Lung Cancer: Diagnosis, Treatment Principles, and Screening

Jeffrey Kim, MD; Hobart Lee, MD; and Brian W. Huang, MD
Loma Linda University School of Medicine, Loma Linda, California

Lung cancer is the second most common cancer in men and women in the United States; however, it remains the leading cause of cancer-related death in the United States and worldwide. The most common but nonspecific symptom of lung cancer is cough. Associated symptoms, including hemoptysis or shortness of breath, or systemic symptoms, including anorexia or weight loss, greatly increase the likelihood of having lung cancer. Referral to a multidisciplinary lung cancer team, imaging, and confirmation through sputum cytology, thoracentesis, fine-needle aspiration, or mediastinoscopy are recommended. If lung cancer is confirmed, treatment options vary based on staging, histology, immunotherapy biomarker testing, and patient health status. Treatments include surgical resection, immunotherapy, chemotherapy, and/or radiotherapy. Family physicians should focus on primary prevention of lung cancer by encouraging tobacco cessation and early recognition by screening at-risk individuals and following guidelines for pulmonary nodules. As of 2021, the U.S. Preventive Services Task Force recommends annual lung cancer screening using low-dose computed tomography starting at 50 years of age in patients with a 20 pack-year history. (*Am Fam Physician*. 2022;105(5):487-494.

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Lung cancer remains the leading cause of cancer-related death in the United States and worldwide; in the United States, it is the second most common cancer among men and women.[1,2] The majority of lung cancers are divided into two histologic types: non–small cell lung cancer (NSCLC; 84%) and small cell lung cancer (SCLC; 13%), which helps guide treatment.[3] Smoking is closely linked to 80% to 90% of lung cancer deaths, whereas radon exposure is a leading cause of nonsmoking-related lung cancer.[4] Several guidelines address the management of lung cancer, with the goal of improving patient outcomes.[5] In the United Kingdom, the National Institute for Health and Care Excellence has developed clinical pathways that were last updated in 2019, whereas in the United States, the most recent comprehensive lung cancer guideline from the American College of Chest Physicians was last updated in 2013, with more recent treatment recommendations from the National Comprehensive Cancer Network.[2,6-8]

Additional content at https://www.aafp.org/afp/2022/0500/p487.html

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Clinical Presentation and Diagnosis

IN-OFFICE EVALUATION

When evaluating a patient for lung cancer, a detailed history and physical examination should be performed, including environmental and work exposures. Current smoking or history of smoking is the single most important risk factor for all types of lung cancer.[9,10] Concomitant chronic lung disease or exposure to radon or asbestos may increase the risk of lung cancer.[10]

Patients with lung cancer typically present with symptoms,[11] the most common of which is cough.[9,11] Hemoptysis in combination with weight loss, loss of appetite, or shortness of breath increases the likelihood of lung cancer.[11] *Table 1* provides signs and symptoms of lung cancer due to local effects,[12] and *Tables 2 and 3* show,

respectively, advanced disease–displaying symptoms of distant metastases and paraneoplastic syndromes associated with lung cancer.[12]

The initial evaluation for patients with a suspicion for lung cancer begins with laboratory testing, including a complete blood count, serum chemistries, calcium levels, and liver function tests, with chest radiography.[2,9] A normal chest radiograph alone should not be used to rule out lung cancer because just under 20% to 25% of normal chest radiographs may miss the disease.[13,14] Patients who have a high level of suspicion for lung cancer based on clinical assessment or initial chest radiography findings should receive computed tomography (CT) of the chest with intravenous contrast media, ideally to include the liver and adrenals.[2,15]

PULMONARY NODULE FOLLOW-UP

Among patients presenting with incidental nodules found on radiographic imaging, follow-up for those older than 35 years is assessed based on features and risk categorization, as recommended by the Fleischner Society, updated in 2017 *(Table 4)*.[16,17] New studies are emerging on the use of genomic classifiers and artificial intelligence to help facilitate clinical management of incidental nodules.[18,19] For patients meeting high-risk criteria and undergoing lung cancer screening, appropriate follow-up recommendations should be determined by the 2019 Lung-RADS guidelines[20] *(eTable A)*.

