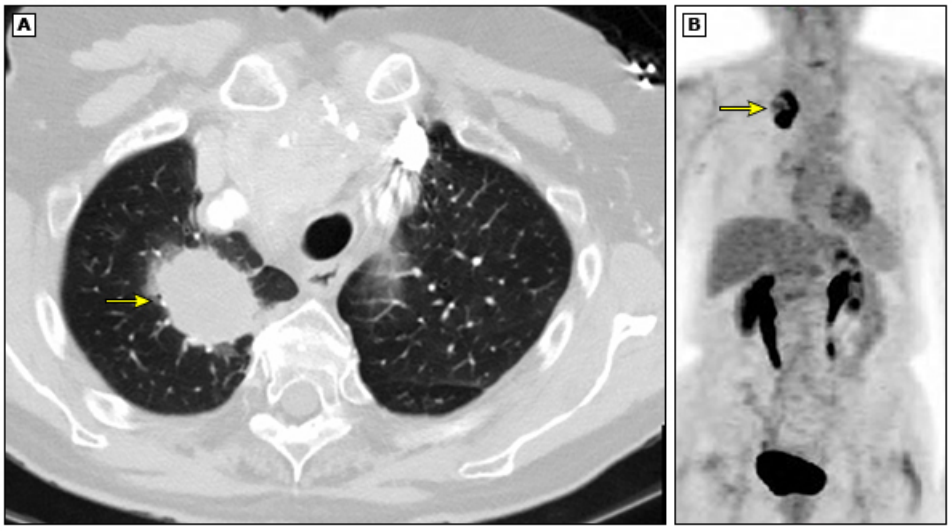


A coronal reconstruction of a chest CT scan (A) shows a 5.1 cm, minimally-cavitating left lower squamous carcinoma (arrow). Image B is an axial scan through the upper chest and shows ipsilateral lymphadenopathy (arrows) and image C shows possible contralateral lymphadenopathy (arrow). EBUS-guided fine needle aspiration biopsy of the mediastinal nodes confirmed T3N3M0 status.

NSCLC: non-small cell lung cancer; CT: computed tomography; EBUS: endobronchial ultrasound.

