

NCCN Guidelines® Insights

Non–Small Cell Lung Cancer, Version 2.2013

Featured Updates to the NCCN Guidelines

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Abstract

These NCCN Guidelines Insights focus on the diagnostic evaluation of suspected lung cancer. This topic was the subject of a major update in the 2013 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non–Small Cell Lung Cancer. The NCCN Guidelines Insights focus on the major updates in the NCCN Guidelines and discuss the new updates in greater detail. (*JNCCN* 2013;11:645–653)

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Disclosures for the NCCN Non–Small Cell Lung Cancer Panel

Individual disclosures of potential conflicts of interest for the NCCN Non–Small Cell Lung Cancer Panel members can be found on page 646.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for NSCLC.
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for NSCLC.

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Disclosure of Affiliations and Significant Relationships

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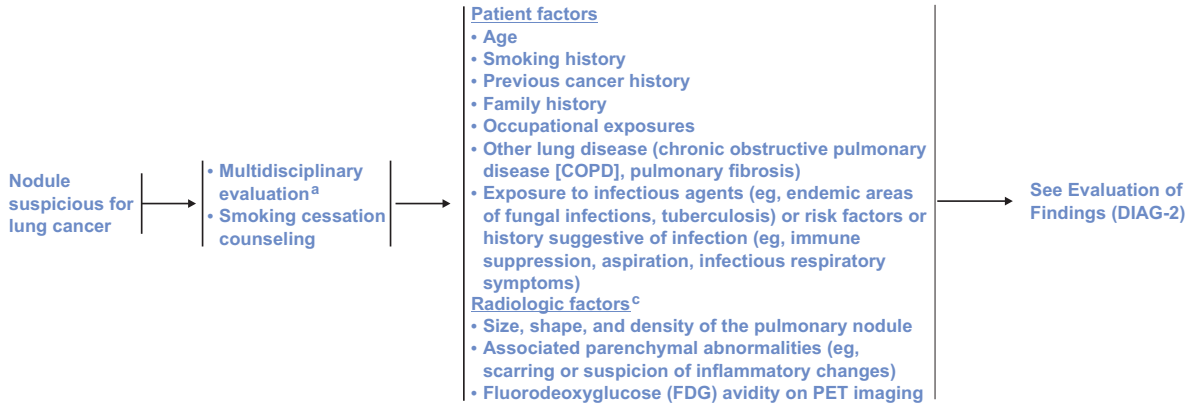
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CLINICAL PRESENTATION

RISK ASSESSMENT^b



^aMultidisciplinary evaluation including thoracic surgeons, thoracic radiologists, and pulmonologists to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy.

^bRisk calculators can be used to quantify individual patient and radiologic factors but do not replace evaluation by a multidisciplinary diagnostic team with substantial experience in the diagnosis of lung cancer.

^cSee Principles of Diagnostic Evaluation (DIAG-A 1 of 2).

