CHEST Supplement

DIAGNOSIS AND MANAGEMENT OF LUNG CANCER, 3RD ED: ACCP GUIDELINES

Executive Summary

Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Frank C. Detterbeck, MD, FCCP; Sandra Zelman Lewis, PhD; Rebecca Diekemper, MPH; Doreen J. Addrizzo-Harris, MD, FCCP; and W. Michael Alberts, MD, MBA, FCCP

CHEST 2013; 143(5)(Suppl):7S–37S

Abbreviations: ACCP = American College of Chest Physicians; AFB = autofluorescence bronchoscopy; APW = Aortopulmonary Window; BSC = best supportive care; CIS = carcinoma in situ; CPET = cardiopulmonary exercise test; CXR = chest radiograph; DLCO = diffusing capacity for carbon monoxide; EBUS = endobronchial ultrasound; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; ES = extensive stage; FA = fine needle aspiration; GGO = ground glass opacity; IASLC = International Association for the Study of Lung Cancer; LC III = 3rd edition of the ACCP Lung Cancer Guidelines; LDCT = low-dose CT; LS = limited stage; LUL = left upper lobe; LVRS = lung volume reduction surgery; MFLC = multifocal lung cancer; MPE = malignant pleural effusion; NA = needle aspiration; NLST = National Lung Cancer Screening Trial; NRS = numerical rating scale; NSAID = nonsteroidal antiinflammatory drug; NSCLC = non-small cell lung cancer; PET = positron emission tomography; PPO = predicted postoperative; PS = performance status; QOL = quality of life; RCT = randomized controlled trial; RT = radiotherapy; SBRT = stereotactic body radiation therapy; SCLC = small cell lung cancer; SVC = superior vena cava; SWT = shuttle walk test; TBNA = transbronchial needle aspiration; TRT = thoracic radiotherapy; TTNA = transthoracic needle aspiration; VAS = visual analog scale; VATS = video-assisted thoracic surgery; VEGF = vascular endothelial growth factor; $\dot{V}O_2max$ = maximal oxygen consumption; WHO = World Health Organization; WLB = white light bronchosopy

Lung cancer causes as many deaths as the next four leading causes of cancer deaths combined.[1] In the developing world, which has seen a dramatic increase in the rate of smoking, the impending number of deaths from this disease is staggering. Although the incidence and death rate in the United States has been declining since around 2000, lung cancer is projected to remain by far the leading cause of cancer deaths for many decades.

For many years, lung cancer was a relatively neglected disease, shrouded in pessimism and with little research funding. However, many advances have occurred, and it is now a vibrant field with a rapid pace of new information. The explosion of literature makes it difficult for anyone to stay current. With more insight comes the identification of many nuances that are important to correctly understand new studies and choose the optimal treatments for patients. Lung cancer has evolved to where it takes a team of individuals, each with lung cancer expertise within their specialty, to be able to provide the necessary up-to-date knowledge base. The crucial aspect here is not to simply have multiple specialties but to develop a forum for ongoing interaction, so that the individuals think and function as a team, making decisions collectively. Such integration and collaboration allow collective knowledge and judgment to be brought to bear on caring for patients. Even for such a team, however, staying abreast of advances is challenging.

Evidence-based guidelines are intended to make the process of providing up-to-date care easier. The third edition of the American College of Chest Physicians (ACCP) Lung Cancer Guidelines (LC III) is a systematic, extensive, comprehensive review of the literature, a structured interpretation of the data, and practical patient management recommendations. The LC III panelists were selected based on expertise and volunteered an astounding number of hours to carefully and systematically provide the basis for and, finally, produce the guidelines. The result is a product that can be accessed superficially to quickly find guideline statements relevant to a particular clinical issue or more in depth by reviewing the data tables and reading the individual articles. The organized process to produce the guidelines helps to ensure that it is not biased and is representative of the current state of knowledge. The LC III documents represent a distillation of thousands of hours to make the insights more easily accessible to the clinicians on the front lines.

Nevertheless, implementation of the guidelines requires some effort. They cannot provide a simple recipe for treatment. Clinical judgment is needed to assess and balance the many factors that go into clinical decision-making. How well do the patients from whom the data are derived match the patient for whom a management plan is being developed? How strong and consistent are the data, and how heavily should other factors or patient preferences influence the plan? The essence of clinical judgment is being able to weigh the strength of the many factors that each patient brings to decision-making. The LC III guidelines are designed to impart insight into these matters to enhance clinical decision making and not merely present a relatively rigid algorithm.

A difficulty in developing guidelines is that implementation must also be tailored to the local setting. In some countries or institutions, certain tests or procedures may not be available. On a more subtle level, although a test may sometimes be available, one cannot assume that the results in every clinical setting match those of the published literature. The best way to implement guidelines is to thoughtfully tailor them to the local setting. This requires assembling the local team of specialists and critically reviewing the major guideline recommendations and the local strengths and challenges. This allows the development of a locally adapted system of care that can significantly streamline the process of care and ensure that patients are receiving thoughtful care to the highest degree possible in that setting. The LC III guidelines were designed to provide enough details to facilitate such local adaptation in an efficient manner. This executive summary provides a brief synopsis of each article, highlights the major points, and lists the recommendations.

Manuscript received September 24, 2012; revision accepted November 30, 2012.

Affiliations: From the Department of Thoracic Surgery (Dr Detterbeck), Yale University School of Medicine, New Haven, CT; the American College of Chest Physicians (Dr Lewis and Ms Diekemper), Northbrook, IL; the Pulmonary Division (Dr Addrizzo-Harris), New York University School of Medicine, New York, NY; and the H. Lee Moffitt Cancer Center (Dr Alberts), Tampa, FL.

Funding/Sponsors: The development of this guideline was supported primarily by the American College of Chest Physicians. The lung cancer guidelines conference was supported in part by a grant from the Lung Cancer Research Foundation. The publication and dissemination of the guidelines was supported in part by a 2009 independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

COI grids reflecting the conflicts of interest that were current as of the date of the conference and voting are posted in the online supplementary materials.

Correspondence to: Frank C. Detterbeck, MD, FCCP, Yale University School of Medicine, 330 Cedar St, PO Box 208062, New Haven, CT 06520-8062; e-mail: frank.detterbeck@yale.edu

DOI: 10.1378/chest.12-2377

2.0 Methodology for Development of Guidelines for Lung Cancer

There have been major advances in the clinical science of lung cancer. There have also been major advances in methodologic science. The ACCP has been at the forefront of these advances and is committed to continuing to evolve the process of literature review, data extraction, and guideline development. With the advancement of methodologic techniques, content experts and methodologists must work hand in hand to bring the best each has to offer to bear on the process. Because resources are not unlimited, and practical aspects and logistics present challenges, how to achieve this collaboration was a process that continued to evolve during the development of LC III guidelines. We were fortunate to have the participation of a small but growing number of individuals who have content expertise as well as formal methodology training. For each article, a methodologist was assigned and involved during the process of research and guideline development.

3.0 Epidemiology of Lung Cancer

The epidemiology of lung cancer is an active field. Researchers in the area of molecular epidemiology are making advances in the identification of biomarkers of risk and for early detection, although these are not yet mature enough for clinical application.

Cigarette smoking remains the predominant risk factor for lung cancer. A dramatic increase in deaths from lung cancer is anticipated in the developing world, given the current high rate of smoking in these regions. This will have significant social and economic impact.

Although smoking is the major risk factor, a better understanding of the risk of developing lung cancer is needed, particularly with the advent of screening with low-dose CT (LDCT) scanning. This article discusses the risk models that have been developed. Further validation of these models is needed to allow prediction of risk for individual patients. Furthermore, a better understanding of other factors is needed, for example, to address the substantial number of patients who develop lung cancer despite being lifelong nonsmokers.

4.0 Molecular Biology of Lung Cancer

Much attention has been directed toward identification of particular genetic mutations that can be treated with targeted therapy, resulting in a major palliative benefit for these patients with advanced non-small cell lung cancer (NSCLC). We appear to be poised to reap more far-reaching benefits by using the tools of molecular biology to gain insight into the development of various lung cancers, determinants of progression, and the identification of specific biomarkers. This has the potential to open up doors for early detection, identification of prognostic and predictive markers, and perhaps prevention. This article discusses the state of the art of research in these areas.

5.0 Chemoprevention of Lung Cancer

The idea of an agent that could prevent the progression to invasive cancer in individuals at high risk is appealing. Unfortunately, despite preliminary data suggesting a possible chemopreventative effect, all of the agents that have been tested in large randomized controlled trials (RCTs) have shown no benefit; some have even turned out to be harmful.

Despite this disappointment, the increasing insight into the fundamental biology of the development of lung cancer provides new opportunities to identify a chemopreventative agent. The field has shifted from large RCTs to smaller studies aimed at achieving a better understanding of the relevant biology and definition of surrogate end points in order to build a solid foundation for future progress.

Summary of Recommendations: Chemoprevention of Lung Cancer

3.1.1.1. For individuals with a greater than 20 pack year history of smoking or with a history of lung cancer, the use of β carotene supplementation is not recommended for primary, secondary, or tertiary chemoprevention of lung cancer (Grade 1A)**.**

Remarks: The dose of β carotene used in these studies was 20-30 mg per day or 50 mg every other day.

3.5.1.1. For individuals at risk for lung cancer and for patients with a history of lung cancer, the use of vitamin E, retinoids, and N-acetylcysteine and isotretinoin is not recommended for primary, secondary, or tertiary prevention of lung cancer (Grade 1A)**.**

3.6.1.1. For individuals at risk for lung cancer and for patients with a history of lung cancer, the use of aspirin is not recommended for primary, secondary, or tertiary prevention of lung cancer (outside of the setting of a well-designed clinical trial) (Grade 1B)**.**

3.7.1.1. In individuals with a history of early stage non-small cell lung cancer (NSCLC), the use of selenium as a tertiary chemopreventive agent of lung cancer is not recommended (Grade 1B)**.**

5.7.1. For individuals at risk for lung cancer or with a history of lung cancer, prostacyclin analogs (iloprost), cyclooxygenase-2 inhibitors (celecoxib), and anethole dithiolethione, are not recommended for use for primary, secondary, or tertiary lung cancer chemoprevention (outside of the setting of a well-designed clinical trial) (Grade 1B)**.**

5.7.2. For individuals at risk for lung cancer or with a history of lung cancer, inhaled steroids are not recommended for use for primary, secondary, or tertiary lung cancer chemoprevention (outside of the setting of a well-designed clinical trial) (Grade 1B)**.**

6.7.1. For individuals at risk for lung cancer or with a history of lung cancer, the use of pioglitazone or myoinositol, for primary, secondary, or tertiary lung cancer chemoprevention is not recommended (outside of the setting of a well-designed clinical trial) (Grade 1B)**.**

6.7.2. In individuals at risk for lung cancer, the use of tea extract, or metformin is not suggested for primary, secondary or tertiary prevention of lung cancer (outside of the setting of a well-designed clinical trial) (Grade 2C)**.**

6.0 Treatment of Tobacco Use in Lung Cancer

Smoking is a difficult addiction to overcome. However, significant advances have been made in understanding some of the reasons for the seemingly paradoxical situation of patients who have developed lung cancer yet have difficulty giving up smoking. More importantly, not only are there several therapeutic interventions that can assist those trying to stop smoking but there is a fairly sophisticated understanding of which intervention or combination of interventions has the best chance of leading to sustained success. Most clinicians managing patients with lung cancer are relatively unaware of the current state of knowledge, and this article is well worth the time to read carefully. The authors provide a practical yet detailed summary of the scientific basis and management strategies of

an up-to-date, sophisticated evidence-based treatment program for treatment of tobacco use.

Summary of Recommendations: Treatment of Tobacco Use

3.1.1.1. We recommend that current smokers undergoing low-dose CT screening be provided with cessation interventions that include counseling and pharmacotherapy (Grade 1B)**.**

Remark: The act of screening alone is insufficient to promote smoking cessation.

Remark: The use of self-help materials is insufficient for achieving an increased rate of smoking abstinence.

3.1.1.2. Among current smokers with demonstrated smoking related pulmonary disease we recommend providing intensive cessation interventions (Grade 1B)**.**

3.2.1.1. Among lung cancer patients undergoing surgery, we recommend perioperative cessation pharmacotherapy as a method for improving abstinence rates (Grade 1B)**.**

3.2.1.2. Among lung cancer patients undergoing surgery for whom pharmacotherapeutic support is either contraindicated or refused, we suggest cessation counseling alone during the perioperative period (Grade 2C)**.**

3.2.1.3. Among lung cancer patients undergoing surgery, the timing of cessation does not appear to increase the risk of post-operative complications; we suggest that cessation interventions be initiated in the pre-operative period (Grade 2C).