Graphic 94803 Version 3.0

Stage 1B II non small cell lung cancer on CT and PET

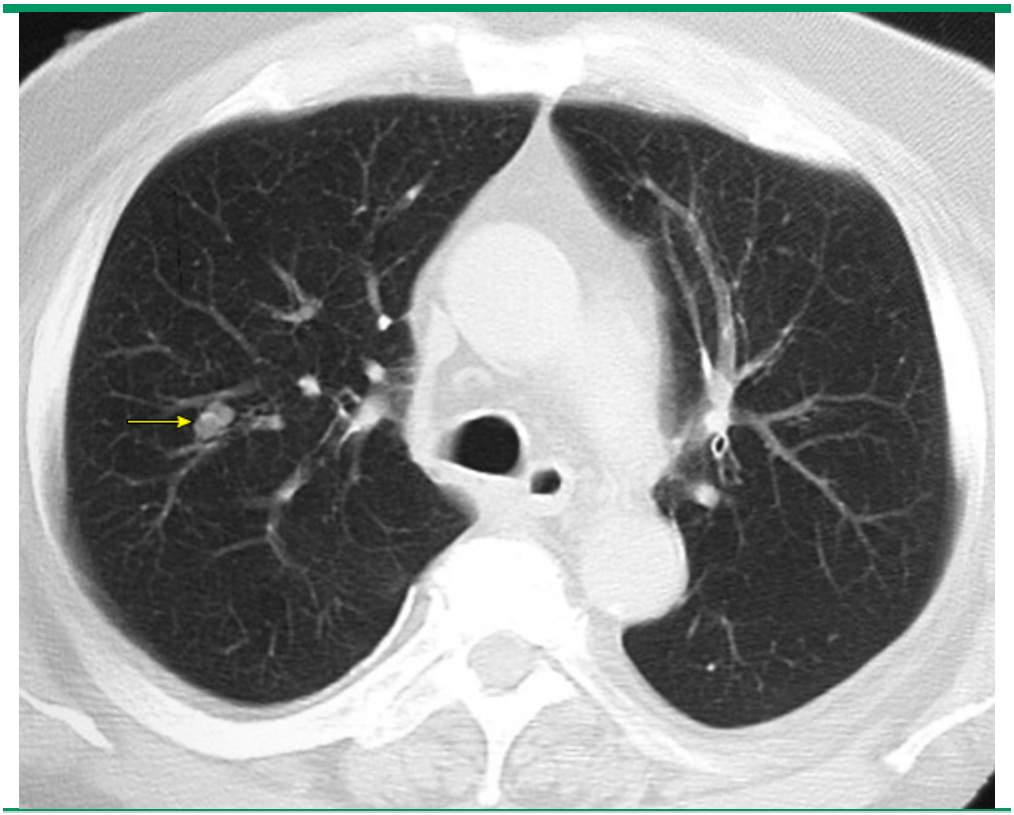


An axial CT scan through the chest (A) shows a 4.2 cm stage 1B/II squamous carcinoma in the right upper lobe (arrow). Image B shows an FDG avid mass (arrow) without FDG-avid metastatic disease. The relative lack of central FDG avidity suggests necrosis of the tumor.

NSCLC: non small cell lung cancer; CT: computed tomography; PET: positron emission tomography; FDG: fluorodeoxyglucose.

Graphic 94801 Version 2.0

T1aN0M0 non-small cell lung cancer on CT

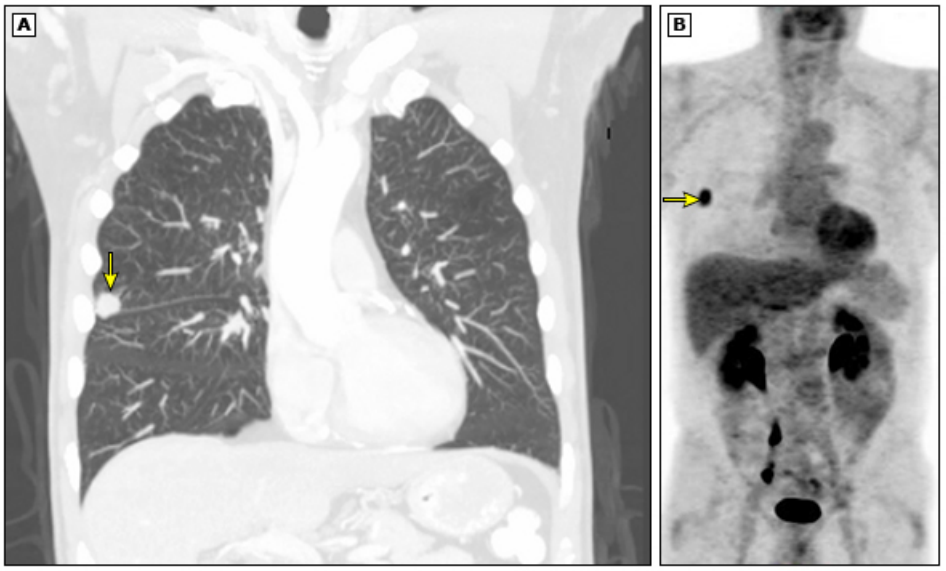


An axial CT scan through chest shows a T1aN0M0, 9 mm adenocarcinoma in the right upper lobe (arrow).

CT: computed tomography; NSCLC: non small cell lung cancer.

Graphic 94798 Version 3.0

T1cN0M0 non-small cell lung cancer on CT and PET scans



A coronal reconstruction of a chest CT scan (A) shows a T1cN0M0, 2.3 cm carcinoma in the right upper lobe (arrow). Image B shows an FDG avid nodule (arrow) without FDG-avid metastatic disease.

NSCLC: non-small cell lung cancer; CT: computed tomography; PET: positron emission tomography; FDG: fluorodeoxyglucose.

Graphic 94799 Version 3.0

TNM staging system for lung cancer (seventh edition)

