Lung Cancer

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KEYWORDS

• Lung cancer • Smoking • Screening • Staging • Chemotherapy

KEY POINTS

- Lung cancer is the leading cancer killer in the world.
- Smoking is the predominant risk factor, but other risk factors exist.
- Low-dose computed tomography for lung cancer screening improves mortality.
- Various modalities exist for diagnosis and staging of lung cancer.
- Treatment depends on several factors and is best guided by a multidisciplinary team to determine the best approach for a given patient.

INTRODUCTION

Lung cancer is the world's leading cause of cancer death.[1] This is largely because it is initially asymptomatic and typically discovered at advanced stages. Screening for lung cancer by low-dose computed tomography (LDCT) has recently been shown to have a mortality benefit, and implementation of this practice is growing. Once suspected, lung cancer must be diagnosed and staged, and there are recent guidelines to aid in this process. Treatment is determined by subtype and stage of cancer and there are several personalized therapies that did not exist just a few years ago. This review provides a broad outline of this disease, helping clinicians identify such patients and familiarizing them with lung cancer care so they are better equipped to guide their patients along this challenging journey.

EPIDEMIOLOGY

Worldwide, lung cancer continues to be the most common cause of cancer death.[1] Approximately 1.8 million new people were diagnosed in 2012, with 1.6 million fatalities. It is estimated that, in 2018, the United States alone will have had more than 230,000 new cases, and that lung cancer will lead to more deaths than breast,

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prostate, and colon cancers combined.[2] Lung cancer is relatively rare before the fifth decade of life; risk increases with age thereafter.[2] Men are more affected than women. Interestingly, although smoking is the exposure most closely tied to lung cancer (an estimated 80%–90% of cases are caused by this), only approximately 15% of smokers develop lung cancer, suggesting a genetic susceptibility.[3] Smoking intensity (eg, how many cigarettes per day) and lifetime duration affect risk proportionately.[4] As a corollary, smoking cessation reduces lung cancer risk. For patients who cannot quit completely, even reducing the number of cigarettes smoked daily has a demonstrated benefit.[5] Generally speaking, any form of smoking exposure increases lung cancer risk, including secondhand smoke and cigar and pipe smoking.[6] The association of marijuana is less clear due to conflicting results, and that of electronic cigarettes is also uncertain, in part due to confounding from prior or concurrent cigarette use, and the lack of long-term data.[7] Asbestos exposure acts synergistically with tobacco use, being associated with higher rates of lung malignancy than either risk factor alone. Other risk factors include radon exposure and some forms of interstitial lung disease. The presence of chronic obstructive lung disease and a family history are also associated with lung cancer, even after adjustment for tobacco exposure.[6]

SCREENING

Until recently, no effective method of lung cancer screening was available. Several studies have investigated the role of LDCT, the largest of which is the National Lung Screening Trial (NLST), which included more than 50,000 patients and had longer follow-up compared with other randomized controlled trials.[8] Researchers demonstrated a 20% reduction in lung cancer mortality by annual LDCT compared with chest radiograph (CXR) with a decrease in overall mortality by 6.7%. A concern raised with screening by LDCT is the high rate of benign nodules detected (more than 90% in most studies). In the NLST, for example, approximately one-quarter of the scans revealed nodules, with 96.4% of these being benign; a similarly high false-positive rate was found in the CXR arm. Another concern with repeated LDCT screening tests is accumulating radiation exposure. It is estimated that a single LDCT will expose a patient to 1.5 mSv of radiation. The average total exposure for each NLST participant over 3 years was approximately 8 mSv. By way of comparison, the average annual dose provided by background radiation (in the United States) is 3 to 4 mSv.[9] Even with the high false-positive rates and radiation risks, available evidence indicates that the reductions in cancer death brought about by screening outweigh the possible risks. Based on these findings, the US Preventive Services Task Force recommends lung cancer screening with LDCT in adults of age 55 to 80 years who have a 30 pack-year smoking history and are currently smoking or have quit within the past 15 years.[10] Approximately 8 million Americans are eligible to receive annual screening with LDCT using these criteria.[11] The current National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Lung Cancer Screening also considers it reasonable to use a statistical risk prediction model (https://brocku.ca/lung-cancer-risk-calculator) to quantify lung cancer risk for individuals who do not meet the NLST criteria but may be at similar risk to the NLST cohort.[12] Because the benefits of screening decrease at lower-risk thresholds, but the harms of screening remain constant, it is challenging to determine the ideal balance of benefit and harm, particularly as the impact of the benefit and harms can vary markedly with patient preferences.[13] The American Thoracic Society/American College of Chest Physicians policy statement on lung cancer screening provides guidelines for implementation of a successful screening program that include structured reporting