Remark: Small observed effect sizes and limitations in experimental design do not justify delaying surgical procedures in favor of longer abstinence duration.

3.2.1.4. For lung cancer patients attempting cessation in conjunction with surgical interventions, we recommend initiating counseling and pharmacotherapy at the outset of surgical intervention (Grade 1B)**.**

Remark: There is substantial evidence suggesting that reliance on short, low intensity cessation interventions such as advice to quit does not improve abstinence outcomes.

3.3.1.1. Among lung cancer patients undergoing chemotherapy, we recommend cessation interventions that include counseling and pharmacotherapy to improve abstinence rates (Grade 1B)**.**

3.3.1.2. Among lung cancer patients with depressive symptoms, we suggest cessation pharmacotherapy with bupropion as a method to improve abstinence rates, depressive symptoms, and quality of life (Grade 2B)**.**

3.3.1.3. Among lung cancer patients for whom pharmacotherapeutic support is either contraindicated or refused, we suggest cessation counseling alone as a method to improve abstinence rates (Grade 2C)**.**

3.4.1.1. Among lung cancer patients undergoing radiotherapy, we recommend cessation interventions that include counseling and pharmacotherapy (Grade 1C)**.**

7.0 Screening for Lung Cancer

Major progress has been made in defining the role of screening for lung cancer. The results of a major RCT evaluating chest radiographs is consistent with earlier RCTs, showing that this is not a useful screening test. There are several RCTs evaluating the role of LDCT scanning. The largest of these is the National Lung Cancer Screening Trial (NLST), which has reported a reduction in lung cancer deaths among screened individuals. This involved patients with a significant risk of lung cancer due to age and smoking history. Two smaller studies have also reported mortality data; although they did not demonstrate a mortality benefit, they are probably best viewed as neither supporting nor refuting the NLST results. The average risk of lung cancer of individuals participating in these smaller trials appears to be slightly less.

LDCT scanning identifies small nodules in 10% to 50% of those screened, the vast majority of which are benign. The rate of nodule detection varies and is not readily explained (eg, size criteria, scanner parameters, population risk, and so forth). All of the controlled LDCT scanning trials have had an organized process in place for evaluation of findings, and this has resulted in relatively few patients undergoing invasive biopsies. Nevertheless, the rate of biopsy for benign lesions is highly variable and averages around 30%. The reason for the variation is poorly understood. Although harms have been relatively few, there is a risk from radiation exposure, and there have been complications and even rare deaths in patients undergoing investigation of what turned out to be a benign, screen-detected nodule.

These results indicate that screening is a complex interplay of baseline risk, the screening test, test interpretation, and management of the findings. There is

a large potential for benefit, but implementation of LDCT screening is made difficult by the lack of data about the impact that various selection, structural, and technical aspects of the screening process have on outcomes. Furthermore, many RCTs of LDCT scanning are still ongoing. The recommendation at this time is to implement screening in settings and patients that match those of the NLST while further data are acquired.

Summary of Recommendations: Screening for Lung Cancer

3.2.1. In patients at risk for developing lung cancer, screening for lung cancer with chest radiograph (CXR) once or at regular intervals is not recommended (Grade 1A)**.**

Remark: These results should not be interpreted as diminishing the role of CXR in evaluating patients with pulmonary symptoms (an entirely different situation than screening asymptomatic individuals).

3.2.2. In patients at risk for developing lung cancer, screening for lung cancer with sputum cytology at regular intervals is not suggested (Grade 2B)**.**

3.4.1. For smokers and former smokers who are age 55 to 74 and who have smoked for 30 pack-years or more and either continue to smoke or have quit within the past 15 years, we suggest that annual screening with low-dose CT (LDCT) should be offered over both annual screening with CXR or no screening, but only in settings that can deliver the comprehensive care provided to National Lung Screening Trial participants (Grade 2B)**.**

Remark: Counseling should include a complete description of potential benefits and harms, so the individual can decide whether to undergo LDCT screening.

Remark: Screening should be conducted in a center similar to those where the National Lung Screening Trial was conducted, with multidisciplinary coordinated care and a comprehensive process for screening, image interpretation, management of findings, and evaluation and treatment of potential cancers.

Remark: A number of important questions about screening could be addressed if individuals who are screened for lung cancer are entered into a registry that captures data on follow-up testing, radiation exposure, patient experience, and smoking behavior.

Remark: Quality metrics should be developed such as those in use for mammography screening, which could help enhance the benefits and minimize the harm for individuals who undergo screening.

Remark: Screening for lung cancer is not a substitute for stopping smoking. The most important thing patients can do to prevent lung cancer is not smoke.

Remark: The most effective duration or frequency of screening is not known.

3.4.2. For individuals who have accumulated fewer than 30 pack-years of smoking or are either younger than age 55 or older than 74, or individuals who quit smoking more than 15 years ago, and for individuals with severe comorbidities that would preclude potentially curative treatment and/or limit life expectancy, we suggest that CT screening should not be performed (Grade 2C)**.**

8.0 Evaluation of Individuals With Pulmonary Nodules: When Is It Lung Cancer?

The management of a solitary pulmonary nodule has been addressed extensively, yet most pulmonologists and thoracic surgeons use an approach that is not closely grounded in solid evidence. The management of these patients is somewhat complex and is influenced by many considerations (eg, the risk of malignancy based on the patient's history and features of the lesion), patient characteristics (eg, lung function), patient values and preferences, and the reliability of various tests.

This article does a superb job of integrating a large amount of data in a complex field into an evidence-based approach. It is extensively researched and well summarized, but the real value is the structure that is provided, which organizes the various factors and considerations (see Fig 2 in Gould et al[2] in LC III). A useful starting point is to assess the risk of lung cancer as well as the patient's risk for an invasive procedure. Larger masses must be approached differently than subcentimeter lesions or ground-glass opacities. Careful observation is reasonable in some settings. If a bronchoscopic or needle-based biopsy is selected, the possibility of a false-negative result must be kept in mind.

Summary of Recommendations: Evaluation of Pulmonary Nodules

General Approach

2.3.1. In the individual with an indeterminate nodule that is visible on chest radiography and/or

chest CT, we recommend that prior imaging tests should be reviewed (Grade 1C)**.**

2.3.2. In the individual with a solid, indeterminate nodule that has been stable for at least 2 years, we suggest that no additional diagnostic evaluation need be performed (Grade 2C)**.**

Remark: This recommendation applies only to solid nodules. For guidance about follow-up of subsolid nodules, see Recommendations 6.5.1. to 6.5.4.

2.3.3. In the individual with an indeterminate nodule that is identified by chest radiography, we recommend that CT of the chest should be performed (preferably with thin sections through the nodule) to help characterize the nodule (Grade 1C)**.**

Solid Nodules > 8 mm

4.1.1.1. In the individual with a solid, indeterminate nodule that measures > 8 mm in diameter, we suggest that clinicians estimate the pretest probability of malignancy either qualitatively by using their clinical judgment and/or quantitatively by using a validated model (Grade 2C)**.**

4.2.4.1. In the individual with a solid, indeterminate nodule that measures > 8 mm in diameter and low to moderate pretest probability of malignancy (5%-65%), we suggest that functional imaging, preferably with PET, should be performed to characterize the nodule (Grade 2C)**.**

4.2.4.2. In the individual with a solid, indeterminate nodule that measures > 8 mm in diameter and a high pretest probability of malignancy (> 65%), we suggest that functional imaging should not be performed to characterize the nodule (Grade 2C)**.**

Remark: PET may be indicated for pretreatment staging among those patients with nodules in whom malignancy is strongly suspected or confirmed.

4.4.1.1. In the individual with a solid, indeterminate nodule that measures > 8 mm in diameter, we recommend that clinicians discuss the risks and benefits of alternative management strategies and elicit patient preferences for management (Grade 1C)**.**

4.5.1.1. In the individual with a solid, indeterminate nodule that measures > 8 mm in diameter, we suggest surveillance with serial CT scans in the following circumstances (Grade 2C)**:**

- **When the clinical probability of malignancy is very low (< 5%)**
- **When clinical probability is low (< 30% to 40%) and the results of a functional imaging test are negative (ie, the lesion is not hypermetabolic by PET or does not enhance > 15 Hounsfield units on dynamic contrast CT), resulting in a very-low posttest probability of malignancy**
- **When needle biopsy is nondiagnostic and the lesion is not hypermetabolic by PET**
- **When a fully informed patient prefers this nonaggressive management approach.**

Remark: CT surveillance of solid nodules ≥ 8 mm should use low-dose, noncontrast techniques.

4.5.1.2. In the individual with a solid, indeterminate nodule that measures > 8 mm in diameter who undergoes surveillance, we suggest that serial CT scans should be performed at 3 to 6, 9 to 12, and 18 to 24 months, using thin sections and noncontrast, low-dose techniques (Grade 2C)**.**

Remark: Serial CT scans should be compared with all available prior studies, especially the initial (index) CT scan.

Remark: Where available, manual and/or computer-assisted measurements of area, volume, and/or mass may facilitate early detection of growth.

4.5.1.3. In the individual with a solid, indeterminate nodule that shows clear evidence of malignant growth on serial imaging, we recommend nonsurgical biopsy and/or surgical resection unless specifically contraindicated (Grade 1C)**.**

Remark: Solid nodules that decrease in size but do not disappear completely should be followed to resolution or lack of growth over 2 years.

4.6.2.1.1. In the individual with a solid, indeterminate nodule that measures > 8 mm in diameter, we suggest nonsurgical biopsy in the following circumstances (Grade 2C)**:**

- **When clinical pretest probability and findings on imaging tests are discordant**
- **When the probability of malignancy is low to moderate (~ 10% to 60%)**
- **When a benign diagnosis requiring specific medical treatment is suspected**
- **When a fully informed patient desires proof of a malignant diagnosis prior to surgery, especially when the risk of surgical complications is high.**

Remark: The type of biopsy should be selected based on nodule size, location, and relation to a patent airway; the risk of complications in the individual patient; and available expertise.

4.6.3.1.1. In the individual with a solid, indeterminate nodule that measures > 8 mm in diameter, we suggest surgical diagnosis in the following circumstances (Grade 2C)**:**

- **When the clinical probability of malignancy is high (> 65%)**
- **When the nodule is intensely hypermetabolic by PET or markedly positive by another functional imaging test**
- **When nonsurgical biopsy is suspicious for malignancy**
- **When a fully informed patient prefers undergoing a definitive diagnostic procedure.**

4.6.3.1.2. In the individual with a solid, indeterminate nodule measuring > 8 mm in diameter who chooses surgical diagnosis, we recommend thoracoscopy to obtain a diagnostic wedge resection (Grade 1C)**.**

Remark: Use of advanced localization techniques or open thoracotomy may be necessary when resecting small or deep nodules.

Solid Nodules ≤ 8 mm

5.3.1. In the individual with a solid nodule that measures ≤ 8 mm in diameter and no risk factors for lung cancer, we suggest that the frequency and duration of CT surveillance be chosen according to the size of the nodule (Grade 2C)**:**

- **Nodules measuring ≤ 4 mm in diameter need not be followed, but the patient should be informed about the potential benefits and harms of this approach**
- **Nodules measuring > 4 mm to 6 mm should be reevaluated at 12 months without the need for additional follow-up if unchanged**
- **Nodules measuring > 6 mm to 8 mm should be followed sometime between 6 and 12 months, and then again at between 18 and 24 months if unchanged.**

Remark: For the individual with multiple small, solid nodules, the frequency and duration of follow-up should be based on the size of the largest nodule.

Remark: CT surveillance of solid nodules ≤ 8 mm should use low-dose, noncontrast techniques.

5.3.2. In the individual with a solid nodule that measures ≤ 8 mm in diameter who has one or more risk factors for lung cancer, we suggest that the frequency and duration of CT surveillance be chosen according to the size of the nodule (Grade 2C)**:**

- **Nodules measuring ≤ 4 mm in diameter should be reevaluated at 12 months without the need for additional follow-up if unchanged**
- **Nodules measuring > 4 mm to 6 mm should be followed sometime between 6 and 12 months and then again between 18 and 24 months if unchanged**
- **Nodules measuring > 6 mm to 8 mm should be followed initially sometime between 3 and 6 months, then subsequently between 9 and 12 months, and again at 24 months if unchanged.**

Remark: For the individual with multiple small, solid nodules, the frequency and duration of follow-up should be based on the size of the largest nodule.