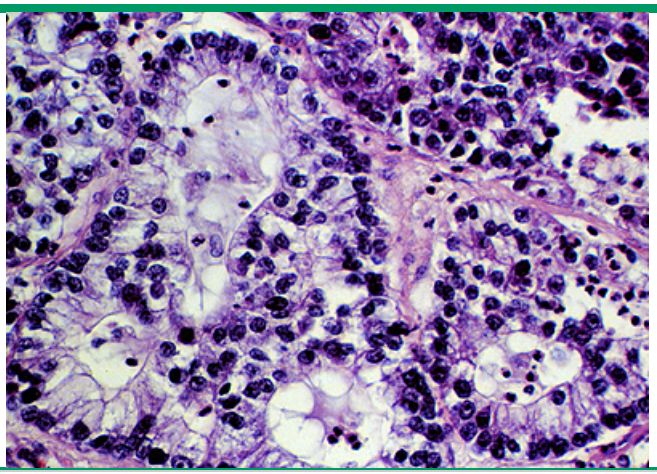
Primary tumor (T)			
T1	Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus*		
T1a	Tumor ≤2 cm in diameter		
T1b	Tumor >2 cm but ≤3 cm in diameter		
T2	Tumor >3 cm but ≤7 cm, or tumor with any of the following features:		
	Involves main bronchus, ≥2 cm distal to carina		
	Invades visceral pleura		
	Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung		
T2a	Tumor >3 cm but ≤5 cm		
T2b	Tumor >5 cm but ≤7 cm		
T3	Tumor >7 cm or any of the following:		
	Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina)		
	Atelectasis or obstructive pneumonitis of the entire lung		
	Separate tumor nodules in the same lobe		
T4	Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe		
Regional lymph nodes (N)			
N0	No regional lymph node metastases		
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension		
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)		
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion		
M1b	Distant metastasis (in extrathoracic organs)		
Stage groupings			
Stage IA	T1a-T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a,T1b,T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,T1b,T2a,T2b	N2	M0
	T3	N1,N2	M0
	T4	N0,N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a or M1b

* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

Adapted from: Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groups in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007; 2:706.

Graphic 80099 Version 6.0

Adenocarcinoma of the lung

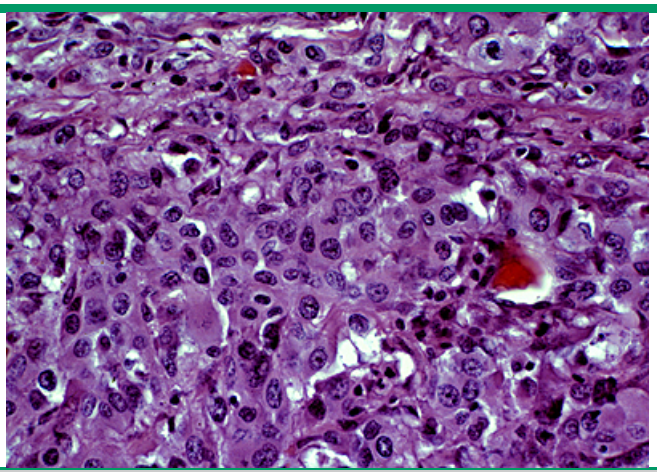


High-powered photomicrograph demonstrating the typical acinar pattern of glandular differentiation observed in adenocarcinoma.

Courtesy of Jeffrey Myers, MD.

Graphic 71512 Version 1.0

Adenocarcinoma of the lung

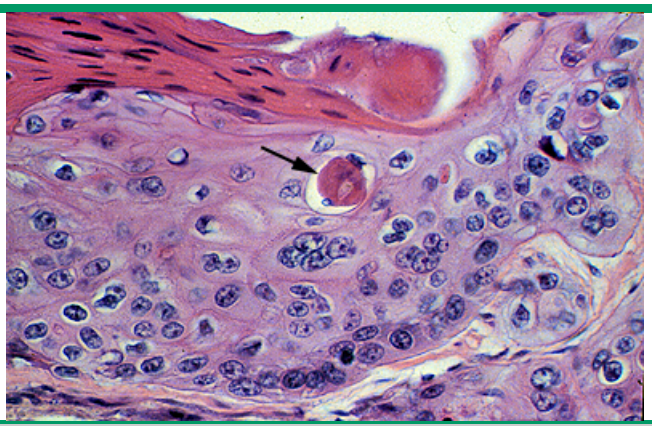


Photomicrograph of a hematoxylin and eosin-stained section of solid adenocarcinoma of the lung.

Courtesy of Jeffrey Myers, MD.