Diagnosis Confirmation

Patients with suspected lung cancer should be referred to a pulmonologist within a multidisciplinary thoracic oncology team to help guide workup.[6] Confirmation of the diagnosis should be made by one or more of the following methods, with further testing if suspicion is high and findings are negative: sputum cytology, thoracentesis of pleural fluid, bronchoscopy (often with endobronchial ultrasonography and/or electromagnetic navigation with or without fine-needle aspiration), or mediastinoscopy depending on local availability and expertise.[21]

STAGING

Staging of lung cancer follows the eighth edition of the American Joint Committee on Cancer's staging manual.[22] Staging revisions from the seventh edition were based on analysis of a database of 94,708 cases by the International Association for the Study of Lung Cancer Staging from 1999 to 2010.[23] The tumor, node, metastasis (TNM) classification describes the anatomic extent of the disease, is based on clinical and pathologic staging, and guides eventual treatment and prognosis[22] *(eTable B)*. Clinical TNM is based on history and physical examination findings, imaging, and staging procedures, and a pathologic TNM based on postsurgical histopathologic classification. The composite of these composes the TNM stage with associated prognostic stage

TABLE 1

Signs and Symptoms of Lung Cancer Due to Local Effects

Sign/symptom of the primary tumor*	LR+	LR–
Digital clubbing	55.0	0.96
Hemoptysis	13.2	0.81
Weight loss	6.2	0.76
Loss of appetite	4.8	0.84
Dyspnea	3.6	0.52
Chest or rib pain	3.3	0.68
Fatigue	2.3	0.76
First visit for cough	2.2	0.50
Second visit for cough	3.2	0.66
Third visit for cough	4.2	0.77
Sign/symptom of intrathoracic spread	**Clinical context**	
Decreased breath sounds and dyspnea	Malignant pleural effusion	
Decreased heart sounds and enlarged cardiac silhouette	Malignant pericardial effusion	
Dysphagia	Esophageal invasion	
Elevated hemidiaphragm	Phrenic nerve paralysis	
Facial swelling, plethora, and upper extremity edema	Superior vena cava syndrome	
Hoarseness, weak cough	Recurrent laryngeal nerve palsy	
Pleuritic chest pain	Chest wall invasion	
Ptosis, miosis, facial anhidrosis	Horner syndrome (sympathetic chain compression)	
Shoulder pain and muscle wasting along C8-T3 nerve root	Pancoast tumor (superior sulcus tumor)	

LR– = negative likelihood ratio; LR+ = positive likelihood ratio.

*—Among patients presenting with lung symptoms, primarily cough.

Adapted with permission from Latimer KM, Mott TF. Lung cancer: diagnosis, treatment principles, and screening. Am Fam Physician. *2015;91(4):252.*

groups I to IV[22] *(eTable C)*. TNM staging is recommended for NSCLC and SCLC for prognostic and tumor stratification purposes.[22] For NSCLC, brain imaging should be performed in stage IIA patients with consideration for stage IB patients; patients with stages III to IV disease should have magnetic resonance imaging of the brain to assess for metastases even in the absence of clinical disease.[7,24] Patients with any stage of SCLC should have brain imaging performed, preferably using magnetic resonance imaging.[8] In patients who may undergo curative treatment, positron emission tomography CT should be performed to assess intrathoracic lymph node involvement and guide subsequent sampling.[2,10]

Treatment

NON–SMALL CELL LUNG CANCER

The treatment of NSCLC varies based on staging, nonsquamous (usually adenocarcinoma) vs. squamous histology, and genetic and immunotherapy biomarker testing. Treatment options presented here provide an overview; however, specific regimens will vary based on the availability of treatment options and clinical experience of the multidisciplinary treatment team. Patients with advanced disease should be offered early palliative care.[7]

Patients with stages I to II NSCLC are usually offered a combination of three treatments: surgery, which can include complete resection of the tumor (usually stages I and II), and mediastinal lymph node dissection or lymph node sampling; radiotherapy; and adjuvant platinum-based chemotherapy.[25] Select patients who have stage III NSCLC but do not have disease progression after chemotherapy may benefit from immunotherapy.[7,26] Video-assisted thoracic surgery has lower mortality and hospital length of stay compared with open thoracotomy.[27] Nonsurgical candidates can be offered radiotherapy and platinum-based chemotherapy.[28] For patients with stage IV disease, palliative care and immunotherapy with or without platinum-based chemotherapy are recommended.[7] In patients with fewer than three brain metastases, stereotactic radiotherapy or surgery with stereotactic radiotherapy is recommended.[29] With more than three brain metastases, whole brain radiation is recommended, although it may not improve neurocognitive symptoms or overall survival.[28,29] Radiotherapy and bisphosphonates are recommended for bone metastases to reduce pain and risk of skeletal fractures.[28,29]

BEST PRACTICES IN PULMONOLOGY

Recommendations From the Choosing Wisely Campaign

Recommendation	Sponsoring organization
Do not perform CT screening for lung cancer among patients at low risk of lung cancer.	American College of Chest Physicians/American Thoracic Society
Do not recommend screening for breast, colorectal, prostate, or lung cancers without considering life expectancy and the risks of testing, overdiagnosis, and overtreatment.	American Geriatrics Society
Do not perform CT surveillance for evaluation of indeterminate pulmonary nodules at more frequent intervals or for a longer period of time than recommended by established guidelines.	American College of Chest Physicians/American Thoracic Society

CT = computed tomography.