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DIAG-1

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

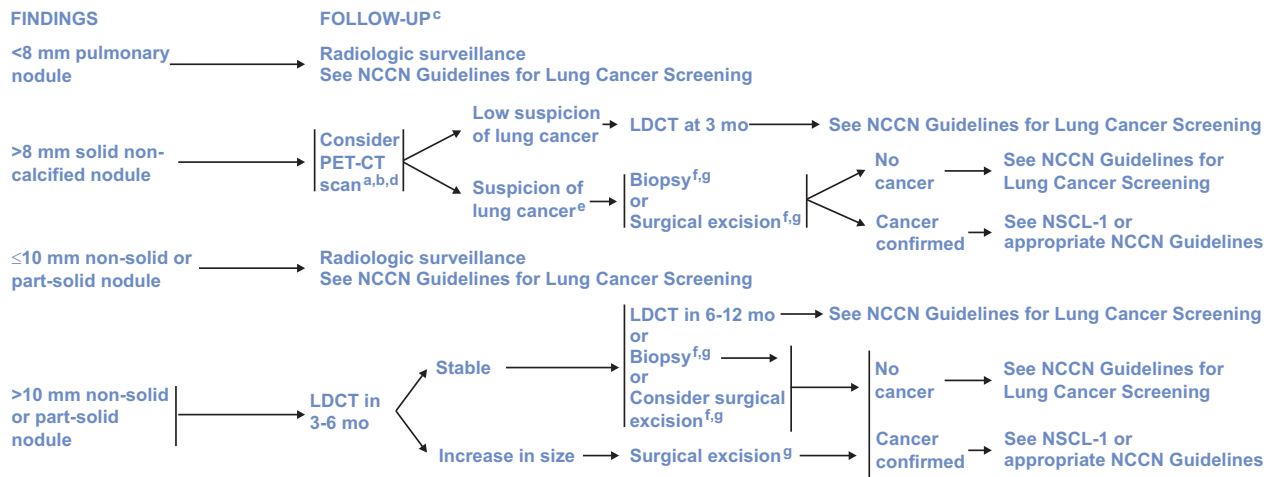
All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Smoking tobacco is the primary risk factor for lung cancer.¹⁻⁴ The risk of lung cancer increases with the number of packs of cigarettes smoked per day and the number of years spent smoking (ie, pack-years of smoking history).⁵⁻⁷ Thus, current smokers should be encouraged to quit (<http://www.smoke-free.gov/>),^{1,8-11} and former smokers should be encouraged to avoid smoking. Agents that can be used to promote smoking cessation include nicotine replacement (eg, gum, inhaler, lozenge, nasal spray, patch), sustained-release bupropion, and varenicline (<http://www.ahrq.gov/clinic/tobacco/medsmoktab.htm>).⁸⁻¹¹ Other risk factors for lung cancer include radon, disease history, family history of lung cancer, and occupational exposure (eg, asbestos, silica, coal smoke, and diesel fumes; see the NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Lung Cancer Screening, available online at [NCCN.org](http://www.nccn.org)).^{1,4,12,13}

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^aMultidisciplinary evaluation including thoracic surgeons, thoracic radiologists, and pulmonologists to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy.

^bRisk calculators can be used to quantify individual patient and radiologic factors but do not replace evaluation by a multidisciplinary diagnostic team with substantial experience in the diagnosis of lung cancer.

^cSee Principles of Diagnostic Evaluation (DIAG-A 1 of 2).

^dA positive PET result is defined as a standard uptake value (SUV) in the lung nodule greater than the baseline mediastinal blood pool. A positive PET scan finding can be caused by infection or inflammation, including absence of lung cancer with localized infection, presence of lung cancer with associated (eg, postobstructive) infection, and presence of lung cancer with related inflammation (nodal, parenchymal, pleural). A false-negative PET scan can be caused by a small nodule, low cellular density (nonsolid nodule or ground glass opacity [GGO]), or low tumor avidity for FDG (eg, adenocarcinoma in situ [previously known as bronchoalveolar carcinoma], carcinoid tumor).

^ePatients with a suspicion of lung cancer after PET-CT require histologic confirmation before any nonsurgical therapy.

^fThe choice of biopsy or surgical excision should be based on the clinical suspicion of lung cancer, location of lesion (feasibility for surgical identification and resection by minimally invasive video-assisted thoracic surgery [VATS]), and patient preferences.

^gPatients with a strong clinical suspicion of stage I or II lung cancer (based on risk factors and radiologic appearance) do not require a biopsy before surgery.

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DIAG-2

Currently, most patients with lung cancer are diagnosed at an advanced stage when curative treatment is not possible. Thus, lung cancer has a higher mortality rate than other types of cancer. Only 15.9% of all patients with lung cancer are alive 5 years or more after diagnosis.¹⁴ In 2013, an estimated 228,000 new diagnoses and 159,500 deaths from lung and bronchial cancer will occur in the United States.¹⁵ Screening with low-dose CT has been shown to decrease the mortality rate from lung cancer.¹⁶ Although screening with low-dose CT can be used to identify possible lung cancer, most cases are currently identified through other means (eg, symptoms, including weight loss, long-term cough, dyspnea), because lung cancer screening is not yet widely available and many insurance companies are not currently paying for screening. Early-stage lung cancer is often detected in patients because a chest radiograph or CT scan (obtained for other reasons) incidentally shows a lung nodule or mass. For patients with suspected lung

cancer, diagnostic and treatment strategies should be decided in a multidisciplinary setting and on an individual basis to maximize outcomes.