Remark: CT surveillance of solid nodules ≤ 8 mm should use low-dose, noncontrast techniques.

Nonsolid (Pure Ground Glass) Nodules

6.5.1. In the individual with a nonsolid (pure ground glass) nodule measuring ≤ 5 mm in diameter, we suggest no further evaluation (Grade 2C)**.**

6.5.2. In the individual with a nonsolid (pure ground glass) nodule measuring > 5 mm in diameter, we suggest annual surveillance with chest CT for at least 3 years (Grade 2C)**.**

Remark: CT surveillance of nonsolid nodules should use noncontrast techniques with thin sections through the nodule of interest.

Remark: Nonsolid nodules that grow or develop a solid component are often malignant, prompting further evaluation and/or consideration of resection.

Remark: Early follow-up at 3 months may be indicated for nonsolid nodules measuring > 10 mm (followed by nonsurgical biopsy and/or surgical resection for nodules that persist).

Remark: Limited duration or no follow-up may be preferred by individuals with life-limiting comorbidities in whom a low-grade malignancy would be of little consequence or by others who place a high value on avoiding treatment of possibly indolent lung cancer.

Part-Solid (>50% Ground Glass) Nodules

6.5.3. In the individual with a part-solid nodule measuring ≤8 mm in diameter, we suggest CT surveillance at approximately 3, 12, and 24 months, followed by annual CT surveillance for an additional 1 to 3 years (Grade 2C)**.**

Remark: CT surveillance of part-solid nodules should use noncontrast techniques with thin sections through the nodule of interest.

Remark: Part-solid nodules that grow or develop a solid component are often malignant, prompting further evaluation and/or consideration of resection.

Remark: Limited duration or no follow-up may be preferred by individuals with life-limiting comorbidities in whom a low-grade malignancy would be of little consequence or by others who place a high value on avoiding treatment of possibly indolent lung cancer.

6.5.4. In the individual with a part-solid nodule measuring >8 mm in diameter, we suggest repeat chest CT at 3 months followed by further evaluation with PET, nonsurgical biopsy, and/or surgical resection for nodules that persist (Grade 2C)**.**

Remark: PET should not be used to characterize part-solid lesions in which the solid component measures ≤8 mm.

Remark: Nonsurgical biopsy can be used to establish the diagnosis and/or be combined with wire, radioactive seed, or dye localization to facilitate subsequent resection. A nondiagnostic biopsy result does not exclude the possibility of malignancy.

Remark: Part-solid nodules measuring >15 mm in diameter should proceed directly to further evaluation with PET, nonsurgical biopsy, and/or surgical resection.

One or More Additional Nodules Detected During Nodule Evaluation

7.1.1. In the individual with a dominant nodule and one or more additional small nodules, we suggest that each nodule be evaluated individually and curative treatment not be denied unless there is histopathological confirmation of metastasis (Grade 2C)**.**

Remark: The classification and appropriate treatment of patients with more than one pulmonary focus of lung cancer is difficult and requires multidisciplinary consideration.

9.0 Clinical and Organizational Factors in the Initial Evaluation of Patients With Lung Cancer

Patients with lung cancer may present with no symptoms, symptoms related to the primary tumor, or symptoms related to distant metastases. A number of paraneoplastic effects are also seen. The evaluation starts with a careful history and physical examination. The tasks of the initial evaluation, namely to establish a diagnosis and clinical stage and develop a treatment plan, proceed in an overlapping, not sequential manner. Involving a multidisciplinary team early during these processes can make the evaluation proceed more quickly with fewer unnecessary tests. However, quantifying the value of multidisciplinary evaluation or more timely care is difficult.

Summary of Recommendations: Initial Evaluation of Patients With Lung Cancer

4.4.1. For patients with known or suspected lung cancer, we suggest that the delivery of care be timely and efficient (Grade 2C)**.**

Remark: Interventions to improve timeliness should be developed locally by addressing barriers to providing timely care that are specific to the local setting.

Remark: Efforts to improve timeliness should be balanced with the need to attend to other dimensions of health-care quality (such as safety, effectiveness, efficiency, equality, and consistency with patient values and preferences).

5.1.1. For patients with lung cancer who require multimodality therapy, we suggest using a multidisciplinary team approach (Grade 2C)**.**

Remark: We suggest that multidisciplinary teams have representatives from pulmonary medicine, thoracic surgery, medical oncology, radiation oncology, palliative care, radiology, and pathology.

10.0 Establishing the Diagnosis of Lung Cancer

In most patients, the diagnosis of lung cancer is best established in a way that simultaneously confirms the stage of disease. If there is a pleural effusion, this represents an obvious target; however, there is a substantial false-negative rate to thoracentesis and cytology. Biopsy of distant sites or mediastinal nodes may be indicated but is covered elsewhere.

Many techniques are available to diagnose the primary tumor. This article extensively reviews the data for these, parsed out for specific situations. This helps guide the selection of which test to perform as well as how to interpret the results (ie, how to proceed if the test does not show cancer in a patient suspected of lung cancer). Bronchoscopy is ideal for central lesions but has low sensitivity and a high false-negative rate for peripheral lesions. Newer navigational techniques have improved sensitivity for peripheral lesions and a lower rate of pneumothorax compared with transthoracic needle aspiration, but all methods have a substantial false-negative rate.

Summary of Recommendations: Establishing the Diagnosis of Lung Cancer

General Approach to Diagnosis

2.3.1. In patients suspected of having small cell lung cancer (SCLC) based on the radiographic and clinical findings, it is recommended that the diagnosis be confirmed by the least invasive method (sputum cytology, thoracentesis, fine needle aspiration [FNA], bronchoscopy including transbronchial needle aspiration [TBNA]), as dictated by the patient's presentation (Grade 1C)**.**

2.3.2. In patients suspected of having lung cancer, who have extensive infiltration of the mediastinum based on radiographic studies and no evidence of extrathoracic metastatic disease (negative PET scan), it is recommended that the diagnosis of lung cancer be established by the least invasive and safest method (bronchoscopy with TBNA, endobronchial ultrasound-guided needle aspiration [EBUS-NA], endoscopic ultrasound-guided needle aspiration [EUS-NA], transthoracic needle aspiration [TTNA], or mediastinoscopy) (Grade 1C)**.**

2.3.3. In patients suspected of having lung cancer who have a solitary extrathoracic site suspicious of a metastasis, it is recommended that tissue confirmation of the metastatic site be obtained if a FNA or biopsy of the site is feasible (Grade 1C)**.**

2.3.4. In patients suspected of having lung cancer, who have lesions in multiple distant sites suspected of metastases but in whom biopsy of a metastatic site would be technically difficult, it is recommended that diagnosis of the primary lung lesion be obtained by the least invasive method (Grade 1C)**.**

2.3.5. In patients suspected of having lung cancer who have an accessible pleural effusion, thoracentesis is recommended to diagnose the cause of the pleural effusion (Grade 1C)**.**

Remark: Ultrasound-guided thoracentesis improves the success rate and decreases the rate of pneumothorax and therefore ultrasound is recommended for performing diagnostic thoracentesis.

2.3.6. In patients suspected of having lung cancer who have an accessible pleural effusion, if pleural fluid cytology is negative, pleural biopsy (via image-guided pleural biopsy, medical or surgical thoracoscopy) is recommended as the next step (Grade 1C)**.**

Remark: If the CT scan of the chest shows pleural thickening or pleural nodules/masses, image-guided needle biopsy may be considered as the first step to obtain a biopsy of the pleura.

Remark: If pleural cytology is negative after the first thoracentesis, a second thoracentesis has been shown to increase the diagnostic yield of pleural fluid cytology. Depending on preferences and values (a simpler and less invasive test vs a more definitive test) a second thoracentesis may be considered before proceeding to biopsy of the pleura.

Diagnosis of the Primary Tumor

3.1.2.1. In patients suspected of having lung cancer, if sputum cytology is done but is negative for carcinoma, it is recommended that further testing be performed (Grade 1C)**.**

Remark: Sputum cytology is an acceptable method of establishing the diagnosis. However, the sensitivity or sputum cytology varies by location of the lung cancer, and with the frequency and processing of the sputum at the center.

3.2.2.1. In patients suspected of having lung cancer, who have a central lesion, bronchoscopy is recommended to confirm the diagnosis. However, it is recommended that further testing be performed if bronchoscopy results are non-diagnostic and suspicion of lung cancer remains (Grade 1B)**.**

Remark: In recent years a number of complementary tools including radial endobronchial ultrasound and electromagnetic navigation have been added to flexible bronchoscopy to aid in the diagnosis of peripheral lung lesions.

3.3.2.1. In patients suspected of having lung cancer, who have a peripheral lung nodule, and a tissue diagnosis is required due to uncertainty of diagnosis or poor surgical candidacy, radial

EBUS is recommended as an adjunct imaging modality (Grade 1C)**.**

Remark: Radial EBUS can confirm in real time the ideal location of bronchoscopic sampling and increase the diagnostic yield over conventional bronchoscopy for peripheral nodules.

3.4.2.1. In patients with peripheral lung lesions difficult to reach with conventional bronchoscopy, electromagnetic navigation guidance is recommended if the equipment and the expertise are available (Grade 1C)**.**

Remark: The procedure can be performed with or without fluoroscopic guidance and it has been found complementary to radial probe ultrasound

Remark: If electromagnetic navigation is not available, TTNA is recommended.

3.5.2.1. In patients suspected of having lung cancer who have a peripheral lesion, and who require tissue diagnosis before further management can be planned, TTNA is a diagnostic option. However, it is recommended that further testing be performed if TTNA results are non-diagnostic and suspicion of lung cancer remains (Grade 1B)**.**

3.6.2.1. In patients suspected of having lung cancer, the diagnosis of non-small cell lung cancer made on cytology (sputum, TTNA, bronchoscopic specimens, or pleural fluid) is reliable. However, it is recommended that adequate tissue be obtained to accurately define the histologic type and to perform molecular analysis when applicable (Grade 1B)**.**

Remark: It is critical to obtain adequate tissue to characterize a lung cancer. Within an institution, effective communication between those obtaining the biopsies, those interpreting them, and those delivering the treatment must be in place so that collectively, the members of various subspecialties involved in the care of the lung cancer patient can decide how best to obtain and optimally use the tissue. If specimens are not adequate for histologic and molecular characterization then obtaining a second biopsy is acceptable given the importance of accurate tumor characterization.

3.6.2.2. The possibility of an erroneous diagnosis of SCLC on a cytology specimen must be kept in mind if the clinical presentation or clinical course is not consistent with that of SCLC. In such a case, it is recommended that further testing be performed to establish a definitive cell type (Grade 1B)**.**

11.0 Physiologic Evaluation of the Patient With Lung Cancer Being Considered for Resectional Surgery

Surgery remains the mainstay of treatment of early-stage lung cancer, and assessment of a patient's ability to tolerate a resection is important. Patients should undergo a simple cardiac risk assessment, with further investigation (ie, cardiopulmonary exercise testing) if this suggests potential complications. Assessment of pulmonary reserve should include both spirometry and diffusion capacity, calculated as a predicted postoperative value (taking into account the intended resection) and expressed as a percent of normal (thus taking into account variations in body size). Patients with moderate impairment should undergo a simple exercise test, such as stair climbing; if performance is limited (stair climb of <22 m), formal cardiopulmonary exercise testing is indicated (see Fig 2 in Brunelli et al[3] in LC III).

An important aspect of physiologic evaluation is that there is a continuum of risk and benefit that is not well served by simple dichotomization into a yes/no categorization of candidacy for pulmonary resection. Furthermore, the available data primarily pertain to open thoracotomy; thoracoscopic resection is clearly better tolerated, although the criteria for preoperative assessment are not well defined. The decision to undertake surgery must take into account aspects such as the possibility of sublobar resection, thoracoscopic resection, alternative (nonsurgical) treatments, and beneficial effects of smoking cessation and preoperative pulmonary rehabilitation.

The available data primarily define outcomes relative to acute morbidity and mortality; the effect on long-term functional status is less well understood. Patients with worse preoperative lung function often lose less function. The evaluation of marginal patients requires multidisciplinary management.