Graphic 50555 Version 1.0

Keratinization in lung cancer

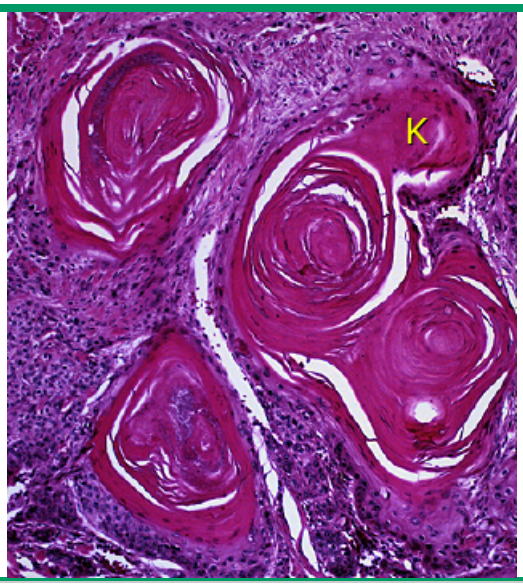


Keratin (arrow) appears as waxy, darkly staining eosinophilic cytoplasm in this high powered photomicrograph of a keratinizing squamous cell carcinoma of the lung.

Courtesy of Jeffrey Myers, MD.

Graphic 72421 Version 2.0

Keratinization in lung cancer



Low magnification photomicrograph showing marked keratinization (K) in a squamous cell carcinoma of the lung.

Courtesy of Jeffrey Myers, MD.

Graphic 73209 Version 2.0

Immunohistochemical and histochemical stains useful in the differential diagnosis of various carcinomas

Tumor type	Immunohistochemical staining
Carcinoma	Positive: Pankeratin, AE 1/3, CAM 5.2, OSCAR, EMA Negative: CD 45 Variable: CK 7, CK 20, S-100, vimentin
Colorectal carcinoma	Positive: CK 20, CDX-2 Negative: CK 7
Lung carcinoma	
Adenocarcinoma	Positive: TTF-1, napsin A, CK 7, mucicarmine, PAS-D Negative: Thyroglobulin
Squamous cell carcinoma	Positive: p 40, p 63, CK 5/6, desmoglein Negative: CK 7 (usually)
Small-cell carcinoma	Positive: TTF-1, high proliferative rate (Ki-67, MIB-1) Variable: Chromogranin, synaptophysin
Neuroendocrine carcinoma	Positive: Chromogranin, synaptophysin, epithelial stains
Germ cell tumor	Positive: HCG, AFP, Oct4 transcription factor, placental alkaline phosphatase, epithelial stains
Hepatocellular carcinoma	Positive: Hep par 1, CEA, AFP, glypican 3 Negative: CK 7, CK 20
Renal cell carcinoma	Positive: Pan keratin, CAM 5.2, Pax-8, CK 7, vimentin, RCC, CD 10 Negative: CK 20, CEA
Prostate carcinoma	Positive: PSA, prostatic acid phosphatase Negative: CK 7, 20
Pancreas carcinoma	Positive: CA 19-9, CK 7, CDX-2, CK 17 Variable: CK 20
Breast carcinoma	Positive: ER, PR, Her-2-neu, CK 7, gross cystic fluid protein 15, epithelial stains, GATA 3, mammaglobin Negative: CK 20
Ovarian carcinoma	Positive: CK 7, WT-1, Pax-8, ER Negative: CK 20, CDX-2
Thyroid carcinoma	Positive: Thyroglobulin, TTF-1, CK 7

EMA: epithelial membrane antigen; CD: luster of differentiation; CK: cytokeratin; S-100: S-100 protein; CDX: caudal-type homeobox transcription factor 2; TTF-1: thyroid transcription factor 1; PAS-D: Periodic Acid Schiff with diastase predigestion; NSE: neuron-specific enolase; HCG: human chorionic gonadotropin; AFP: alpha-fetoprotein; Hep par: hepatocyte paraffin 1 monoclonal antibody; CEA: carcinoembryonic antigen; Pax: paired box gene; RCC: renal cell carcinoma; PSA: prostate-specific antigen; CA: carbohydrate antigen 19-9; ER: estrogen receptor; PR: progesterone receptor; WT-1: Wilms tumor 1 protein.

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3. *http://www.immunoquery.com (Accessed on September 30, 2014).*
4. *Kandalaft PL, Gown AM. Practical application in immunohistochemistry: carcinoma of unknown primary site. Arch Pathol Lab Med 2016; 140:508.*

Graphic 56518 Version 13.0

Contributor Disclosures

Karl W Thomas, MD Nothing to disclose **Michael K Gould, MD, MS** Grant/Research/Clinical Trial Support: Medial EarlySign [Lung cancer]. Other Financial Interest: American Thoracic Society/Annals of the American Thoracic Society [Thoracic oncology]. **David E Midthun, MD** Nothing to disclose **Geraldine Finlay, MD** Nothing to disclose

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