and a smoking cessation program. Screening should be discontinued once an individual has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative treatment.[14]

INCIDENTAL VERSUS SCREEN-DETECTED PULMONARY NODULE MANAGEMENT

There are important distinctions between nodules found incidentally and those found on screening LDCT. The Fleischner Society guidelines are typically used for management of incidental detected pulmonary nodules on computed tomography (CT). The more recent guidelines revised in 2017 recommend longer intervals between scans even for high-risk individuals with nodules >6 mm. To estimate high risk, the American College of Chest Physicians intermediate-risk (5%–65% risk) and high-risk (>65% risk) categories are combined into one category. High-risk factors include older age, heavy smoking, larger nodule size, irregular or spiculated margins, and upper lobe location. The NCCN clinical practice guidelines in oncology provide management recommendations for screen-detected nodules. In 2018, the NCCN cutoff thresholds for lung nodules were revised to reflect the Lung Imaging Reporting and Data System (Lung-RADS) cutoffs. Lung-RADS is a structured decision-oriented reporting system published in 2014 that aimed to reduce the false-positive result rate and suggest management recommendations based on estimated lung cancer risk.[15] **Table 1** summarizes the current recommendations based on these guidelines.

CLINICAL MANIFESTATIONS

Occurring in approximately half of patients with lung cancer, a new cough in a smoker or former smoker should raise concern for lung cancer. Recurrent pneumonia in the same anatomic location or frequent exacerbations of chronic obstructive pulmonary disease also should trigger concern for neoplasm as a root cause.[18] Dyspnea is present in approximately one-third to one-half of patients with lung cancer, and could be

Table 1
Guidelines for pulmonary nodule management

		Recommended Follow-up, mo		
Nodule type	Size, mm	Fleischner 2017[16]	NCCN 2018[12]	Lung-RADS 2014[17]
Applicable population	All	Incidental	LDCT screening	LDCT Screening
Solid	<6	None for low risk, 12 mo optional for high risk	AS	AS
	6–8	6–12 mo, 18–24 mo	6 mo	6 mo, AS
	>8	3 mo, PET, or tissue sampling	3 mo, PET, tissue sampling for high risk	3 mo, AS
Part solid	<6	None	AS	AS
	≥6	3–6 mo, every 12 mo × 5 y	Based on size of solid component	Based on size of solid component
Ground glass	<6	None	AS	AS
	≥6	6–12 mo, every 24 mo until 5 y	AS	AS up to 20 mm

Abbreviations: AS, annual screening; LDCT, low-dose computed tomography; Lung-RADS, lung imaging reporting and data system; NCCN, national comprehensive cancer network.