Data show that low-dose CT can be used to detect lung cancer at an early stage when it is more likely curable.¹⁶ The NCCN Guidelines for Lung Cancer Screening recommend screening with low-dose CT for select high-risk current and former smokers without symptoms of lung cancer¹⁷ (to view the most recent version of these guidelines, visit [NCCN.org](http://www.nccn.org)). Other organizations also recommend screening with low-dose CT for select high-risk patients (eg, American College of Chest Physicians, American Cancer Society, American Lung Association, ASCO, and American Thoracic Society) (<http://www.lung.org/lungdisease/lungcancer/lungcancerscreeningguidelines/>).^{18–20}

The NCCN Guidelines for Non–Small Cell Lung Cancer (NSCLC) discuss management of non-squamous NSCLC (eg, adenocarcinoma), which is the most common type of lung cancer, and also less

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PRINCIPLES OF DIAGNOSTIC EVALUATION

- Patients with a strong clinical suspicion of stage I or II lung cancer (based on risk factors and radiologic appearance) do not require a biopsy before surgery.
 - ▶ A biopsy adds time, costs, and procedural risk and may not be needed for treatment decisions.
 - ▶ A preoperative biopsy may be appropriate if a non-lung cancer diagnosis is strongly suspected that can be diagnosed by FNA.
 - ▶ A preoperative biopsy may be appropriate if an intraoperative diagnosis appears difficult or very risky.
 - ▶ If a preoperative tissue diagnosis has not been obtained, then an intraoperative diagnosis (ie, wedge resection or needle biopsy) is necessary before lobectomy, bilobectomy, or pneumonectomy.
- Bronchoscopy should preferably be performed during the planned surgical resection, rather than as a separate procedure.
 - ▶ Bronchoscopy is required before surgical resection (see NSCL-2).
 - ▶ A separate bronchoscopy may not be needed for treatment decisions before the time of surgery and adds time, costs, and procedural risk.
 - ▶ A preoperative bronchoscopy may be appropriate if a central tumor requires pre-resection evaluation for biopsy, surgical planning (eg, potential sleeve resection), or preoperative airway preparation (eg, coring out an obstructive lesion).
- Invasive mediastinal staging is recommended before surgical resection for most patients with clinical stage I or II lung cancer (see NSCL-2).
 - ▶ Patients should preferably undergo invasive mediastinal staging as the initial step before the planned resection (during the same anesthetic procedure), rather than as a separate procedure.
 - ▶ A separate staging procedure adds time, costs, coordination of care, inconvenience, and an additional anesthetic risk.
 - ▶ Preoperative invasive mediastinal staging may be appropriate for a strong clinical suspicion of N2 or N3 nodal disease or when intraoperative cytology or frozen section analysis is not available.
- In patients with suspected NSCLC, many techniques are available for tissue diagnosis.
 - ▶ Diagnostic tools that should be routinely available include:
 - ◊ Sputum cytology
 - ◊ Bronchoscopy with biopsy and transbronchial needle aspiration (TBNA)
 - ◊ Image-guided transthoracic needle aspiration (TTNA)
 - ◊ Thoracentesis
 - ◊ Mediastinoscopy
 - ◊ Video-assisted thoracic surgery (VATS) and open surgical biopsy
 - ▶ Diagnostic tools that provide important additional strategies for biopsy include:
 - ◊ Endobronchial ultrasound (EBUS)–guided biopsy
 - ◊ Navigational bronchoscopy

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common types of lung cancer (eg, squamous cell carcinoma, large cell carcinoma).²¹ Other types of thoracic cancer are discussed in the NCCN Guidelines for Malignant Pleural Mesothelioma, Small Cell Lung Cancer, and Thymomas and Thymic Carcinomas (to view the most recent version of these guidelines, visit NCCN.org).

Principles of Diagnostic Evaluation

A new section on diagnostic evaluation of suspected lung cancer was added for the 2013 update (see DIAG-A, pages 649 and 650). This new section includes an algorithm for evaluating suspicious lung nodules observed on chest radiograph or CT scan (see DIAG-1 and DIAG-2, page 647 and 648).