Source: For more information on the Choosing Wisely Campaign, see https://www.choosingwisely.org. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see https://www.aafp.org/afp/recommendations/search.htm.

TABLE 2

Signs and Symptoms of Lung Cancer Due to Distant Metastases

Site	Sign or symptom	Frequency (%)
Any	Any sign or symptom	33
Liver	Weakness, weight loss, anorexia, hepatomegaly	Up to 60
Bone	Pain, fracture, elevated alkaline phosphatase	Up to 25
Lymphatics	Lymphadenopathy	15 to 20
Brain	Headaches, seizures, nausea and vomiting, mental status changes	Up to 10
Adrenals	Adrenal insufficiency	Rare
Skin	Subcutaneous nodules	Rare

Adapted with permission from Latimer KM, Mott TF. Lung cancer: diagnosis, treatment principles, and screening. Am Fam Physician. *2015;91(4):252.*

All patients who have NSCLC with nonsquamous NSCLC, mixed histology, or small-volume biopsies should be offered genetic and immunotherapy testing (e.g., broad-based, next-generation sequencing).[7] Common driver

mutations, preferred treatment options, and common adverse effects are listed in *eTable D*. Genetic testing can predict overall prognosis and responsiveness to targeted therapies; however, U.S. Food and Drug Administration–approved therapies depend on histologic subtype, disease progression, and timing with first-line systemic chemotherapy.[7] Standard first-line therapy for advanced NSCLC is immunotherapy with or without chemotherapy, based on *PD-L1* (programmed death-ligand 1) status of expression on tumor cells.[7]

PD-L1 expression (listed as a percentage between 0 and 100) of 50% or more can change the recommended immunotherapy regimen[7,29,30] *(eTable E)*.

In 2017, five-year survival for localized NSCLC was 59%, with only 5.8% for five-year survival in patients with distant metastases; however, there have been reductions in mortality since 2013 likely due to a decrease in incidence and advancements in therapies, as described previously[31] *(Table 5[22])*.

SMALL CELL LUNG CANCER

For patients with limited-stage SCLC, the standard of care is etoposide (Etopophos) plus cisplatin chemotherapy and concurrent thoracic radiotherapy, with surgical resection offered in select patients.[8,32] Patients with significant comorbidities, including chronic kidney disease, may be offered an alternative carboplatin (Paraplatin)–based chemotherapy regimen with similar effectiveness.[32] For patients with extensive-stage SCLC, four to six cycles of one of several combination chemotherapy/immunotherapy regimens should be offered with maintenance immunotherapy.[8] Consolidative thoracic radiation may be considered for select patients with residual intrathoracic disease who have responded to systemic chemotherapy.[8] In patients with limited-stage SCLC, prophylactic cranial irradiation for brain metastases reduces mortality.[33] Localized palliative radiation for nonpulmonary sites, including whole brain radiotherapy for brain metastases, should be offered.[28] Patients with relapse after initial therapy have overall poor prognosis; however, several second-line systemic therapy options are available.[8,34] Prognosis remains poor, with only 20% to 25% five-year survival for limited-stage SCLC and less than 10% two-year survival for extensive-stage SCLC[35] *(Table 5[22])*.

Screening

As of 2021, the U.S. Preventive Services Task Force (USPSTF) has recommended annual low-dose CT screening in adults 50 to 80 years of age who have a 20 pack-year smoking history and currently smoke or have quit smoking within the past 15 years.[36] This replaces the 2013 recommendation of annual CT screenings for patients 55 to 80 years of age with at least a 30 pack-year history.[37] The criteria for discontinuing screening are unchanged, including patients who have quit smoking for more than 15 years, have limited life expectancies (less than 10 years), or are not willing to undergo curative lung surgery.[36]

The updated recommendation is based on two major randomized controlled trials, the National Lung Screening Trial and the Dutch–Belgian lung-cancer screening trial (Nederlands–Leuvens Longkanker Screenings Onderzoek).[38,39] Both of these trials found reductions in lung cancer mortality, with a number needed to screen to prevent

TABLE 3

Paraneoplastic Syndromes Associated With Lung Cancer

Syndrome	Frequency (%)	Comments
Systemic (anorexia, cachexia, weight loss, fatigue, fever)	0 to 68	May be readily apparent and striking
Digital clubbing	29	More common with non–small cell lung cancer
Hypercalcemia	10 to 20	Ectopic production of parathyroid hormone–related peptide; may be life-threatening
Hyponatremia	1 to 5	Syndrome of inappropriate antidiuretic hormone or ectopic production of atrial natriuretic peptide
Paraneoplastic encephalitis	0.2	Mental status changes
Cushing syndrome	Rare	Ectopic production of adrenocorticotropic hormone
Hypertrophic osteoarthropathy	Rare	Triad of clubbing, arthralgias, and ossifying periostitis
Muscular weakness	Rare	Lambert-Eaton myasthenic syndrome