due to direct malignant airway, or parenchymal or pleural involvement. Patients also are at risk of developing pulmonary emboli, pneumothoraces, pleural effusions, and/or pericardial effusions. Other less common symptoms include chest pain from regional tumor invasion and hoarseness from involvement of the recurrent laryngeal nerve. Hemoptysis is the presenting symptom in approximately one-quarter of patients with lung cancer and is rarely massive.[19] Other manifestations of intrathoracic spread are the superior vena cava syndrome, dysphagia, or arm/shoulder pain; these are all due to mass effect on various structures. Patients also can present with symptoms from extrathoracic metastases. Often these are nonspecific, such as weight loss, anorexia, and fatigue.[18] Bone metastases are frequently painful; brain metastases can be asymptomatic, although neurologic sequelae do manifest based on size and location. Finally, paraneoplastic syndromes can occur, including the syndrome of inappropriate antidiuretic hormone, neurologic syndromes, such as Lambert-Eaton myasthenic syndrome and cerebellar ataxia, or hypercalcemia from bone metastases or secretion of parathyroid hormone–related protein.[20]

Box 1 reviews when a pulmonary consultation should be considered.

DIAGNOSIS AND STAGING

All patients with known or suspected non–small-cell lung cancer (NSCLC) should have a thorough clinical evaluation and a CT chest with contrast.[21] If both clinical evaluation and CT scan are without extrathoracic abnormalities, a PET scan is recommended to evaluate for metastases.[9] Notably, a PET scan may not be required if the primary lung lesion is a ground glass opacity or a peripheral nodule 3 cm or smaller, as these have a low likelihood of metastasis, assuming negative intrathoracic nodal involvement on CT.[21] Such patients may proceed directly to curative-intent treatment immediately after tissue confirmation. For patients who do not clearly have very early or advanced NSCLC, staging of intrathoracic lymph nodes is recommended. However, if the mediastinum is extensively infiltrated, invasive staging may not be necessary.[21] When sampling is needed, endobronchial ultrasound (EBUS)-guided bronchoscopic sampling is recommended over surgical staging by mediastinoscopy. Direct comparison trials have shown EBUS-guided sampling of thoracic lymph nodes to perform as well as or better than surgical sampling while also being less invasive and having fewer complications.[22] However, if suspicion of nodal involvement remains after a negative result by bronchoscopy, surgical confirmation should be performed.[21] Given the previously described complexities, it is advisable that any patient with suspected lung cancer be referred to a pulmonologist, and multidisciplinary care is recommended.

Various methods for diagnosis and staging (bronchoscopic, surgical, and transthoracic) exist, and a pulmonologist can provide guidance for further steps as needed.

Box 1
Recommendations on when to call a pulmonary consultation

To determine a patient's candidacy for lung cancer screening
To decide how to approach the diagnosis of a lung nodule (or if a diagnosis is necessary)
History of pneumonia that does not resolve completely (either symptomatically or radiographically)
The presence of any pleural effusion, particularly if exudative without a clear etiology
Any patient with lung cancer with shortness of breath
Hemoptysis

Table 2 summarizes the various diagnostic modalities along with their diagnostic yield. Minimizing invasive procedures is desirable, such as attempting to diagnose and stage with a single procedure if possible. For example, if a patient with a lung mass has any sign of metastasis (eg, enlarged mediastinal lymph nodes, pleural effusion, and adrenal mass), the highest-stage location should be sampled first, if feasible and technically safe to do so.[23] The reason is that the finding of lung cancer at a metastatic site would adequately provide both diagnostic and staging information. Finally, the aforementioned diagnostic approaches apply largely to NSCLC rather than small-cell lung cancer (SCLC). Current guidelines suggest that if SCLC is suspected (based on certain characteristics, such as massive adenopathy, direct mediastinal invasion, or the presence of a paraneoplastic syndrome, for example), then diagnosis should be sought via the least-invasive method.[23]

BRIEF UPDATE ON THE EIGHTH EDITION TUMOR-NODE-METASTASIS CLASSIFICATION OF LUNG CANCER

The eighth edition of the tumor-node-metastasis (TNM) classification for lung cancer has some clinically important updates. There are 24 T descriptors and the "p" or "c" T-stage designators correspond to the pathologic versus the clinical stage, respectively. Size measurement in part-solid nodules uses the size of solid component for clinical size, and size of invasive component for pathologic size. Tumor size itself is a descriptor in all T categories and every centimeter increment in size affects prognosis.[28] To ensure accurate radiographic assessment of T stage, the International Association for the Study of Lung Cancer recommends that tumor size be measured in the lung window. The new T categories are Tis, denoting carcinoma in situ (squamous or adenocarcinoma), and T1a (mi), for minimally invasive adenocarcinoma. T2 and T3 endobronchial tumors have similar prognosis, even with total atelectasis and pneumonitis. T3 with involvement of the diaphragm has been reclassified as a T4 tumor.[29]