Summary of Recommendations: Physiologic Evaluation Prior to Resectional Surgery

2.6.1. In patients with lung cancer who are potential candidates for curative surgical resection, it is recommended that they be assessed by a multidisciplinary team, which includes a thoracic surgeon specializing in lung cancer, medical oncologist, radiation oncologist and pulmonologist (Grade 1C)**.**

2.6.2. In elderly patients with lung cancer who are potential candidates for curative surgical

resection it is recommended that they be fully evaluated regardless of age (Grade 1C).

2.6.3. In patients with lung cancer being considered for surgery who have increased perioperative cardiovascular risk, a preoperative cardiologic evaluation is recommended, with further management according to existing cardiologic guidelines for non cardiac surgery (Grade 1C).

3.1.1.1. In patients with lung cancer being considered for surgery, it is recommended that both FEV_1 and diffusing capacity for carbon monoxide (DLCO) be measured in all patients and that both predicted postoperative (PPO) FEV_1 and PPO DLCO are calculated (Grade 1B).

3.2.1.1. In patients with lung cancer being considered for surgery, if both PPO FEV_1 and PPO DLCO are > 60% predicted, no further tests are recommended (Grade 1C).

Remark: Values of both PPO FEV_1 and PPO DLCO > 60% indicate low risk for perioperative death and cardiopulmonary complications following resection including pneumonectomy.

3.2.1.2. In patients with lung cancer being considered for surgery, if either the PPO FEV_1 or PPO DLCO are < 60% predicted and both are above 30% predicted, it is recommended that a low technology exercise test (stair climb or shuttle walk test [SWT]) is performed (Grade 1C).

3.2.1.3. In patients with lung cancer being considered for surgery, with either a PPO FEV_1 < 30% predicted or a PPO DLCO < 30% predicted performance of a formal cardiopulmonary exercise test (CPET) with measurement of maximal oxygen consumption ($\dot{V}o_2$max) is recommended (Grade 1B).

Remark: Either a PPO FEV_1 < 30% predicted or a PPO DLCO < 30% predicted indicate an increased risk for perioperative death and cardiopulmonary complications with anatomic lung resection.

3.9.1. In patients with lung cancer being considered for surgery who walk < 25 shuttles (or < 400m) on the SWT or climb < 22m at symptom limited stair climbing test, performance of a formal CPET with measurement of $\dot{V}o_2$max is recommended (Grade 1C).

Remark: Walking < 25 shuttles (or < 400m) on the SWT or climbing < 22m at symptom limited stair climbing test suggests an increased risk for perioperative death and cardiopulmonary complications with anatomic lung resection.

3.9.2. In patients with lung cancer being considered for surgery and a $\dot{V}o_2$max < 10mL/kg/min or < 35% predicted it is recommended that they are counseled about minimally invasive surgery, sublobar resections or nonoperative treatment options for their lung cancer (Grade 1C).

Remark: a $\dot{V}o_2$max < 10mL/kg/min or < 35% predicted indicates a high risk for perioperative death and cardiopulmonary complications with major anatomic lung resection through thoracotomy.

Remark: For values of $\dot{V}o_2$max in the range of 10 to 15 mL/kg/min an increased risk of mortality is expected. However, data are less definitive for making decisions based solely on those values without taking into account other factors like PPO FEV_1 and DLCO as well as patient comorbidities.

6.1.1. In patients with lung cancer being considered for surgery who undergo neoadjuvant therapy, it is suggested that repeat pulmonary function testing with diffusion capacity be performed after completion of neoadjuvant therapy (Grade 2C).

7.4.1. In patients with lung cancer in an area of upper lobe emphysema who are candidates for lung volume reduction surgery (LVRS), combined LVRS and lung cancer resection is suggested (Grade 2C).

7.4.2. In all patients with lung cancer being considered for surgery who are actively smoking, tobacco dependence treatment is recommended (Grade 1C).

Remark: Smoking cessation is associated with short-term perioperative and long-term survival benefits (see also specific recommendations in chapter 6, 3.1.1, 3.1.2, 3.1.3).

7.4.3. In patients with lung cancer being considered for surgery and deemed at high risk (as defined by the proposed functional algorithm, ie, PPO FEV_1 or PPO DLCO < 60% and $\dot{V}o_2$max < 10 mL/kg/min or < 35%), preoperative or postoperative pulmonary rehabilitation is recommended (Grade 1C).

12.0 The Stage Classification of Lung Cancer

Having a consistent nomenclature is crucial to being able to communicate and compare data from different studies and centers. The official worldwide

stage classification system (seventh edition) is based on an unprecedented initiative of the International Association for the Study of Lung Cancer involving a database of > 100,000 patients diagnosed between 1990 and 2000. This system is the basis for the nomenclature used in the third edition of the ACCP Lung Cancer Guidelines. This article discusses the basics as well as the many details of the system. An Internet-accessible tool to navigate the stage classification is also available at www.staginglungcancer.org.

As with any detailed and complex system, there are areas that are confusing and ambiguous (eg, measurement of ground-glass opacities; the use of clinical and pathologic stage for individual T, N, and M descriptors; and classification of synchronous primary cancers, additional pulmonary nodules, and multifocal lung cancer). This article also provides some guidance about how to deal with these issues.

13.0 Methods of Staging for Non-small Cell Lung Cancer

Accurately defining the anatomic extent of disease is critical to selecting the appropriate therapy for patients with lung cancer. Many studies have provided additional data regarding how best to achieve this. PET imaging has assumed a prominent role, but it is important to confirm positive PET findings with a biopsy in most situations. The clinical setting and the extent of additional staging tests influences the impact of PET—the benefit being most marked in patients at greater risk of distant metastases (weight loss, mediastinal node enlargement) and those who do not undergo extensive imaging for distant metastases or invasive mediastinal staging in addition to PET imaging.

Invasive mediastinal staging is important for most patients who do not have distant metastases. The role of endobronchial ultrasound has become well founded, with many studies being available. It is important to note, however, that details of how a procedure is performed likely influence how well the test functions in practice. Data from reported studies often involve a thorough sampling. In general practice, node sampling during mediastinoscopy has been more limited; whether this will be true of endobronchial ultrasound with wider application is yet to be determined.

Summary of Recommendations: Methods of Staging for Non-small Cell Lung Cancer

General Approach

2.1.1. For patients with either a known or suspected lung cancer who are eligible for treatment, a CT scan of the chest with contrast is recommended (Grade 1B)**.**

Remark: If PET scan is unavailable for staging, the CT of the chest should be extended to include the liver and adrenal glands to assess for metastatic disease.

2.1.2. For patients with either a known or suspected lung cancer, it is recommended that a thorough clinical evaluation be performed to provide an initial definition of tumor stage (Grade 1B)**.**

2.1.3. In patients with either a known or suspected lung cancer who have an abnormal clinical evaluation and no suspicious extrathoracic abnormalities on chest CT, additional imaging for metastases is recommended (Grade 1B)**.**

Remark: Site specific symptoms warrant directed evaluation of that site with the most appropriate study.

Extrathoracic Staging

3.1.1. In patients with a normal clinical evaluation and no suspicious extrathoracic abnormalities on chest CT being considered for curative-intent treatment, PET imaging (where available) is recommended to evaluate for metastases (except the brain) (Grade 1B)**.**

Remark: Ground glass opacities and an otherwise normal chest CT do not require a PET scan for staging.

Remark: In patients with peripheral stage cIA tumors a PET scan is not required.

Remark: If PET is unavailable, bone scan and abdominal CT are reasonable alternatives to evaluate for extrathoracic disease.

3.1.2. In patients with an imaging finding (eg, by PET) suggestive of a metastasis, further evaluation of the abnormality with tissue sampling to pathologically confirm the clinical stage is recommended prior to choosing treatment (Grade 1B)**.**

Remark: Tissue sampling of the abnormal site is imperative so that the patient is not excluded from potentially curative treatment.

Remark: Tissue sampling of a distant metastatic site is not necessary if there is overwhelming radiographic evidence of metastatic disease in multiple sites.

Remark: Tissue sampling of the mediastinal lymph nodes does not necessarily need to be performed if there is overwhelming radiographic evidence of metastatic disease in multiple distant sites.

3.4.1. In patients with clinical stage III or IV non-small cell lung cancer (NSCLC) it is suggested

that routine imaging of the brain with head MRI (or CT if MRI is not available) should be performed, even if they have a negative clinical evaluation (Grade 2C)**.**

Mediastinal Staging

4.4.2.1. For patients with extensive mediastinal infiltration of tumor and no distant metastases, it is suggested that radiographic (CT) assessment of the mediastinal stage is usually sufficient without invasive confirmation (Grade 2C)**.**

4.4.4.1. In patients with discrete mediastinal lymph node enlargement (and no distant metastases) with or without PET uptake in mediastinal nodes, invasive staging of the mediastinum is recommended over staging by imaging alone (Grade 1C)**.**

4.4.4.2. In patients with PET activity in a mediastinal lymph node and normal appearing nodes by CT (and no distant metastases), invasive staging of the mediastinum is recommended over staging by imaging alone (Grade 1C)**.**

4.4.4.3. In patients with high suspicion of N2,3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no distant metastases), a needle technique (endobronchial ultrasound [EBUS]-needle aspiration [NA], EUS-NA or combined EBUS/EUS-NA) is recommended over surgical staging as a best first test (Grade 1B)**.**

Remark: This recommendation is based on the availability of these technologies (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) and the appropriate experience and skill of the operator.

Remark: In cases where the clinical suspicion of mediastinal node involvement remains high after a negative result using a needle technique, surgical staging (eg, mediastinoscopy, video-assisted thoracic surgery [VATS], etc) should be performed.

Remark: The reliability of mediastinal staging may be more dependent on the thoroughness with which the procedure is performed than by which test is used.

4.4.6.1. In patients with an intermediate suspicion of N2,3 involvement, ie, a radiographically normal mediastinum (by CT and PET) and a central tumor or N1 lymph node enlargement (and no distant metastases), invasive staging of the mediastinum is recommended over staging by imaging alone (Grade 1C)**.**

4.4.6.2. In patients with an intermediate suspicion of N2,3 involvement, ie, a radiographically normal mediastinum (by CT and PET) and a central tumor or N1 lymph node enlargement (and no distant metastases), a needle technique (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) is suggested over surgical staging as a best first test (Grade 2B)**.**

Remark: This recommendation is based on the availability of these technologies (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) and the appropriate experience and skill of the operator.

Remark: In cases where the clinical suspicion of mediastinal node involvement remains high after a negative result using a needle technique, surgical staging (eg, mediastinoscopy, VATS, etc) should be performed.

Remark: The reliability of mediastinal staging may be more dependent on the thoroughness with which the procedure is performed than by which test is used.

4.4.8.1. For patients with a peripheral clinical stage IA tumor (negative nodal involvement by CT and PET), it is suggested that invasive preoperative evaluation of the mediastinal nodes is not required (Grade 2B)**.**

4.4.10.1. For the patients with a left upper lobe (LUL) cancer in whom invasive mediastinal staging is indicated as defined by the previous recommendations, it is suggested that invasive assessment of the Aortopulmonary Window (APW) nodes be performed (via Chamberlain, VATS, or extended cervical mediastinoscopy) if other mediastinal node stations are found to be uninvolved (Grade 2B)**.**

14.0 Diagnostic Surgical Pathology in Lung Cancer

Details of the pathologic assessment of lung cancer have become more important. Definition of the histologic subtype of NSCLC is crucial in selection of chemotherapy regimens. Further subtyping of adenocarcinoma may be important in determining biologic behavior and the extent of local therapy. This article provides a framework for the pathologist in assessment of lung cancers with immunohistochemical and genetic tests. Reporting is ideally done in a standardized form, but communication with clinicians to discuss nuances remains important.

Summary of Recommendations: Diagnostic Surgical Pathology in Lung Cancer

2.1.1. When pathologically diagnosing patients with lung cancer, the synoptic reporting of histologic type, tumor size and location, tumor grade (if appropriate), lymphovascular invasion, pleural involvement, surgical margins, and status and location of lymph nodes by station is recommended (Grade 1B)**.**

3.1.1. In individuals with pleural-based tumors, a designated limited panel of histochemical and immunohistochemical assays or ultrastructural analysis is recommended to distinguish between pleural adenocarcinoma and malignant mesothelioma in order to increase diagnostic accuracy (Grade 1B)**.**

4.1.1. In individuals with parenchymal-based tumors, distinguishing between small cell carcinoma and non-small cell carcinoma of the lung is recommended. For challenging cases, a diagnostic panel of immunohistochemical assays or ultrastructural analysis is recommended to increase the diagnostic accuracy (Grade 1B)**.**

5.1.1. For individuals with glandular producing tumors, distinguishing adenocarcinoma in situ and minimally invasive adenocarcinomas from invasive adenocarcinomas is recommended (Grade 1C)**.**

Remark: Pathologic discrimination among these diagnostic entities are made on complete review of the tumor and not on needle biopsies.