Adapted with permission from Latimer KM, Mott TF. Lung cancer: diagnosis, treatment principles, and screening. Am Fam Physician. *2015;91(4):253.*

TABLE 4

Fleischner Society 2017 Guidelines for Management of Incidentally Detected Pulmonary Nodules in Adults

Solid nodules*

Nodule type	Size: < 6 mm (< 100 mm^3)	Size: 6 to 8 mm (100 to 250 mm^3)	Size: > 8 mm (> 250 mm^3)	Comments
Single				
Low risk†	No routine follow-up	Follow-up CT at 6 to 12 months, then consider follow-up CT at 18 to 24 months	Consider PET/CT, tissue sampling, or follow-up CT at 3 months	Nodules < 6 mm do not require routine follow-up in low-risk patients (recommendation 1A)
High risk†	Optional follow-up CT at 12 months	Follow-up CT at 6 to 12 months and at 18 to 24 months	Consider PET/CT, tissue sampling, or follow-up CT at 3 months	Certain patients at risk with suspicious nodule morphology, upper lobe locations, or both may warrant 12-month follow-up (recommendation 1A)
Multiple				
Low risk†	No routine follow-up	Follow-up CT at 3 to 6 months, then consider follow-up CT at 18 to 24 months	Follow-up CT at 3 to 6 months, then consider follow-up CT at 18 to 24 months	Use most suspicious nodule to guide management; follow-up intervals may vary according to size of nodule and risk (recommendation 2A)
High risk†	Optional follow-up CT at 12 months	Follow-up CT at 3 to 6 months and at 18 to 24 months	Follow-up CT at 3 to 6 months and at 18 to 24 months	Use most suspicious nodule to guide management; follow-up intervals may vary according to size of nodule and risk (recommendation 2A)

Subsolid nodules*

Nodule type	Size: < 6 mm (< 100 mm^3)	Size: ≥ 6 mm (> 100 mm^3)	Comments
Single			
Ground glass	No routine follow-up	Follow-up CT at 6 to 12 months to confirm persistence, then CT every 2 years until 5 years	In certain suspicious nodules < 6 mm, consider follow-up CT at 2 and 4 years; if solid component(s) or growth develops, consider resection (recommendations 3A and 4A)
Part solid	No routine follow-up	Follow-up CT at 3 to 6 months to confirm persistence; if unchanged and solid component remains < 6 mm, annual CT should be performed for 5 years	In practice, part-solid nodules cannot be defined as such until ≥ 6 mm, and nodules < 6 mm do not usually require follow-up; persistent part-solid nodules with solid components ≥ 6 mm should be considered highly suspicious (recommendations 4A-4C)
Multiple	Follow-up CT at 3 to 6 months; if stable, consider CT at 2 and 4 years	Follow-up CT at 3 to 6 months; subsequent management based on the most suspicious nodule(s)	Multiple pure ground-glass nodules < 6 mm are usually benign, but consider follow-up at 2 and 4 years in select patients at high risk (recommendation 5A)

Note: These recommendations do not apply to lung cancer screening, patients with immunosuppression, or patients with known primary cancer.

CT = computed tomography; PET/CT = positron emission tomography/computed tomography.

*—Dimensions are average of long and short axes, rounded to the nearest millimeter.
†—Consider all relevant risk factors, per the American College of Chest Physicians guidelines, including older age, heavy smoking, prior cancer, larger nodule size, irregular/spiculated margins, and/or upper-lobe location of the nodule, which increases the risk of lung cancer.

Adapted with permission from MacMahon H, Naidich DP, Goo JN, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology. *2017;284(1):230, with additional information from reference 17.*

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	Comments
The initial evaluation for lung cancer begins with laboratory testing, including a complete blood count, serum chemistries, calcium levels, liver function tests, and chest radiography; CT of the chest with intravenous contrast media should be performed when there is a high level of suspicion, even if radiographic results are normal.[2,9,10,13-15]	C	Practice guidelines, expert opinion, disease-oriented studies
Adults 50 to 80 years of age who have a 20 pack-year smoking history and currently smoke or have quit smoking within the past 15 years should undergo annual low-dose CT screening.[36,40,44]	B	USPSTF and AAFP guidelines and limited evidence from one large, randomized controlled trial showing moderate benefit
Patients with lung cancer should be offered smoking cessation interventions.[45]	B	Cochrane review that shows reduction in morbidity and mortality; no randomized controlled trials to identify specific smoking cessation interventions are recommended
Patients with lung cancer can improve symptoms with exercise training and nurse counseling.[46,47]	B	Cochrane reviews, with studies limited by heterogeneity, small sample sizes, and high risk of bias