For the N component, it is important to quantify nodal disease both clinically and pathologically. Apart from keeping the seventh edition N descriptors as they are, new subclass descriptors have been added for prospective testing and validation. pN1a will denote involvement of single pN1 nodal station, whereas pN1b will be assigned to involvement of multiple pN1 nodal stations. pN2a1 will be designated for involvement of single pN2 nodal station without pN1 (skip pN2), and pN2a2 will

Table 2
Diagnostic modalities for tissue diagnosis of lung cancer and their yield

Diagnostic Modality	Yield, %
Convex probe endobronchial ultrasound transbronchial needle aspiration[24]	94.5
Peripheral bronchoscopy with radial probe[25]	53–84
Electromagnetic navigation bronchoscopy[26]	38–71
Computed tomography–guided transthoracic needle aspiration[27]	90
Image-guided closed pleural biopsy[23]	75–88
Pleuroscopy with pleural biopsy[23]	95–97
Thoracentesis[23]	72
Conventional bronchoscopy with endobronchial biopsy, brushings, and washings[23]	88

be involvement of single pN2 nodal station with pN1. Last, pN2b will be involvement of multiple pN2 nodal stations.

Finally, for the M component, number of metastases is more important than their location. Cancers with multiple lesions are defined by disease pattern. For multiple primary tumors, 1 TNM is assigned for each tumor. These changes in the eighth edition of the TNM classification of lung cancer aim to facilitate more homogeneous tumor classification and collection of prospective data to improve tumor stratification for future research trials.[30]

TREATMENT

For early-stage lung cancer, surgical resection is the preferred treatment.[31] The extent of resection depends on the size and location of the tumor as well as the patient's preoperative pulmonary reserve. Adjuvant chemotherapy is recommended for completely resected stage II NSCLC but not usually stage I. Postoperative radiation is not recommended except for incomplete resection. For those with early-stage NSCLC who are not surgical candidates, stereotactic ablative body radiotherapy (SABR), can be considered.[32] Comparative studies are under way as to whether this is equivalent to surgery in terms of long-term outcomes.[33,34] An alternative to SABR is percutaneous ablation for select peripheral tumors, but there is scant evidence of efficacy and a substantial pneumothorax rate.[35] Transbronchial ablation may have certain advantages and is currently in investigational stages.[36]

Stage III NSCLC encompasses a heterogeneous group of patients. Patients with limited nodal (N1) involvement may be candidates for surgical resection upfront followed by chemotherapy and/or radiation.[37] Those with more advanced nodal (N2) involvement may still be candidates for surgery, although usually only after induction therapy because data have consistently shown better outcomes with this approach.[38] Nevertheless, whether there is greater benefit from tri-modality therapy (surgery, chemotherapy, radiation) versus chemo-radiation alone is still unclear, and further studies of subgroups of patients with N2 disease are needed.[38] Patients with most advanced nodal (N3) involvement are not generally considered to be surgical candidates.