6.1.1. In individuals with pathologically diagnosed non-small cell lung cancer, additional discrimination between adenocarcinoma and squamous cell carcinoma, even on cytologic material or small tissue samples, is recommended (Grade 1B)**.**

Remark: The precise subclassification is achieved in most cases by conventional histo- and cytomorphology. Immunohistochemical assays are recommended in cases where routine histopathologic differentiation is difficult to ascertain.

7.1.1. For individuals with lung tumors whose differential includes primary lung carcinoma vs metastatic carcinoma, a directed panel of immunohistochemical assays is recommended to increase the diagnostic accuracy (Grade 1C)**.**

15.0 Diagnosis and Treatment of Bronchial Intraepithelial Neoplasia and Early Lung Cancer of the Central Airways

A small number of patients present with a superficial neoplastic lesion of the central airways (ie, high-grade dysplasia, carcinoma in situ, and small foci of invasive cancer). Autofluorescence bronchoscopy is more sensitive at detecting such lesions. A number of endobronchial treatments have been tried, most prominently photodynamic therapy. However, the natural history of these precancerous lesions is poorly defined, and many appear to regress over time. Therefore the impact of detection and treatment is somewhat unclear. At this time standard white light bronchoscopy remains the diagnostic tool of greatest clinical relevance.

Summary of Recommendations: Bronchial Intraepithelial Neoplasia

3.1.1.1. In patients with severe dysplasia or carcinoma in situ (CIS) in sputum cytology who have chest imaging studies showing no localizing abnormality, standard white light bronchoscopy (WLB) is suggested to exclude an endobronchial lesion (Grade 2C)**.**

Remark: Autofluorescence bronchoscopy (AFB) may be used as an adjunct to WLB when available.

3.2.1.1. For patients with known severe dysplasia or CIS in the central airways on biopsy, follow-up WLB is suggested (Grade 2C)**.**

Remark: AFB may be used when available. The timing and duration of follow-up are unknown.

Remark: Physicians and patients should discuss potential risk and benefits of follow-up bronchoscopy.

3.3.3.1. For patients with early lung cancer undergoing resection, WLB is suggested for the delineation of tumor margins and the assessment of synchronous lesions (Grade 2C)**.**

Remark: AFB or narrow band imaging may be used when available.

3.4.1.1. For patients being considered for curative endobronchial therapy to treat CIS or early central lung cancer, WLB is suggested over routine use of AFB (Grade 2C)**.**

4.6.1. For patients with superficial limited mucosal lung cancer in the central airway who are not candidates for surgical resection, endobronchial

treatment with photodynamic therapy, brachytherapy, cryotherapy, or electrocautery is recommended (Grade 1C)**.**

16.0 Treatment of Stage I and II Non-small Cell Lung Cancer

Although the mainstay of treatment of stage I or II NSCLC remains surgical resection, significant advances in understanding nuances have occurred. An extensive body of data demonstrates better outcomes when resection is performed by surgeons with specialty training, or when done in a higher-volume center or in a teaching facility. However, the understanding is lacking of exactly what processes lead to these outcomes, making it difficult to disseminate successful practices to improve outcomes more broadly. Data have accumulated regarding video-assisted thoracic surgery resection, making a minimally invasive approach to resection the preferred technique, which should include at least a systematic lymph node sampling. Lobectomy remains the procedure of choice; sublobar resection is reserved for patients unable to tolerate lobectomy, those with major competing causes of death, or those with a predominantly ground-glass opacity < 2 cm in diameter. Details of the sublobar resection are probably important but are incompletely defined. A margin of > 2 cm, or, for smaller tumors, larger than the diameter of the tumor, appears to be important. Anatomic sublobar resection (ie, segmentectomy) appears to result in better outcomes than a wedge resection. A sublobar resection is recommended over nonsurgical therapy in patients able to tolerate this, but nonsurgical ablative treatment is preferred over no therapy in those who cannot.

The role of adjuvant chemotherapy is firmly established for patients with stage II NSCLC. Evaluation of the long-term results of RCTs does not support the use of adjuvant chemotherapy for stage I NSCLC. Adjuvant radiotherapy (RT) is not beneficial for completely resected stage I,II NSCLC.

Summary of Recommendations: Stage I and II Non-small Cell Lung Cancer

General Approach

2.1.1. For patients with clinical stage I and II non-small cell lung cancer (NSCLC) and no medical contraindications to operative intervention, surgical resection is recommended (Grade 1B)**.**

2.1.2. For patients with clinical stage I and II NSCLC, it is suggested that they be evaluated by a thoracic surgical oncologist or a multidisciplinary team even if the patients are considered for nonsurgical therapies such as percutaneous ablation or stereotactic body radiation therapy (Grade 2C)**.**

Remark: At a minimum, we suggest that multidisciplinary teams have representatives from pulmonary medicine, thoracic surgery, medical oncology, radiation oncology, radiology, and pathology.

2.2.4.1. For patients with clinical stage I or II NSCLC and who are medically fit, it is recommended that they be treated by a board certified thoracic surgeon with a focus on lung cancer (Grade 1B)**.**

Remark: Ideally general thoracic surgical procedures would constitute $> 75\%$ of the thoracic surgeon's clinical practice, and involve an average of ≥ 4 anatomic surgical resections performed per month at the center to maintain the experience and smooth function of the care teams.

Lobectomy: Surgical Issues

3.2.1. For patients with clinical stage I NSCLC, a minimally invasive approach such as video-assisted thoracic surgery (thoracoscopy) is preferred over a thoracotomy for anatomic pulmonary resection and is suggested in experienced centers (Grade 2C).

3.3.4.1. For patients with clinical stage I and II NSCLC, systematic mediastinal lymph node sampling or dissection at the time of anatomic resection is recommended over selective or no sampling for accurate pathologic staging (Grade 1B)**.**

3.3.4.2. For patients with clinical stage I NSCLC undergoing anatomic resection who have undergone systematic hilar and mediastinal lymph node staging showing intraoperative N0 status, the addition of a mediastinal lymph node dissection does not provide a survival benefit and is not suggested (Grade 2A)**.**

3.3.4.3. For patients with clinical stage II NSCLC undergoing anatomic resection, mediastinal lymph node dissection may provide additional survival benefit over mediastinal lymph node sampling and is suggested (Grade 2B)**.**

3.5.1. For patients with clinical stage I or II central NSCLC in whom a complete resection can be achieved, a sleeve or bronchoplastic resection is suggested over a pneumonectomy (Grade 2C)**.**

Sublobar Resection

4.3.1. For patients with clinical stage I and II NSCLC who are medically fit for surgical resection, a lobectomy rather than sublobar resection is recommended (Grade1B)**.**

4.8.1. For patients with clinical stage I NSCLC who may tolerate operative intervention but not a lobar resection due to decreased pulmonary function or comorbid disease, sublobar resection is recommended over nonsurgical therapy (Grade 1B)**.**

Remark: Regardless of whether patients undergo wedge or segmentectomy, adequate margins should be achieved.

Remark: Sublobar resection should involve an anatomic segmentectomy whenever possible.

4.8.2. During sublobar resection of solid tumors in compromised patients, it is recommended that margins greater than the maximal tumor diameter for lesions less than 2 cm should be achieved; for tumors larger than 2 cm at least 2 cm gross margins should be sought to minimize the likelihood of a positive margin and/or local recurrence (Grade 1C)**.**

Remark: The data regarding the appropriate gross margin necessary to achieve a pathologically negative margin or minimize local recurrence in larger tumors (>2 cm) is less well established. It may be that larger margins for larger tumors are required.

Remark: In patients undergoing resection of solid stage cI NSCLC in whom the ability to achieve an adequate margin is compromised, the addition of brachytherapy mesh to sublobar resection may improve local control.

4.10.1. In patients with major increased risk of perioperative mortality or competing causes of death (due to age related or other co-morbidities), an anatomic sublobar resection (segmentectomy) over a lobectomy is suggested (Grade 2C)**.**

4.12.1. For patients with a clinical stage I predominantly ground glass opacity (GGO) lesion $\leq$2 cm, a sublobar resection with negative margins is suggested over lobectomy (Grade 2C)**.**

Nonresectional Treatment Approaches

5.3.1. For patients with clinical stage I NSCLC who cannot tolerate a lobectomy or segmentectomy, stereotactic body radiation therapy (SBRT) and surgical wedge resection are suggested over no therapy (Grade 2C)**.**

Remark: Surgical resection has the potential benefit of definitive histologic analysis (eg, adenocarcinoma subtype) and pathologic nodal information. In compromised patients for whom such information would not change management SBRT is a preferred option. Also, SBRT is favored in patients for whom an adequate margin in unlikely with a surgical wedge resection.

Remark: Radiofrequency ablation may also be considered for peripheral tumors <3 cm in inoperable patients.

Adjuvant Therapy

6.1.5.1. For patients with completely resected pathologic stage IA,B NSCLC, it is recommended that postoperative chemotherapy not be used (outside of a clinical trial) (Grade 1B)**.**

6.1.5.2. For patients with completely resected pathologic stage IIA,B(N1) NSCLC and good performance status, postoperative platinum-based chemotherapy is recommended (Grade 1A)**.**

Remark: No clear recommendation is possible regarding adjuvant chemotherapy for larger tumors without lymph node involvement.

6.2.5.1. For patients with completely resected pathologic stage I NSCLC, it is recommended that postoperative radiation therapy should not be used (Grade 1A)**.**

6.2.5.2. For patients with completely resected pathologic stage II NSCLC, it is suggested that postoperative radiation therapy should not be used (Grade 2A)**.**

6.2.5.3. For patients with stage I and II NSCLC and a positive bronchial margin (R1 resection), postoperative radiation therapy is suggested (Grade 2C)**.**

17.0 Treatment of Stage III Non-small Cell Lung Cancer

The management of stage III NSCLC is among the most confusing and controversial areas, despite the many papers published on the subject. In part, this stems from the fact that stage III involves a broad spectrum of disease burden, from patients with extensive mediastinal infiltration, others with discrete mediastinal node involvement, and those only found to have a small focus of nodal involvement after resection

despite negative preoperative invasive mediastinal staging. For some questions there are clear data from RCTs; in other areas the data are more limited and difficult to interpret because of many confounding factors. This article of the ACCP Lung Cancer Guidelines does a good job of summarizing the data in areas of clarity as well as providing a structure that more clearly demonstrates the factors at play in the more confusing areas to allow a more clear interpretation of what we know and what we can only speculate about.

Extensive data from RCTs demonstrate that for the majority of patients with N2,3 node involvement (who have a good performance status [PS] and minimal weight loss), aggressive curative-intent treatment is indicated using a combination of chemotherapy and RT, delivered concurrently. The role of induction or consolidation chemotherapy or targeted therapy before or following definitive chemoradiation for stage III NSCLC is unclear and requires further study. The RT should involve once-daily fractionation and a total dose of 60 to 66 Gy; further dose escalation or prophylactic cranial irradiation is not supported by the data. Details of treatment and management of toxicities are important and best addressed in a multidisciplinary team setting. Tailoring the aggressiveness and the intent of treatment (curative or palliative) in patients with comorbidities, weight loss, or impaired PS requires judgment and consideration of patients' values and preferences.

For patients with discrete N2 node involvement, data from RCTs show similar outcomes with either chemotherapy and RT or neoadjuvant (preoperative) treatment followed by resection. Arguments that particular subgroups of patients benefit from a trimodality approach are confounded and not supported by the available data. Various markers with prognostic value have been identified (eg, response to neoadjuvant therapy), but there are no data that demonstrate these have predictive value of a benefit from surgical resection (see Fig 8 in Ramnath et al,[4] in LC III). Patient values and preferences should play a role in decision-making. Management of toxicities, particularly perioperative mortality, is critical, and a trimodality approach should be undertaken by an experienced team that tracks and manages its outcomes. Trimodality treatment should be planned at the outset by a multidisciplinary team.