Diagnostic Evaluation of Lung Nodules

This new diagnostic section describes the evaluation of suspicious pulmonary nodules or masses that are seen on chest radiograph and CT. Patient factors

(eg, age, smoking history, occupational exposure) and radiologic characteristics (eg, nodule size, shape, other lung pathology) must be carefully evaluated by a multidisciplinary diagnostic team to help formulate decisions about how to proceed with the workup of a suspicious lung nodule. The NCCN Guidelines recommend biopsy or surgical excision for highly suspicious nodules or further surveillance for nodules with a low suspicion of cancer, depending on the type of nodule and a multidisciplinary evaluation of other patient factors (see DIAG-1, page 647). PET/CT scans also may be used to aid the decision-making process. Several factors, including the size of the pulmonary nodule, whether the nodule is changing in size, and the type of nodule (eg, solid noncalcified nodule vs nonsolid nodule), are used to determine whether the nodule is more or less likely to be lung cancer (see DIAG-2, page 648).^{22–25}

Diagnostic Evaluation of Suspected Lung Cancer

The diagnostic strategy benefits from a multidisciplinary

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PRINCIPLES OF DIAGNOSTIC EVALUATION

- The preferred diagnostic strategy for an individual patient depends on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (such as pulmonary pathology and/or other significant comorbidities), and local experience and expertise.
 - ▶ Factors to be considered in choosing the optimal diagnostic step include:
 - ◊ Anticipated diagnostic yield (sensitivity)
 - ◊ Diagnostic accuracy including specificity and particularly the reliability of a negative diagnostic study (that is, true negative)
 - ◊ Adequate volume of tissue specimen for diagnosis and molecular testing
 - ◊ Invasiveness and risk of procedure
 - ◊ Efficiency of evaluation
 - Access and timeliness of procedure
 - Concomitant staging is beneficial, because it avoids additional biopsies or procedures. It is preferable to biopsy the pathology that would confer the highest stage (that is, to biopsy a suspected metastasis or mediastinal lymph node rather than the pulmonary lesion).
 - ◊ Technologies and expertise available
 - ▶ Decisions about the optimal diagnostic steps for suspected stage I to III lung cancer should be made by thoracic radiologists, interventional radiologists, and board-certified thoracic surgeons who devote a significant portion of their practice to thoracic oncology. Multidisciplinary evaluation may also benefit from involvement of a pulmonologist with experience in advanced bronchoscopic techniques for diagnosis, depending on local expertise.
 - ▶ The least invasive biopsy with the highest yield is preferred as the first diagnostic study.
 - ◊ Patients with central masses and suspected endobronchial involvement should undergo bronchoscopy.
 - ◊ Patients with peripheral (outer one-third) nodules should have navigational bronchoscopy, radial EBUS, or TTNA
 - ◊ Patients with suspected nodal disease should be biopsied by EBUS, navigational bronchoscopy, or mediastinoscopy.
 - Esophageal ultrasound (EUS)-guided biopsy provides additional access to station 5, 7, 8, and 9 lymph nodes if these are clinically suspicious.
 - TTNA and anterior mediastinotomy (that is, Chamberlain procedure) provide additional access to anterior mediastinal (station 5 and 6) lymph nodes if these are clinically suspicious.
 - ◊ Lung cancer patients with an associated pleural effusion should undergo thoracentesis and cytology. A negative cytology result on initial thoracentesis does not exclude pleural involvement. An additional thoracentesis and/or thoracoscopic evaluation of the pleura should be considered before starting curative intent therapy.
 - ◊ Patients suspected of having a solitary site of metastatic disease should preferably have tissue confirmation of that site if feasible.
 - ◊ Patients suspected of having metastatic disease should have confirmation from one of the metastatic sites if feasible.
 - ◊ Patients who may have multiple sites of metastatic disease—based on a strong clinical suspicion—should have biopsy of the primary lung lesion or mediastinal lymph nodes if it is technically difficult or very risky to biopsy a metastatic site.