For patients with stage IV NSCLC, chemotherapy with platinum-based (eg, cisplatin, carboplatin) 2-drug, regimens is standard, but the past several years have seen the significant additional therapies directed at specific driver mutations.[39] As such, efforts should be made to not only determine the histologic subtype but also to obtain sufficient tissue for molecular analysis. Each institution has its own approach to molecular testing, but typically, testing tumor tissue for epidermal growth factor receptor gene mutations, anaplastic lymphoma kinase gene rearrangements, reactive oxygen species proto-oncogene-1 gene rearrangements, B-raf proto-oncogene point mutations and KRAS proto-oncogene (KRAS) point mutations is recommended.[37] The presence of such genetic alterations can guide the choice of targeted therapies, as they can predict responsiveness (or lack thereof) to certain agents. In addition, testing for programmed death ligand-1 expression levels can be used to guide treatment with certain immunotherapies. Indeed, the armamentarium against stage IV disease is greater than it has ever been. This will all be managed by a medical oncologist, but it is useful for the referring clinician to be familiar with the options. **Table 3** summarizes the commonly used molecular targeted therapies and immunotherapies currently approved by the Food and Drug Administration.

Aside from systemic therapy, local treatment is sometimes needed in stage IV disease if a given metastatic focus is causing localized symptoms.[37,40] Airway

Table 3
Molecularly targeted therapies and immunotherapeutics currently approved by the Food and Drug Administration

Lung Cancer	Target	Drug	Type of Therapy
NSCLC	The anti-programmed death-1 (PD-1)/PD-ligand 1 pathway[44]	Nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab	Immunotherapy
	Anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) pathway[44]	Ipilimumab, tremelimumab	
	Epidermal growth factor receptor (EGFR)+[45]	Tyrosine kinase inhibitors: erlotinib, gefitinib, afatinib, osimertinib	Molecular targeted therapy
	Anaplastic lymphoma kinase (ALK)+ [46]	Tyrosine kinase inhibitors: crizotinib, ceritinib, alectinib, brigatinib	
	B-raf proto-oncogene [47]	Dabrafenib and trametinib combination	
	Vascular endothelial growth factor (VEGF) receptor[45]	Ramucirumab	
SCLC	Mammalian target of rapamycin (mTOR)[48]	Everolimus	
	PD-1 pathway[49]	Nivolumab	

Abbreviations: NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer.

obstruction by tumor may cause dyspnea, postobstructive pneumonia, or hemoptysis, for example, An interventional pulmonologist may be able to alleviate these symptoms and possibly improve performance status, thereby improving candidacy for systemic therapy.[41] Bone or brain metastases may undergo radiation therapy or even surgical treatment in specific circumstances.[40] Recurrent, symptomatic malignant pleural effusions are usually best treated with tunneled pleural catheters or chemical pleurodesis, but repeated thoracentesis is an alternative if a patient's life expectancy is very short.

SCLC is treated with a more simplified approach compared with NSCLC; all patients receive systemic therapy.[42] Those with confirmed limited stage disease also receive radiation. Patients with extensive disease initially receive systemic therapy alone, although palliative radiation can be given at sites in which tumor burden is causing clinically significant symptoms. Surgical resection is reserved for fewer than 5% of all SCLC where stage I disease is found and confirmed with invasive nodal staging and PET scan.[42] Even in these cases, adjuvant postoperative chemotherapy is given. Prophylactic cranial irradiation is usually offered to all patients who have had some response to therapy, regardless of initial stage, as this confers a survival benefit.[43]

PROGNOSIS

In the United States, from 2007 to 2013, the overall 5-year relative survival rate was 23.6% for NSCLC and only 7% for SCLC.[50] Given these statistics, guidelines recommend that physicians begin discussions about a patient's prognosis and goals of care at the time of lung cancer diagnosis, and that they continue such conversations throughout treatment.[51] Particularly for advanced disease, initiation of palliative care is recommended to be done as early as possible. In fact, there are data to suggest

that the addition of palliation to usual care may prolong survival compared with usual care alone in addition to improving quality of life.[40,52]

SUMMARY

Lung cancer remains a highly lethal disease. The implementation of widespread lung cancer screening holds promise for the future. Given the nonspecific clinical presentation, clinicians should consider the diagnosis in any former or current smoker who presents with worrisome symptoms. If lung cancer is suspected, referral to a pulmonologist is strongly recommended. There are various minimally invasive diagnostic and staging modalities currently available and there has been tremendous advancement in our understanding of lung cancer biology leading to various new treatment options.