For N2 involvement discovered during or after primary surgical resection for clinical stage I,II NSCLC, the key prognostic factor is the diligence with which preoperative staging was conducted. If preoperative staging was thorough, resection should be completed (provided an R0 resection is possible). RCT data support the use of adjuvant chemotherapy; the role or adjuvant RT is unclear.

Summary of Recommendations: Stage III NSCLC

Infiltrative Stage III (N2,3) Non-small Cell Lung Cancer

2.3.1. In patients with infiltrative stage III (N2,3) non-small cell lung cancer (NSCLC) and performance status 0-1 being considered for curative-intent treatment, radiotherapy alone is not recommended (Grade 1A)**.**

2.3.2. In patients with infiltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, combination platinum-based chemotherapy and radiotherapy (60-66 Gy) are recommended (Grade 1A)**.**

Remark: Dose escalation of radiotherapy is not recommended (except in a clinical trial).

Remark: For patients with stage III NSCLC, once daily thoracic radiotherapy plus platinum-based doublet chemotherapy is recommended.

2.3.3. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy (Grade 1A)**.**

Remark: We cannot currently recommend for or against induction chemotherapy (ie, before) concurrent chemoradiotherapy, and patients should be referred for clinical trials to answer this question.

Remark: We cannot currently recommend for or against consolidation chemotherapy (ie, after) concurrent chemoradiotherapy, and patients should be referred to clinical trials to answer this question.

2.3.4. In patients with infiltrative stage III (N2,3) NSCLC with a complete response after treatment with concurrent chemoradiotherapy, we suggest that prophylactic cranial irradiation should not be given (outside of a clinical trial) (Grade 2C)**.**

2.3.5. In patients with infiltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, treatment with neoadjuvant (induction) chemotherapy or chemoradiotherapy followed by surgery is not recommended (Grade 1C)**.**

2.3.6. In patients with infiltrative stage III (N2,3) NSCLC and performance status 2 or those with substantial weight loss (> 10%), concurrent

chemoradiotherapy is suggested but with careful consideration of the potential risks and benefits (Grade 2C)**.**

Remark: Patient-related and tumor-related factors can influence the balance of risks vs benefits; patient preferences should also play a significant role.

2.3.7. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, a platinum-based doublet chemotherapy is suggested (Grade 2C)**.**

Remark: An optimal agent to be combined with platinum cannot be defined; one should choose a regimen with an acceptable toxicity profile for the individual patient among several combinations that have demonstrated activity when used concurrently with radiation in stage III NSCLC.

2.3.8. In patients with symptomatic infiltrative stage III (N2,3) NSCLC and either performance status 3-4, comorbidities, or disease too extensive to treat with curative intent, palliative radiotherapy is recommended. The fractionation pattern should be chosen based on the physician's judgment and patient's needs (Grade 1C)**.**

Discrete Mediastinal Node Involvement

3.5.1. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), we recommend the treatment plan should be made with the input from a multidisciplinary team (Grade 1C)**.**

Remark: The multidisciplinary team should include at a minimum a thoracic surgeon, medical oncologist, and radiation oncologist.

Remark: The decision should be made collaboratively by the entire team so as to reflect collective judgment.

Remark: The plan should include the entire proposed treatment, including plans contingent on the results of reevaluations (ie, initial treatment response or nonresponse), not simply a first step.

3.5.2. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), either definitive chemoradiation therapy or induction therapy followed by surgery is recommended over either surgery or radiation alone (Grade 1A)**.**

Remark: As the data do not permit the selection of one option or the other as superior, patient values and preferences should factor significantly in the decision.

Remark: All multimodality therapy should be performed in centers with experienced multidisciplinary teams that track their relevant clinical outcomes and are capable of minimizing and managing the toxicity and complications involved.

Remark: Further identification of patients more likely to benefit from surgical resection after induction therapy is not possible based upon pretreatment characteristics. Decisions to pursue surgical resection after induction therapy should be made prior to initiation of any therapy.

3.5.3. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), primary surgical resection followed by adjuvant therapy is not recommended (except as part of a clinical trial) (Grade 1C)**.**

Occult N2 Involvement Discovered at Resection Despite Thorough Preoperative Staging (Stage IIIA)

Surgical Considerations

4.5.1. In patients with NSCLC undergoing surgical resection, systematic mediastinal lymph node sampling or complete mediastinal lymph node dissection is recommended (Grade 1B)**.**

Remark: At least a systematic sampling is needed to accurately assess the pathologic stage; this is critical to direct adjuvant therapy.

Remark: It is unclear whether lymphadenectomy offers a survival benefit over systematic sampling, but in general, lymphadenectomy is suggested if there is evidence of N2 node involvement.

4.5.2. In patients with NSCLC who have incidental (occult) N2 disease (IIIA) found at surgical resection despite thorough preoperative staging and in whom complete resection of the lymph nodes and primary tumor is technically possible, completion of the planned lung resection and mediastinal lymphadenectomy is suggested (Grade 2C)**.**

Remark: This recommendation assumes that staging for distant disease and invasive preoperative mediastinal staging according to guidelines have been carried out.

Remark: In a patient who has not received preoperative staging despite clinical suspicion of N2 node involvement (ie, enlarged on CT, uptake on PET, or negative CT and PET but with a central tumor or N1 involvement), the operation should be aborted and staging completed if N2 disease is identified intraoperatively.

Adjuvant Therapy

4.5.3. In patients with resected NSCLC (R0) who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and who have good performance status, adjuvant platinum-based chemotherapy is recommended (Grade 1A)**.**

Remark: We suggest this should typically involve a doublet regimen for 3 to 4 cycles initiated within 12 weeks.

4.5.4. In patients with R0 resected NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging, sequential adjuvant radiotherapy is suggested when concern for a local recurrence is high (Grade 2C)**.**

Remark: Adjuvant postoperative radiotherapy reduces the incidence of local recurrence, but it is unclear whether it improves survival.

Remark: Adjuvant chemotherapy should be used initially followed by radiotherapy; concurrent chemoradiotherapy is not recommended (except in a clinical trial).

4.5.5. In patients with NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and were incompletely resected (R1,2), combined postoperative concurrent chemotherapy and radiotherapy is suggested (Grade 2C)**.**

18.0 Treatment of Stage IV NSCLC

Significant advances continue to be made in the treatment of stage IV NSCLC; although cure is not possible, significant palliation in terms of improved quality of life (QOL) and duration of survival can be accomplished. Significant clarity has been achieved in terms of which agents to use in very specific situations. The choice of chemotherapy is directed to a large extent by the histologic type of NSCLC, making it all the more important to have adequate material for a detailed diagnosis. Furthermore, targeted therapy is the first-line treatment of choice for patients with an epidermal growth factor receptor mutation.

Maintenance chemotherapy has been established to be useful in many situations, with the details of which agents being determined by the histologic type and the choice of the initial regimen. Furthermore, the safety and efficacy of chemotherapy have been extended. Vascular endothelial growth factor inhibitors are safe and useful in patients initially believed to potentially be at greater risk for toxicity. The value of second-line chemotherapy has been further strengthened. Finally, patient groups believed to be poor candidates for more aggressive treatment based on age, PS, or other criteria have been shown to benefit from doublet chemotherapy without undue toxicity in some situations.

Summary of Recommendations: Stage IV NSCLC

General Approach

2.1.1. In patients with a good performance status (PS) (ie, Eastern Cooperative Oncology Group [ECOG] level 0 or 1) and stage IV non-small cell lung cancer (NSCLC), a platinum-based chemotherapy regimen is recommended based on the survival advantage and improvement in quality of life (QOL) over best supportive care (BSC). (Grade 1A)**.**

Remark: Patients may be treated with several chemotherapy regimens (carboplatin and cisplatin are acceptable, and can be combined with paclitaxel, docetaxel, gemcitabine, pemetrexed or vinorelbine)

2.2.2. In patients with stage IV NSCLC and a good PS, two-drug combination chemotherapy is recommended. The addition of a third cytotoxic chemotherapeutic agent is not recommended because it provides no survival benefit and may be harmful. (Grade 1A)**.**

First Line Treatment

3.1.1.1. In patients receiving palliative chemotherapy for stage IV NSCLC, it is recommended that the choice of chemotherapy is guided by the histologic type of NSCLC (Grade 1B)**.**

Remark: The use of pemetrexed (either alone or in combination) should be limited to patients with nonsquamous NSCLC.

Remark: Squamous histology has not been identified as predictive of better response to any particular chemotherapy agent.

3.2.1.1. In patients with known epidermal growth factor receptor (EGFR) mutations and stage IV NSCLC, first-line therapy with an EGFR tyrosine kinase inhibitor (gefitinib or erlotinib) is recommended based on superior response rates, progression-free survival and toxicity profiles compared with platinum-based doublets (Grade 1A)**.**

3.3.1.1. Bevacizumab improves survival combined with carboplatin and paclitaxel in a clinically

selected subset of patients with stage IV NSCLC and good PS (nonsquamous histology, lack of brain metastases, and no hemoptysis). In these patients, addition of bevacizumab to carboplatin and paclitaxel is recommended (Grade 1A)**.**

3.3.1.2. In patients with stage IV non-squamous NSCLC and treated, stable brain metastases, who are otherwise candidates for bevacizumab therapy, the addition of bevacizumab to first-line, platinum-based chemotherapy is a safe therapeutic option (Grade 2B)**.**

Remark: No recommendation can be given about the use of bevacizumab in patients receiving therapeutic anticoagulation or with an ECOG PS of 2.

Maintenance Therapy

3.4.4.1. In patients with stage IV non-squamous NSCLC who do not experience disease progression after 4 cycles of platinum-based therapy (which does not include pemetrexed), treatment with switch maintenance pemetrexed is suggested (Grade 2B)**.**

3.4.4.2. In patients with stage IV NSCLC, switch maintenance therapy with chemotherapy agents other than pemetrexed has not demonstrated an improvement in overall survival and is not recommended (Grade 1B)**.**

3.4.4.3. In patients with stage IV non-squamous NSCLC who do not experience disease progression after 4 cycles of platinum-pemetrexed therapy, continuation pemetrexed maintenance therapy is suggested (Grade 2B)**.**

3.4.4.4. In patients with stage IV NSCLC who do not experience disease progression after 4 cycles of platinum-based double agent chemotherapy, maintenance therapy with erlotinib is suggested (Grade 2B)**.**

3.5.1.1. In patients with stage IV NSCLC the addition of cetuximab in combination with chemotherapy is suggested not to be used outside of a clinical trial (Grade 2B)**.**

Second and Third Line Treatment

4.1.1. In patients with stage IV NSCLC who have good PS (ECOG 0-2), second-line treatment with erlotinib or docetaxel (or equivalent single-agent such as pemetrexed) is recommended (Grade 1A)**.**

4.1.2. In patients with stage IV NSCLC who have good PS (ECOG 0-2), third-line treatment with erlotinib improves survival compared with BSC and is recommended (Grade 1B)**.**

Remark: No recommendation can be given about the optimal chemotherapeutic strategy in patients with stage IV NSCLC who have received three prior regimens for advanced disease.

Special Patient Populations and Considerations

5.1.1. In elderly patients (age ≥ 70–79 years) with stage IV NSCLC who have good PS and limited co-morbidities, treatment with the two drug combination of monthly carboplatin and weekly paclitaxel is recommended (Grade 1A)**.**

Remark: In patients with stage IV NSCLC who are 80 years or over, the benefit of chemotherapy is unclear and should be decided based on individual circumstances.

6.2.1. For patients with stage IV NSCLC with a PS of 2 in whom the PS is caused by the cancer itself, double agent chemotherapy is suggested over single agent chemotherapy (Grade 2B)**.**

6.2.2. In patients with stage IV NSCLC who are an ECOG PS of 2 or greater, it is suggested not to add bevacizumab to chemotherapy outside of a clinical trial (Grade 2B)**.**

7.1.1. In patients with stage IV NSCLC early initiation of palliative care is suggested to improve both QOL and duration of survival (Grade 2B)**.**

19.0 Special Treatment Issues in NSCLC

There are several relatively unusual presentations of NSCLC for which the anatomic and biologic issues dictate a different approach. This includes patients with Pancoast tumors, T4N0,1M0 central tumors, chest wall involvement, additional pulmonary tumor nodules, synchronous and metachronous second primary lung cancers, multifocal lung cancer, and solitary metastases.