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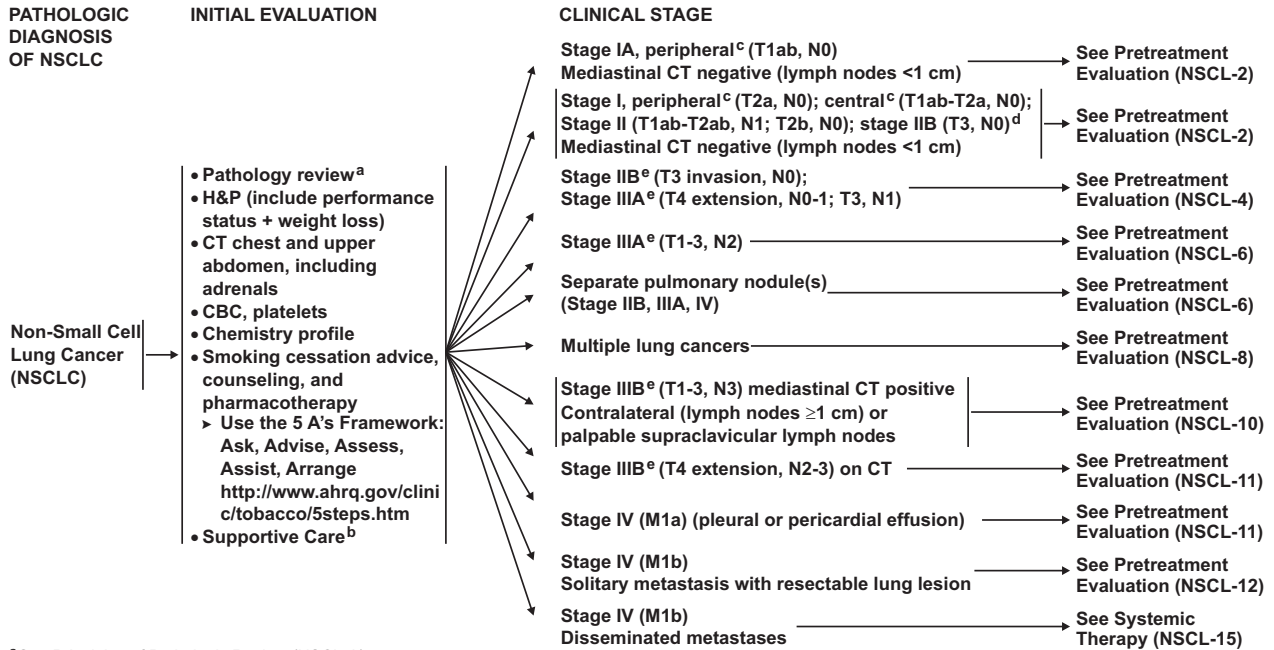
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plinary evaluation that includes thoracic radiologists, thoracic surgeons, and pulmonary physicians. The NCCN Guidelines recommend that the diagnostic strategy be individualized for each patient depending on the size and location of the tumor or nodule, the presence of mediastinal or distant disease, patient characteristics (eg, comorbidities), and local experience. Decisions regarding whether a biopsy (including what type of biopsy) or surgical excision is appropriate depend on several factors, as outlined in the NCCN algorithm (see DIAG-A, pages 649 and 650). In many situations when the suspicion of lung cancer is high and the patient is a surgical candidate, preoperative biopsy may be unnecessary, because it adds time, cost, and procedural risk but is unlikely to alter the plan for surgical resection (ie, pathologic diagnosis is established intraoperatively). However, if an intraoperative diagnosis is risky or difficult or if there is a significant suspicion of an alternative diag-

nosis, then a preoperative biopsy may be beneficial.

The optimal biopsy approach depends on various factors, including size and location of the nodule, associated lung disease (eg, emphysema), proximity to other structures, and experience and technologies available in the local health care system. Factors to be considered in choosing a biopsy technique include diagnostic yield (sensitivity), diagnostic accuracy (especially true-negative yield), adequacy of tissue volume, risk of the procedure, efficiency (access and timeliness of biopsy), and local experience and expertise. In general, the least-invasive biopsy technique with the highest diagnostic yield should be selected, and the NCCN Guidelines outline general principles to help direct clinicians in this process (see DIAG-A, pages 649 and 650). Radial probe endobronchial ultrasound (EBUS), navigational bronchoscopy, or transthoracic needle aspiration is recommended for patients with suspected peripheral nodules.^{26–32} Routine bronchos-

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^aSee Principles of Pathologic Review (NSCL-A).

^bTemel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010;363:733-742.

^cBased on the CT of the chest: Peripheral = outer third of lung. Central = inner two thirds of lung.