REFERENCES

1. World Health Organization. Lung cancer. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed August 11, 2018.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68(1):7–30.
3. Spitz MR, Wei Q, Dong Q, et al. Genetic susceptibility to lung cancer: the role of DNA damage and repair. Cancer Epidemiol Biomarkers Prev 2003;12(8):689–98.
4. Mattson ME, Pollack ES, Cullen JW. What are the odds that smoking will kill you? Am J Public Health 1987;77(4):425–31.
5. Godtfredsen NS, Prescott E, Osler M. Effect of smoking reduction on lung cancer risk. JAMA 2005;294(12):1505–10.
6. Alberg AJ, Brock MV, Ford JG, et al. Epidemiology of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e1S–29S.
7. de Groot PM, Wu CC, Carter BW, et al. The epidemiology of lung cancer. Transl Lung Cancer Res 2018;7(3):220–33.
8. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365(5):395–409.
9. Detterbeck FC, Mazzone PJ, Naidich DP, et al. Screening for lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e78S–92S.
10. Moyer VA, U.S. Preventive Services Task Force. Screening for lung cancer: U.S. preventive services task force recommendation statement. Ann Intern Med 2014;160(5):330–8.
11. Cheung LC, Katki HA, Chaturvedi AK, et al. Preventing lung cancer mortality by computed tomography screening: the effect of risk-based versus U.S. Preventive Services Task Force eligibility criteria, 2005-2015. Ann Intern Med 2018;168(3):229–32.
12. Wood DE, Kazerooni EA, Baum SL, et al. Lung cancer screening, version 3.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2018;16(4):412–41.
13. Kanodra NM, Pope C, Halbert CH, et al. Primary care provider and patient perspectives on lung cancer screening. A qualitative study. Ann Am Thorac Soc 2016;13(11):1977–82.
14. Wiener RS, Gould MK, Arenberg DA, et al. An official American Thoracic Society/American College of Chest Physicians policy statement: implementation of

low-dose computed tomography lung cancer screening programs in clinical practice. Am J Respir Crit Care Med 2015;192(7):881–91.
15. Pinsky PF, Gierada DS, Black W, et al. Performance of lung-RADS in the National Lung Screening Trial: a retrospective assessment. Ann Intern Med 2015;162(7):485–91.
16. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology 2017;284(1):228–43.
17. Lung-RADS Assessment Categories, Version 1.0. American College of Radiology. Lung CT Screening Reporting and Data System (Lung-RADS™). Available at: http://www.acr.org/Quality-Safety/Resources/LungRADS. Release date April 28, 2014. Accessed March 10, 2019.
18. Ost DE, Jim Yeung SC, Tanoue LT, et al. Clinical and organizational factors in the initial evaluation of patients with lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e121S–41S.
19. Kocher F, Hilbe W, Seeber A, et al. Longitudinal analysis of 2293 NSCLC patients: a comprehensive study from the TYROL registry. Lung Cancer 2015;87(2):193–200.
20. Kanaji N, Watanabe N, Kita N, et al. Paraneoplastic syndromes associated with lung cancer. World J Clin Oncol 2014;5(3):197–223.
21. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e211S–50S.
22. Um SW, Kim HK, Jung SH, et al. Endobronchial ultrasound versus mediastinoscopy for mediastinal nodal staging of non-small-cell lung cancer. J Thorac Oncol 2015;10(2):331–7.
23. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e142S–65S.
24. Labarca G, Folch E, Jantz M, et al. Adequacy of samples obtained by EBUS-TBNA for molecular analysis in patients with non-small cell lung cancer: systematic review and meta-analysis. Ann Am Thorac Soc 2018;15(10):1205–16.
25. Kokkonouzis I, Strimpakos AS, Lampaditis I, et al. The role of endobronchial ultrasound in lung cancer diagnosis and staging: a comprehensive review. Clin Lung Cancer 2012;13(6):408–15.
26. Patrucco F, Gavelli F, Daverio M, et al. Electromagnetic navigation bronchoscopy: where are we now? five years of a single-center experience. Lung 2018;196(6):721–7.
27. Deng CJ, Dai FQ, Qian K, et al. Clinical updates of approaches for biopsy of pulmonary lesions based on systematic review. BMC Pulm Med 2018;18(1):146.
28. 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(1):39–51.
29. Detterbeck FC, Boffa DJ, Kim AW, et al. The eighth edition lung cancer stage classification. Chest 2017;151(1):193–203.
30. Detterbeck FC, Chansky K, Groome P, et al. The IASLC lung cancer staging project: methodology and validation used in the development of proposals for