Patients with Pancoast tumors appear to have the best outcomes after preoperative chemoradiotherapy and surgical resection, although preoperative RT is a reasonable alternative. Advances in surgical techniques allow a complete resection to be achieved in specialized centers in situations traditionally considered unresectable. Similarly, good results can be achieved in the relatively small number of patients with a T4 (due to local invasion) N0,1M0 tumor by surgical resection in specialized centers.

Patients with a lung cancer and an additional malignant nodule are difficult to categorize, and the current stage classification rules are ambiguous. Such patients should be evaluated by an experienced multidisciplinary team to determine whether the additional lesion represents a second primary lung cancer or an additional tumor nodule corresponding to the dominant cancer. A careful search for metastatic disease is warranted before assuming two malignant foci represent synchronous primary cancers, but then management as dictated by each tumor individually is probably best, provided the patient has adequate reserve. Additional pulmonary nodules in the same lobe ($T3_{Satell}$) are probably best managed by lobectomy, whereas the management of additional nodules in other lobes is less well defined.

Patients with an isolated brain or adrenal metastasis should undergo careful investigation for other distant or mediastinal metastases. If such additional metastases are not found, a curative-intent treatment strategy involving definitive local therapy for the primary and the metastasis as well as adjuvant chemotherapy appears to be justified.

Summary of Recommendations: Special Treatment Issues in NSCLC

Pancoast Tumor

2.4.1. In patients with a Pancoast tumor, it is recommended that a tissue diagnosis be obtained prior to the initiation of therapy (Grade 1C)**.**

2.4.2. In patients with a Pancoast tumor being considered for curative-intent surgical resection, an MRI of the thoracic inlet and brachial plexus is recommended to characterize possible tumor invasion of vascular structures or the extradural space (Grade 1C)**.**

2.4.3. In patients with a Pancoast tumor being considered for curative resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended (Grade 1C)**.**

Remark: Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection.

2.4.4. In patients with a potentially resectable Pancoast tumor (and good performance status), it is suggested that preoperative concurrent chemoradiotherapy is given prior to resection (Grade 2B)**.**

2.4.5. In patients undergoing resection of a Pancoast tumor, it is recommended that every effort be made to achieve a complete resection (Grade 1B)**.**

2.4.6. In patients undergoing resection of a Pancoast tumor, it is suggested that the resection consist of a lobectomy (instead of a nonanatomic wedge resection), as well as the involved chest wall structures (Grade 2C)**.**

2.4.7. In patients with an unresectable, nonmetastatic Pancoast tumor who have good performance status, definitive concurrent chemotherapy and radiotherapy are suggested (Grade 2C)**.**

2.4.8. In patients with Pancoast tumors who are not candidates for curative-intent treatment, palliative radiotherapy is suggested (Grade 2B)**.**

Tumors Invading Chest Wall

3.3.1. In patients with a non-small cell lung cancer (NSCLC) invading the chest wall who are being considered for curative-intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are suggested (Grade 2C)**.**

3.3.2. In patients with an NSCLC invading the chest wall, involvement of mediastinal nodes and/or metastatic disease represent a contraindication to resection, and definitive chemoradiotherapy is suggested for these patients (Grade 2C)**.**

3.3.3. At the time of resection of a tumor invading the chest wall, it is recommended that every effort be made to achieve a complete resection (Grade 1B)**.**

Central T4 N0,1 M0 Tumors

4.3.1. In patients with a clinical T4 N0,1 M0 NSCLC being considered for curative resection, it is recommended that extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) be undertaken (Grade 1C)**.**

Remark: Metastatic disease represents a contraindication to resection.

4.3.2. In patients with a clinical T4 N0,1 M0 NSCLC without distant metastases being considered for curative resection, it is suggested

that invasive mediastinal staging be undertaken. Involvement of mediastinal nodes represents a contraindication to primary resection (Grade 2C)**.**

Remark: Preoperative chemotherapy and resection has resulted in long-term survival in experienced centers in patients with mediastinal nodal involvement.

4.3.3. In patients with a clinical T4 N0,1 M0 NSCLC being considered for curative resection, it is suggested that resection be undertaken only at a specialized center (Grade 2C)**.**

Second Primary Lung Cancer

5.2.4.1. In patients with two foci typical of a primary lung cancer (either proven or suspected, ie, solid, spiculated masses), it is suggested that identification of these as second primary lung cancers (either synchronous or metachronous) should be based on the judgment of a multidisciplinary team, taking into account clinical, radiologic, and (if available) tumor cytologic/histologic features (Grade 2C)**.**

Remark: The multidisciplinary team should include a thoracic radiologist, pulmonologist, thoracic surgeon, and pathologist.

5.2.4.2. In patients with two primary NSCLCs (synchronous or metachronous) being considered for curative surgical resection, invasive mediastinal staging and extra-thoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended (Grade 1B)**.**

Remark: Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection.

5.2.4.3. In patients (not suspected of having a second focus of cancer) who are found intraoperatively to have a second cancer in a different lobe, resection of each lesion is suggested, provided the patient has adequate pulmonary reserve and there is no N2 nodal involvement (Grade 2C)**.**

Additional Tumor Nodules in the Same Lobe ($T3_{Satell}$)

5.3.2.3.1. In patients with suspected or proven lung cancer and an additional (suspected) tumor nodule within the same lobe, it is recommended that no further diagnostic workup of the additional nodule is undertaken (Grade 1B)**.**

5.3.2.3.2. In patients with an additional (suspected) tumor nodule within the same lobe as a suspected or proven primary lung cancer, it is recommended that evaluation of extrathoracic metastases and confirmation of the mediastinal node status should be carried out as dictated by the primary lung cancer alone and not modified due to the presence of the additional lesion (Grade 1C)**.**

5.3.2.3.3. In patients with NSCLC and an additional focus of cancer within the same lobe (and no mediastinal or distant metastases), resection via a lobectomy is the recommended treatment (Grade 1B)**.**

Ipsilateral Different Lobe Tumor Nodules ($T4_{Ipsi\ Nod}$)

5.3.3.3.1. In patients with suspected or proven lung cancer and an ipsilateral different lobe nodule(s), it is recommended that the judgment of a multidisciplinary team should reasonably exclude the possibility that this represents a benign lesion or a synchronous primary lung cancer, taking into account clinical, radiologic, and (if available) tumor cytologic/histologic features (Grade 1C)**.**

Remark: The multidisciplinary team should include a thoracic radiologist, pulmonologist, thoracic surgeon, and pathologist at a minimum.

5.3.3.3.2. In patients with an ipsilateral different lobe tumor nodule(s), it is suggested that evaluation for possible extrathoracic metastases (eg, PET and brain MRI/CT) should be carried out (Grade 2C)**.**

Remark: The presence of distant metastases indicates the pulmonary nodule most likely represents metastatic (M1b) disease.

5.3.3.3.3. In patients with an ipsilateral different lobe tumor nodule(s), it is suggested that invasive evaluation to rule out mediastinal node involvement should be carried out (Grade 2C)**.**

Remark: Such involvement rules out curative-intent treatment.

5.3.3.3.4. In patients with NSCLC and an ipsilateral different lobe tumor nodule(s) (and no mediastinal or distant metastases), resection of each lesion is recommended, provided the patient has adequate pulmonary reserve (Grade 1B)**.**

Contralateral Lobe Tumor Nodules ($M1a_{Contr\ Nod}$)

5.3.4.3.1 In patients with a contralateral lobe tumor nodule(s), it is suggested that evaluation of extrathoracic metastases (eg, PET and brain

MRI/CT) and invasive evaluation to rule out mediastinal node involvement should be carried out (Grade 2C)**.**

Remark: Such involvement represents a contraindication curative-intent treatment.

5.3.4.3.2. In patients with NSCLC and a contralateral lobe tumor nodule(s) (and no mediastinal or distant metastases), resection of each lesion is suggested, provided the patient has adequate pulmonary reserve (Grade 2C)**.**

Multifocal Lung Cancer

5.4.4.1. In patients with multiple lesions that are at least partially ground glass and are suspected to be malignant, it is suggested that these are classified as multifocal lung cancer (MFLC) (Grade 2C)**.**

5.4.4.2. In patients with suspected or proven MFLC who have a negative clinical evaluation and normal mediastinum by CT, it is suggested that distant and mediastinal staging are not routinely necessary (Grade 2C)**.**

5.4.4.3. In patients with suspected or proven MFLC, it is suggested that curative-intent treatment should be pursued (Grade 2C)**.**

5.4.4.4. In patients with suspected or proven MFLC, it is suggested that sublobar resection of all lesions suspected of being malignant be performed, if feasible (Grade 2C)**.**

Isolated Brain Metastasis

6.3.1. In patients with an isolated brain metastasis from NSCLC being considered for curative treatment, invasive mediastinal staging and extrathoracic imaging (either whole-body PET or abdominal CT plus bone scan) are suggested (Grade 2C)**.**

Remark: Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to curative-intent treatment.

6.3.2. In patients with no other sites of metastases and a *synchronous* resectable N0,1 primary NSCLC, resection or radiosurgical ablation of an isolated brain metastasis is recommended (as well as resection of the primary tumor) (Grade 1C)**.**

6.3.3. In patients with no other sites of metastases and a previously completely resected primary NSCLC (*metachronous* presentation), resection or radiosurgical ablation of an isolated brain metastasis is recommended (Grade 1C)**.**

6.3.4. In patients who have undergone a curative resection of an isolated brain metastasis, adjuvant whole-brain radiotherapy is suggested (Grade 2B)**.**

Remark: Adjuvant chemotherapy is reasonable in patients with a good performance status with the goal of decreasing the incidence of brain recurrences, although no studies have specifically addressed this.

6.3.5. In patients who have undergone a curative resection of an isolated brain metastasis, adjuvant chemotherapy is suggested (Grade 2B)**.**

Remark: Adjuvant chemotherapy is reasonable in patients with a good performance status, although no studies have specifically addressed this.

Isolated Adrenal Metastasis

7.2.1. In patients with an isolated adrenal metastasis from NSCLC being considered for curative-intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are suggested (Grade 2C)**.**

Remark: Involvement of mediastinal nodes and/or other sites of distant metastases represent a contraindication to resection.

7.2.2. In patients with a *synchronous* resectable N0,1 primary NSCLC and an isolated adrenal metastasis with no other sites of metastases, resection of the primary tumor and the adrenal metastasis is recommended (Grade 1C)**.**

7.2.3. In patients with no other sites of metastases and a previously completely resected primary NSCLC (*metachronous* presentation), resection of an isolated adrenal metastasis is recommended (Grade 1C)**.**

7.2.4. In patients who have undergone a curative resection of an isolated adrenal metastasis, adjuvant chemotherapy is suggested (Grade 2B)**.**

Remark: Adjuvant chemotherapy is reasonable in patients with a good performance status, although no studies have specifically addressed this.

20.0 Treatment of Small Cell Lung Cancer

The stage classification of SCLC should now include TNM staging. Definition of the stage is improved

through the use of PET imaging, which results in both upstaging and downstaging of some patients. It is well established that for limited-stage (LS) SCLC concurrent chemoradiotherapy is best, with the radiation being included early in the treatment course. A platinum agent combined with a topoisomerase inhibitor is standard, although irinotecan can also be used in patients with extensive-stage (ES) disease. The search for better chemotherapy agents or treatment combinations has not yielded a major breakthrough. Although almost one-fourth of patients with LS-SCLC are cured, and marked palliation can be achieved in ES-SCLC, further advances are clearly needed.

Summary of Recommendations: Small Cell Lung Cancer

2.4.1 In patients with small cell lung cancer (SCLC) (proven or suspected), a staging evaluation is recommended consisting of a medical history and physical examination, CBC and comprehensive chemistry panel with renal and hepatic function tests, CT of the chest and abdomen with intravenous contrast or CT scan of the chest extending through the liver and adrenal glands, MRI or CT of the brain, and bone scan (Grade 1B)**.**

2.4.2. In patients with clinically limited-stage (LS)-SCLC, PET imaging is suggested (Grade 2C)**.**

Remark: If PET is obtained, then bone scan may be omitted.