AAFP = American Academy of Family Physicians; CT = computed tomography; USPSTF = U.S. Preventive Services Task Force.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to https://www.aafp.org/afpsort.

one lung cancer death of 323 over 6.5 years of follow-up and 130 over 10 years of follow-up, respectively.[38-40] Through systematic review of these trials and modeling studies from the Cancer Intervention and Surveillance Modeling Network, the USPSTF updated its criteria for screening.[36] Earlier screening recommendations are based on studies that suggest this may help address screening disparities for certain populations, including women and Black and Hispanic people.[41,42] Compared with the previous USPSTF 2013 guideline, Cancer Intervention and Surveillance Modeling Network data suggest that earlier screenings would be associated with an increase in the reduction of lung cancer mortality, from a 9.8% reduction to 12.1% to 14.4%, and life-years gained, from 4,882 life-years to 6,018 to 7,596 per 100,000.[37,43] The American Academy of Family Physicians supports the USPSTF's grade B recommendation of lung cancer screening in adults at increased risk; however, the harms of annual CT screenings are still not well documented, and further research is needed.[44] Research gaps include evaluating potential harms associated with increased radiation exposure, identifying better technology to differentiate benign and malignant lung nodules to avoid overdiagnosis, and addressing the cost and availability of increased screening in economically disadvantaged populations.[44]

Smoking Cessation and Counseling

Smoking cessation reduces morbidity and mortality in patients with lung cancer; however, no randomized controlled trials have compared specific cessation interventions in this population.[29,45] Exercise training may improve exercise capacity and quality of life.[46] Nursing interventions can help patients with dyspnea, and a range of psychological interventions may improve coping skills and quality of life.[47]

TABLE 5

Five-Year Survival (%) After Diagnosis of Lung Cancer

Type	IA1	IA2	IA3	IB	IIA	IIB	IIIA	IIIB	IIIC	IVA	IVB
Clinical	92	83	77	68	60	53	36	26	13	10	0
Pathologic	90	85	80	73	65	56	41	24	12	–	–

Adapted with permission from Detterbeck FC, Boffa DJ, Kim AW, et al. The eighth edition lung cancer stage classification. Chest. *2017;151(1):201.*

Although all actively smoking patients should be offered cessation support, lung cancer screening for eligible patients coupled with cessation support may be associated with higher quitting rates.[48] This combination is believed to serve as a teachable moment during a time when patients are the most receptive to quitting advice. Cessation assistance in combination with CT screening has been associated with a reduction in lung cancer–specific mortality and the potential to improve the cost-effectiveness ratio of screening.[49,50] Patients who quit smoking have been shown to reduce their risk of lung cancer by 39.1% after five years.[51] Patients should also be counseled that quitting smoking will reduce their risk of all second cancers by 3.5 times.[52]

This article updates previous articles on this topic by Latimer and Mott[12] and Collins, et al.[53]

Data Sources: A PubMed search was completed in Clinical Queries using the key terms lung cancer, diagnosis, treatment, and screening. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. The Agency for Healthcare Research and Quality Effective Healthcare Reports, the U.S. Preventive Services Task Force, the Cochrane Database of Systematic Reviews, DynaMed, Essential Evidence Plus, the National Institute for Health and Care Excellence, and the National Comprehensive Cancer Network were also searched. Search dates: April and May 2021, and January 28, 2022.

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The Authors

JEFFREY KIM, MD, FAAFP, is director of Family Medicine Inpatient Service, the thread director of telehealth, and an assistant professor in the Department of Family Medicine at Loma Linda (Calif.) University School of Medicine.

HOBART LEE, MD, is director of the Family Medicine Residency Program and an associate professor in the Department of Family Medicine at Loma Linda University School of Medicine.

BRIAN W. HUANG, MD, is co-chief resident in the Department of Family Medicine at Loma Linda University Health Education Consortium.

Address correspondence to Jeffrey Kim, MD, FAAFP, Loma Linda University, 1200 California St., Ste. 240, Redlands, CA 92374 (email: jlkim@llu.edu). Reprints are not available from the authors.

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eTABLE A

Category Descriptors of Lung Nodules From the American College of Radiology Committee on Lung-RADS