^dT3, N0 related to size or satellite nodules.

^eFor patients considered to have stage IIB and stage III tumors, where more than one treatment modality (surgery, radiation therapy, or chemotherapy) is usually considered, a multidisciplinary evaluation should be performed.

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NSCL-1

copy with (or without) EBUS is preferable for centrally located masses. Mediastinoscopy, EBUS, or navigational bronchoscopy is recommended for patients with suspected nodal disease.^{33,34} Another general principle is to preferentially biopsy the abnormality that would simultaneously confer the highest tumor stage. For example, in a patient with a suspicious liver lesion or pleural effusion, liver biopsy or thoracentesis would most efficiently obtain a tissue diagnosis and establish stage IV disease. Communication among the pathologist, medical oncologist, and practitioner performing the biopsy is of the utmost importance to ensure that sufficient tissue is obtained and processed properly to facilitate molecular testing for genetic alterations (eg, epidermal growth factor receptor mutations, ALK gene rearrangements).

If pathology results from biopsy or surgical excision indicate a diagnosis of NSCLC (see Principles of Pathologic Review in the NCCN Guidelines

for NSCLC; to view the complete version of these guidelines, visit NCCN.org), then further evaluation and clinical staging must be performed so that the patient's health care team can determine the most appropriate and effective treatment plan (see NSCL-1, above). Accurate histology must be determined (eg, adenocarcinoma, squamous cell carcinoma) before initiating systemic therapy; a general diagnosis of NSCLC is not recommended.²¹ Diagnosis, staging, and planned resection (eg, lobectomy) are ideally a single operative procedure for patients with early-stage disease (see DIAG-A, pages 649 and 650). Confirmation and staging of lung cancer are essential before lobectomy or pneumonectomy, although they can be performed with intraoperative diagnosis and concomitant mediastinal staging. The mediastinal lymph nodes must be assessed, because upstaging can occur in patients with presumed early-stage NSCLC based on imaging alone.³⁴⁻³⁶

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Conclusions

Most patients with lung cancer are currently identified by symptoms, including weight loss, long-term cough, and dyspnea. For patients with suspected lung cancer, diagnostic and treatment strategies should be decided in a multidisciplinary setting and on an individual basis to maximize outcomes. A new section on diagnostic evaluation of suspected lung cancer was added for the 2013 update of the NCCN Guidelines for NSCLC (to view the most recent version of these guidelines, visit NCCN.org). This new diagnostic section describes the evaluation of suspicious pulmonary nodules or masses that are seen on chest radiograph and CT. Patient factors and radiologic characteristics must be carefully evaluated by a multidisciplinary diagnostic team to help formulate decisions about how to proceed with workup of a suspicious lung nodule. The NCCN Guidelines recommend that the diagnostic strategy be individualized for each patient depending on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics, and local experience. The least-invasive biopsy technique with the highest diagnostic yield should be selected; the NCCN Guidelines outline general principles for this process. When obtaining a biopsy specimen, it is essential that the pathologist, medical oncologist, and practitioner confer to ensure that sufficient tissue is obtained and processed properly to facilitate molecular testing. If NSCLC is diagnosed, then further evaluation and clinical staging must be performed so that the patient's health care team can determine the most appropriate and effective treatment plan.

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Posttest Questions

1. For patients who appear to have early-stage lung cancer, which of the following is/are TRUE?
 - a. Diagnosis, staging, and resection can be a single operative procedure.
 - b. Multidisciplinary evaluation is not recommended.
 - c. Preoperative biopsy is essential.
 - d. All of the above
 - e. None of the above
2. Which of the following is/are TRUE about biopsies for lung cancer?
 - a. The least invasive biopsy technique with the highest yield should be selected.
 - b. Radial probe endobronchial ultrasound, navigational bronchoscopy, or transthoracic needle aspiration is recommended for patients with suspected peripheral nodules.
 - c. Diagnostic yield (sensitivity), diagnostic accuracy (especially true negative yield), adequacy of tissue volume, risk of the procedure, efficiency (access and timeliness of biopsy), and local experience and expertise should be considered.
 - d. All of the above
 - e. None of the above
3. True or False: All lung nodules observed on low-dose CT scans should be biopsied as soon as possible.