revision of the stage classification of NSCLC in the forthcoming (eighth) edition of the TNM classification of lung cancer. J Thorac Oncol 2016;11(9):1433–46.
31. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e278S–313S.
32. Stokes WA, Rusthoven CG. Surgery vs. SBRT in retrospective analyses: confounding by operability is the elephant in the room. J Thorac Dis 2018; 10(Suppl 17):S2007–10.
33. Detterbeck FC. The eighth edition TNM stage classification for lung cancer: what does it mean on main street? J Thorac Cardiovasc Surg 2018;155(1):356–9.
34. Bryant AK, Mundt RC, Sandhu AP, et al. Stereotactic body radiation therapy versus surgery for early lung cancer among US veterans. Ann Thorac Surg 2018;105(2):425–31.
35. Ye X, Fan W, Wang H, et al. Expert consensus workshop report: guidelines for thermal ablation of primary and metastatic lung tumors (2018 edition). J Cancer Res Ther 2018;14(4):730–44.
36. Casal RF, Walsh G, McArthur M, et al. Bronchoscopic laser interstitial thermal therapy: an experimental study in normal porcine lung parenchyma. J Bronchology Interv Pulmonol 2018;25(4):322–9.
37. National Comprehensive Cancer Network. Non-small cell lung cancer (Version 6.2018). Available at. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed September 21, 2018.
38. Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of stage III non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e314S–40S.
39. Socinski MA, Evans T, Gettinger S, et al. Treatment of stage IV non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e341S–68S.
40. Simoff MJ, Lally B, Slade MG, et al. Symptom management in patients with lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e455S–97S.
41. Sabath BF, Ost DE. Update on airway stents. Curr Opin Pulm Med 2018;24(4): 343–9.
42. National Comprehensive Cancer Network. Small cell lung cancer (Version 2.2018). Available at: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed September 21, 2018.
43. Jett JR, Schild SE, Kesler KA, et al. Treatment of small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl): e400S–19S.
44. Qin H, Wang F, Liu H, et al. New advances in immunotherapy for non-small cell lung cancer. Am J Transl Res 2018;10(8):2234–45.
45. Gridelli C, Ascierto PA, Grossi F, et al. Second-line treatment of advanced non-small cell lung cancer non-oncogene addicted: new treatment algorithm in the era of novel immunotherapy. Curr Clin Pharmacol 2018;13(2):76–84.
46. Sullivan I, Planchard D. ALK inhibitors in non-small cell lung cancer: the latest evidence and developments. Ther Adv Med Oncol 2016;8(1):32–47.

47. Mayekar MK, Bivona TG. Current landscape of targeted therapy in lung cancer. Clin Pharmacol Ther 2017;102(5):757–64.
48. Pavel ME, Singh S, Strosberg JR, et al. Health-related quality of life for everolimus versus placebo in patients with advanced, non-functional, well-differentiated gastrointestinal or lung neuroendocrine tumours (RADIANT-4): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18(10):1411–22.
49. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol 2016;17(7):883–95.
50. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD. Available at: https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017. Accessed September 21, 2018.
51. Ford DW, Koch KA, Ray DE, et al. Palliative and end-of-life care in lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e498S–512S.
52. Temel 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(8):733–42.