Category descriptor	Lung-RADS score	Findings	Management	Risk of malignancy	Estimated population prevalence
Incomplete	0	Prior chest CT examination(s) being located for comparison Part or all of lungs cannot be evaluated	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed	NA	1%
Negative: no nodules and definitely benign nodules	1	No lung nodules Nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat-containing nodules	Continue annual screening with low-dose CT in 12 months	< 1%	90%
Benign appearance or behavior: nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	Perifissural nodule(s)* < 10 mm (524 mm^3) Solid nodule(s) < 6 mm total diameter (< 113 mm^3) New < 4 mm (< 34 mm^3) Part-solid nodule(s) < 6 mm total diameter (< 113 mm^3) on baseline screening Nonsolid nodule(s) (ground-glass nodules) < 30 mm (< 14,137 mm^3) *or* ≥ 30 mm (≥ 14,137 mm^3) and unchanged or slowly growing Category 3 or 4 nodules unchanged for ≥ 3 months	Continue annual screening with low-dose CT in 12 months	< 1%	90%
Probably benign finding(s): short-term follow-up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	Solid nodule(s) ≥ 6 mm to < 8 mm (≥ 113 mm^3 to < 268 mm^3) at baseline *or* New 4 mm to < 6 mm (34 mm^3 to < 113 mm^3) Part-solid nodule(s) ≥ 6 mm total diameter (≥ 113 mm^3) with solid component < 6 mm (< 113 mm^3) *or* New < 6 mm total diameter (< 113 mm^3) Nonsolid nodule(s) Ground-glass nodule ≥ 30 mm (≥ 14,137 mm^3) on baseline CT or new	6-month low-dose CT	1% to 2%	5%

continues

CT = computed tomography; NA = not applicable; PET/CT = positron emission tomography/computed tomography; S = significant.

*—Solid nodules with smooth margins; an oval, lentiform, or triangular shape; and maximum diameter < 10 mm or 524 mm^3 (perifissural nodules) should be classified as category 2.
†—Additional resources available at https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads. Link to Lung-RADS calculator: https://brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators.

eTABLE A *(continued)*

Category Descriptors of Lung Nodules From the American College of Radiology Committee on Lung-RADS

Category descriptor	Lung-RADS score	Findings	Management	Risk of malignancy	Estimated population prevalence
Suspicious: findings for which additional diagnostic testing is recommended	4A	Solid nodules ≥ 8 mm to < 15 mm (≥ 268 mm^3 to < 1,767 mm^3) at baseline *or* Growing < 8 mm (< 268 mm^3) *or* New 6 mm to < 8 mm (113 mm^3 to < 268 mm^3) Part-solid nodules ≥ 6 mm (≥ 113 mm^3) with solid component ≥ 6 mm to < 8 mm (113 mm^3 to 268 mm^3) *or* With new or growing < 4 mm (< 34 mm^3) solid component Endobronchial nodule	3-month low-dose CT; PET/CT may be used when there is a ≥ 8 mm (≥ 268 mm^3) solid component	5% to 15%	2%
Very suspicious: findings for which additional diagnostic testing and/or tissue sampling is recommended	4B	Solid nodule(s) ≥ 15 mm (≥ 1,767 mm^3) *or* New or growing, and ≥ 8 mm (268 mm^3) Part-solid nodule(s) with: A solid component ≥ 8 mm (≥ 268 mm^3) *or* A new or growing ≥ 4 mm (≥ 34 mm^3) solid component	Chest CT with or without contrast media, PET/CT, and/or tissue sampling depending on the probability of malignancy and comorbidities.† PET/CT may be used when there is a ≥ 8 mm (≥ 268 mm^3) solid component. For new large nodules that develop on an annual repeat-screening CT, a 1-month low-dose CT may be recommended to address potentially infectious or inflammatory conditions	> 15%	2%
	4X	Category 3 or 4 nodules with additional features or imaging findings that increase the suspicion of malignancy			
Other: clinically significant or potentially clinically significant findings (non-lung cancer)	S	Modifier: may add on to category 0-4 coding	As appropriate to the specific finding	NA	10%

CT = computed tomography; NA = not applicable; PET/CT = positron emission tomography/computed tomography; S = significant.

*—Solid nodules with smooth margins; an oval, lentiform, or triangular shape; and maximum diameter < 10 mm or 524 mm^3 (perifissural nodules) should be classified as category 2.
†—Additional resources available at https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads. Link to Lung-RADS calculator: https://brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators/.

Adapted with permission from American College of Radiology. Lung-RADS version 1.1; 2019. Accessed May 18, 2021. https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADSAssessmentCategoriesv1-1.pdf

eTABLE B

Definitions for TNM Cancer Staging Descriptors

		Label
T (Primary)		
T0	No primary tumor	
Tis	Carcinoma in situ (squamous or adenocarcinoma)	Tis
T1	Tumor ≤ 3 cm	
T1a(mi)	Minimally invasive adenocarcinoma	T1a*(mi)*
T1a	Superficial spreading tumor in central airways*	T1a*SS*
T1a	Tumor ≤ 1 cm	T1a ≤ *1*
T1b	Tumor > 1 cm but ≤ 2 cm	T1b > *1–2*
T1c	Tumor > 2 cm but ≤ 3 cm	T1c > *2–3*
T2	Tumor > 3 cm but ≤ 5 cm	T2 *Visc Pl*
	or	T2 *Centr*
	Tumor involving visceral pleura, main bronchus (not carina), or atelectasis to hilum†	
T2a	Tumor > 3 cm but ≤ 4 cm	T2a > *3–4*
T2b	Tumor > 4 cm but ≤ 5 cm	T2b > *4–5*
T3	Tumor > 5 cm but ≤ 7 cm	T3 > *5–7*
	or	
	Tumor invading chest wall, pericardium, phrenic nerve	T3 *Inv*
	or	
	Separate tumor nodule(s) in the same lobe	T3 *Satell*
T4	Tumor > 7 cm	T4 > *7*
	or	
	Tumor invading mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine	T4 *Inv*
	or	
	Tumor nodule(s) in a different ipsilateral lobe	T4 *Ipsi Nod*
N (Regional lymph nodes)		
N0	No regional node metastasis	
N1	Metastasis in ipsilateral pulmonary or hilar nodes	
N2	Metastasis in ipsilateral mediastinal/subcarinal nodes	
N3	Metastasis in contralateral, mediastinal/hilar, or supraclavicular nodes	
M (Distant metastasis)		
M0	No distant metastasis	M1a *Pl Dissem*
M1a	Malignant pleural/pericardial effusion‡ or pleural/pericardial nodules	M1a *Contr Nod*
	or	
	Separate tumor nodule(s) in a contralateral lobe	
M1b	Single extrathoracic metastasis	M1b *Single*
M1c	Multiple extrathoracic metastases (1 or > 1 organ)	M1c *Multi*
TX, NX	T or N status not able to be assessed	NA

NA = not applicable; TNM = tumor, node, metastasis.

*—Superficial spreading tumor of any size but confined to the tracheal or bronchial wall.
†—Classified as T2a if > 3 cm and ≤ 4 cm; T2b if > 4 cm and ≤ 5 cm.
‡—Pleural effusions are excluded if they are cytologically negative, non-bloody, transudative, and clinically not judged to be caused by cancer.

Adapted with permission from Detterbeck FC, Boffa DJ, Kim AW, et al. The eighth edition lung cancer stage classification. Chest. *2017;151(1):195.*

eTABLE C

Lung Cancer Stage Grouping

T/M	Label	N0	N1	N2	N3
T1	T1a ≤ *1*	IA1	IIB	IIIA	IIIB
	T1b > *1-2*	IA2	IIB	IIIA	IIIB
	T1c > *2-3*	IA3	IIB	IIIA	IIIB
T2	T2 *Centr, Visc Pl*	IB	IIB	IIIA	IIIB
	T2a > *3-4*	IB	IIB	IIIA	IIIB
	T2b > *4-5*	IIA	IIB	IIIA	IIIB
T3	T3 > *5-7*	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 > *7*	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a *Contr Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

T/M = tumor, metastasis.

Adapted with permission from Detterbeck FC, Boffa DJ, Kim AW, et al. The eighth edition lung cancer stage classification. Chest. *2017; 151(1):198.*

eTABLE D

Lung Cancer Mutations and Their Associated Immunotherapies

Genetic mutation	National Comprehensive Cancer Network preferred therapy	Common adverse effects (> 20%)
Anaplastic lymphoma kinase	Alectinib (Alecensa), brigatinib (Alunbrig), or lorlatinib (Lorbrena)	Anemia, arthralgia, constipation, cough, diarrhea, edema, fatigue, headache, mood effects, myalgia, nausea, weight gain
BRAF V600E	Dabrafenib (Tafinlar) plus trametinib (Mekinist)	Chills, cough, decreased appetite, diarrhea, dry skin, dyspnea, edema, fatigue, hemorrhage, nausea, pyrexia, rash, vomiting
Epidermal growth factor receptor	Osimertinib (Tagrisso)	Anemia, cough, diarrhea, dry skin, fatigue, leukopenia, lymphopenia, musculoskeletal pain, nail toxicity, neutropenia, rash, stomatitis, thrombocytopenia
MET ex 14 skipping	Capmatinib (Tabrecta) or tepotinib (Tepmetko)	Decreased appetite, diarrhea, dyspnea, fatigue, musculoskeletal pain, nausea, peripheral edema, vomiting
NTRK gene fusion	Larotrectinib (Vitrakvi) or entrectinib	Arthralgia, cognitive impairment, constipation, cough, diarrhea, dizziness, dysesthesia, dysgeusia, dyspnea, edema, fatigue, increased AST/ALT, myalgia, nausea, pyrexia, vision disorders, vomiting, weight gain
PD-L1/*PD-1*	Pembrolizumab (Keytruda)	Abdominal pain, constipation, cough, decreased appetite, diarrhea, dyspnea, fatigue, musculoskeletal pain, nausea, pruritus, pyrexia, rash
	Atezolizumab (Tecentriq)	Cough, decreased appetite, dyspnea, fatigue/asthenia, nausea
	Durvalumab (Imfinzi)	Cough, dyspnea, fatigue, pneumonitis/radiation pneumonitis, rash, upper respiratory tract infections
RET	Selpercatinib (Retevmo) or pralsetinib (Gavreto)	Constipation, decreased albumin, decreased calcium, decreased leukocytes, decreased lymphocytes, decreased platelets, decreased sodium, diarrhea, dry mouth, edema, fatigue, hypertension, increased alkaline phosphatase, increased AST/ALT, increased creatinine, increased glucose, increased total cholesterol, musculoskeletal pain, rash
ROS1	Entrectinib (Rozlytrek) or crizotinib (Xalkori)	Arthralgia, cognitive impairment, constipation, cough, decreased appetite, diarrhea, dizziness, dysesthesia, dysgeusia, dyspnea, edema, fatigue, increased AST/ALT, myalgia, nausea, neuropathy, pyrexia, upper respiratory infection, vision disorders, vomiting, weight gain

AST/ALT = aspartate transaminase/alanine transaminase; *PD-1* = programmed death-1; *PD-L1* = programmed death-ligand 1.

Information from U.S. Food and Drug Administration. Drugs@FDA: FDA-approved drugs. Accessed June 29, 2021. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

eTABLE E

Non–Small Cell and Small Cell Lung Cancer: First-Line Systemic Therapy Regimens Without Positive Driver Mutation

Non–small cell lung cancer first-line systemic therapy

Genetic mutation	Type	First-line therapy	Response or stable disease*
PD-L1 ≥ 50%	Nonsquamous cell	Pembrolizumab (Keytruda)	Pembrolizumab
		Carboplatin (Paraplatin) or cisplatin *plus* Pemetrexed (Alimta) *plus* Pembrolizumab	Pembrolizumab *plus* Pemetrexed
		Atezolizumab (Tecentriq)	Atezolizumab *plus* Bevacizumab (Avastin)
		Cemiplimab (Libtayo)	Atezolizumab
			Nivolumab (Opdivo) *plus* Ipilimumab (Yervoy)
			Cemiplimab
	Squamous cell	Pembrolizumab	Pembrolizumab
		Carboplatin *plus* Paclitaxel or albumin-bound paclitaxel (Abraxane) *plus* Pembrolizumab	Atezolizumab
		Atezolizumab	Nivolumab *plus* Ipilimumab
		Cemiplimab	Cemiplimab

continues

PD-L1 = programmed death-ligand 1.

*—Maintenance regimens vary depending on initial first-line therapy chosen.
†—If relapse is ≤ 6 months; for relapse > 6 months, the original systemic treatment regimen is recommended.

eTABLE E *(continued)*

Non–Small Cell and Small Cell Lung Cancer: First-Line Systemic Therapy Regimens Without Positive Driver Mutation

Non–small cell lung cancer first-line systemic therapy *(continued)*

Genetic mutation	Type	First-line therapy	Response or stable disease*
PD-L1 ≥ 1% to < 50%	Nonsquamous cell	Carboplatin or cisplatin *plus* Pemetrexed *plus* Pembrolizumab	Pembrolizumab
			Pembrolizumab *plus* Pemetrexed
			Atezolizumab *plus* Bevacizumab
			Atezolizumab
			Nivolumab *plus* Ipilimumab
	Squamous cell	Carboplatin *plus* Paclitaxel or albumin-bound paclitaxel *plus* Pembrolizumab	Pembrolizumab
			Nivolumab *plus* Ipilimumab

Small cell lung cancer first-line systemic therapy

Stage	First-line therapy (4 cycles)	Subsequent systemic therapy†
Limited stage	Cisplatin and etoposide (Etopophos)	Topotecan (Hycamtin) Lurbinectedin (Zepzelca) Enroll in clinical trial
Extensive stage	Carboplatin and etoposide and atezolizumab, followed by maintenance atezolizumab Carboplatin and etoposide and durvalumab (Imfinzi), followed by maintenance durvalumab Cisplatin and etoposide and durvalumab, followed by maintenance durvalumab	Topotecan Lurbinectedin Enroll in clinical trial

PD-L1 = programmed death-ligand 1.

*—Maintenance regimens vary depending on initial first-line therapy chosen.
†—If relapse is ≤ 6 months; for relapse > 6 months, the original systemic treatment regimen is recommended.

Information from:
Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al.; KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. *2018;378(22):2078-2092.*
National Comprehensive Cancer Network. Non-small cell lung cancer (version 04.2021). Accessed May 7, 2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
National Comprehensive Cancer Network. Small cell lung cancer (version 03.2021). Accessed May 5, 2021. https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf
Planchard D, Popat S, Kerr K, et al.; ESMO Guidelines Committee. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up [published correction appears in Ann Oncol. *2019;30(5):863-870].* Ann Oncol. *2018;29(suppl 4):iv192-iv237.*