2.4.3. In patients with SCLC, it is recommended that both the Veterans Administration system (LS vs extensive stage [ES]) and the American Joint Committee on Cancer/International Union Against Cancer seventh edition system (TNM) should be used to classify the tumor stage (Grade 1B)**.**

3.1.1. In patients with clinical stage I SCLC, who are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head MRI/CT and PET or abdominal CT plus bone scan) is recommended (Grade 1B)**.**

3.1.2. In patients with clinical stage I SCLC after a thorough evaluation for distant metastases and invasive mediastinal stage evaluation, surgical resection is suggested over non-surgical treatment (Grade 2C)**.**

3.1.3. In patients with stage I SCLC who have undergone curative-intent surgical resection, platinum-based adjuvant chemotherapy is recommended (Grade 1C)**.**

4.3.1. In patients with LS-SCLC, early chemoradiotherapy, with accelerated hyper-fractionated radiation therapy (twice-daily treatment) concurrently with platinum-based chemotherapy, is recommended (Grade 1B)**.**

4.3.2. In patients with LS- or ES-SCLC who achieve a complete or partial response to initial therapy, prophylactic cranial irradiation is recommended (Grade 1B)**.**

Remark: The regimen of 25 Gy in 10 daily fractions has the greatest supporting data for safety and efficacy.

4.3.3. In patients with ES-SCLC who have completed chemotherapy and achieved a complete response outside the chest and complete or partial response in the chest, a course of consolidative thoracic radiotherapy (TRT) is suggested (Grade 2C)**.**

6.1.1. In patients with either LS- or ES-SCLC, four to six cycles of platinum-based chemotherapy with either cisplatin or carboplatin plus either etoposide or irinotecan is recommended over other chemotherapy regimens (Grade 1A)**.**

7.1.1. In patients with relapsed or refractory SCLC, the administration of second-line, single-agent chemotherapy is recommended (Grade 1B)**.**

Remark: Reinitiation of the previously administered first-line chemotherapy regimen is recommended in patients who relapse $>$ 6 months from completion of initial chemotherapy. Enrollment in a clinical trial is encouraged.

8.1.1. In elderly patients with LS-SCLC and good performance status (PS) (Eastern Cooperative Oncology Group [ECOG] 0-2), treatment with platinum-based chemotherapy plus TRT is suggested, with close attention to management of treatment-related toxicity (Grade 2B)**.**

8.1.2. In elderly patients with ES-SCLC and good PS (ECOG 0-2), treatment with carboplatin-based chemotherapy is suggested (Grade 2A)**.**

8.1.3. In elderly patients with SCLC and poor PS, treatment with chemotherapy is suggested if the poor PS is due to SCLC (Grade 2C)**.**

21.0 Complementary Therapies and Integrative Medicine in Lung Cancer

Complementary therapies are rational, evidence-based techniques that alleviate physical and emotional

symptoms, improve QOL, and may improve adherence to oncology treatment regimens. Integrative medicine describes the adjunctive role played by complementary therapies as part of multidisciplinary mainstream cancer care. This is an area that most lung cancer clinicians know relatively little about. The degree to which these techniques have been subjected to careful scientific evaluation surprises most people. Because these therapies are frequently used by patients, and many have demonstrated efficacy, this topic represents a gap in knowledge for most clinicians that deserves attention. This article provides a systematic review and critical summary of the data for various complementary therapies.

Mind-body modalities focus on the interactions among the brain, mind, body, and behavior, and include meditation, mindfulness-based stress reduction, yoga, tai chi, qigong, psychosocial, hypnosis, and mind-body relaxation techniques. RCT data demonstrate benefits in managing chronic pain, chemotherapy-induced nausea and vomiting, fatigue, mood disturbances, and QOL. Massage therapy in addition to usual measures has been shown in RCTs to have an effect in reducing pain and anxiety. Acupuncture can reduce pain and treatment-related symptoms of neuropathy, nausea, and vomiting. Attention to diet and exercise may also have benefits, but the data are less robust.

It is important to recognize that these complementary therapies are done in an integrated fashion with other "standard" interventions, such as drug management of pain, anxiety, nausea, and vomiting. It is also worth noting again the amount of formal research that has been done to define the role of complementary therapies. This article is a succinct review that is worth reading for clinicians involved with caring for patients with lung cancer.

Summary of Recommendations: Complementary Therapies and Integrative Medicine in Lung Cancer

2.1.1.1. It is suggested that all lung cancer patients should be asked about their interest in and usage of complementary therapies. Counseling on the benefits and risks of those therapies should be provided (Grade 2C)**.**

2.2.7.1. In lung cancer patients experiencing the symptoms, mind-body modalities are suggested as part of a multidisciplinary approach to reduce anxiety, mood disturbance, sleep disturbance, and improve quality of life (QOL) (Grade 2B)**.**

2.2.7.2. In lung cancer patients experiencing the symptoms, mind-body modalities are suggested as part of a multidisciplinary approach to reduce acute or chronic pain (Grade 2B)**.**

2.2.7.3. In lung cancer patients experiencing the symptoms, mind-body modalities are suggested as part of a multidisciplinary approach to reduce anticipatory chemotherapy-induced nausea and vomiting (Grade 2B)**.**

2.2.7.4. In lung cancer patients experiencing the symptoms, yoga, a movement-based mind-body modality is suggested as part of a multidisciplinary approach to reduce fatigue and sleep disturbance while improving mood and QOL (Grade 2B)**.**

2.3.1.1. In lung cancer patients whose anxiety or pain is not adequately controlled by usual care, addition of massage therapy performed by trained professionals is suggested as part of a multi-modality cancer supportive care program (Grade 2B)**.**

2.4.3.1. In patients awaiting pulmonary resection for suspected lung cancer with compromised lung function, supervised exercise-based pulmonary rehabilitation is suggested to improve cardiorespiratory fitness and functional capacity (Grade 2C)**.**

2.4.3.2. In post-surgical lung cancer patients with compromised lung function, supervised exercise-based pulmonary rehabilitation is suggested to improve cardiorespiratory fitness and functional capacity (Grade 2C)**.**

2.4.3.3. In advanced (inoperable) lung cancer patients receiving palliative anticancer therapy and compromised lung function, supervised exercise-based pulmonary rehabilitation is suggested to improve cardiorespiratory fitness and functional capacity (Grade 2C)**.**

2.5.3.1. In patients having nausea and vomiting from either chemotherapy or radiation therapy, acupuncture or related techniques is suggested as an adjunct treatment option (Grade 2B)**.**

2.5.3.2. In patients with cancer related pain and peripheral neuropathy, acupuncture is suggested as an adjunct treatment in patients with inadequate control of symptoms (Grade 2C)**.**

2.6.3.1. In people who might develop lung cancer a diet rich in non-starchy vegetables and fruits is suggested to reduce the risk of lung cancer (Grade 2C)**.**

2.6.3.2. In people who might develop lung cancer, limiting the consumption of a large amount of red meat and processed meat is suggested;

lower meat consumption may reduce the risk of lung cancer (Grade 2C).

2.6.3.3. In patients undergoing treatment of lung cancer who have experienced weight loss, the addition of high calorie and protein supplements (1.5 kcal/mL) as a nutritional adjunct is suggested to achieve weight stabilization (Grade 2C).

2.6.3.4. In patients with lung cancer who have sarcopenia, oral nutritional supplementation with n-3 fatty acids is suggested in order to improve the nutritional status (Grade 2C).

22.0 Follow-up and Surveillance of the Patient With Lung Cancer After Curative-Intent Therapy

Variation exists in the type and schedule of follow-up of patients who have undergone curative-intent therapy for lung cancer (see Fig 1 in Colt et al[5] in LC III). This article includes a very extensive literature search and summary of the data to define this. It is interesting that there are more data available for relatively infrequent situations and treatments (eg, endobronchial therapies, carcinoid tumors) than for the much larger cohort of patients treated with surgery, chemotherapy, or radiation for lung cancer. There are data supporting the involvement of the treating physician in the long-term follow-up and interpretation of imaging studies, and there appears to be value in including a formal QOL assessment in the follow-up. Data do not support extensive imaging or use of biomarkers for surveillance. A chest CT scan every 6 months for 2 years and annually thereafter is a reasonable schedule, although further research in this area is needed.

Summary of Recommendations: Follow-up and Surveillance of the Patient With Lung Cancer

3.5.1. In patients who have undergone curative-intent surgical resection of non-small cell lung cancer (NSCLC), it is suggested that chest CT be performed every 6 months for the first 2 years after resection and every year thereafter (Grade 2C).

3.5.2. For patients with NSCLC or carcinoid tumor who have undergone curative-intent therapy, it is recommended that the original treating physicians participate in the decision-making process during the follow-up and surveillance (Grade 1C).

3.5.3. After curative-intent therapy in patients with NSCLC or carcinoid tumors, routine surveillance with PET imaging, somatostatin receptor scintigraphy, or abdominal ultrasonography is not recommended (Grade 1C).

4.1.1. In NSCLC patients who have undergone curative-intent therapy, it is suggested that a validated health-related quality-of-life (QOL) instrument be used at baseline clinic visits and during follow-up (Grade 2C).

5.1.1. For lung cancer patients treated with curative intent, it is suggested that surveillance biomarker testing not be done (outside of clinical trials) (Grade 2C).

6.4.1. For patients with early central airway squamous cell carcinoma treated by curative-intent photodynamic therapy, it is recommended that surveillance bronchoscopy be done at 1, 2, and 3 months and thereafter at 3-month intervals during the first year, then every 6 months until 5 years (Grade 1C).

Remark: Autofluorescence bronchoscopy may be used if available (Grade 2C).

6.4.2. For patients with intraluminal bronchial carcinoid tumor who have undergone curative-intent bronchoscopic treatment using Nd:YAG or electrocautery, it is suggested that surveillance bronchoscopy be done within 6 weeks after endobronchial resection, every 6 months for 2 years, and annually thereafter (Grade 2C).

23.0 Symptom Management in Patients With Lung Cancer

Many patients with lung cancer suffer from symptoms such as pain, dyspnea, cough, neurologic symptoms, fatigue, depression, anxiety, and other psychologic difficulties. This is especially true of those with advanced disease, and a specific focus on palliation of symptoms is tremendously important for these patients. Many tools have been developed that can facilitate and streamline the process of providing palliative care.

The symptom management article provides an evidence-based structure for pain management, including which drugs and combinations to select, how to dose them, and how to gauge effectiveness and address side effects. Cough is best managed by addressing the source of the symptom whenever possible. In the absence of a treatable cause, opioids are the mainstay of treatment; steroids are reserved for inflammatory conditions, including toxicities to active treatment.

Management of bone metastases with bisphosphonates is supported by high-quality data. RT is also beneficial, with single fractionation being supported

by randomized studies. Surgical intervention is indicated in some patients with long bone metastases to maintain mobility and in patients with vertebral metastases to maintain neurologic function. The treatment of brain metastases has become more sophisticated: resection or stereotactic radiosurgery is recommended for patients with one to three foci (depending on size, location, and symptoms) and whole-brain RT is used for those with many metastases or as an adjunct reserved for those with a high risk of development of additional metastases.

Management of hemoptysis involves a combination of endobronchial procedures, RT, and interventional radiologic techniques. Similarly, the approach to pleural effusions depends on many features of the patient's presentation and condition. A framework based on the available data provides guidance on how to choose among various interventions for these conditions.

Psychologic and physical symptoms, such as depression and fatigue, are major causes of poor QOL. Data are available to guide the choice of interventions. Involvement of a dedicated palliative care team may yield the greatest benefit. Short of this, use of validated assessment tools can help facilitate development of an organized and timely approach to these issues.

The extent of data regarding optimal management of palliative care creates a need for people with in-depth knowledge. Palliative care teams are being developed in many centers, but often these services are used for end-of-life issues rather than integrated into the care from the point of diagnosis. It is important for everyone involved in actively treating these patients to have a reasonable understanding of the science and techniques available to deliver effective palliation and to develop appropriate integration of their care with that of a palliative care team.

Summary of Recommendations: Symptom Management

Pain Control

2.13.1. In patients with lung cancer who experience chronic pain, it is suggested that thorough assessment of the patient and his or her pain should be performed (Grade 2C)**.**

Remark: A patient-reported pain scale should be the principal tool to assess their pain.

Remark: Visual analog scales (VASs), numerical rating scales (NRSs) and verbal rating scales are also suggested tools for rating pain.

2.13.2. In patients with lung cancer who experience chronic pain, the use of the World Health Organization (WHO) analgesic ladder to plan treatment is suggested (Grade 2C)**.**

2.13.3. In patients with lung cancer who are being treated at all stages of the WHO analgesic ladder, it is recommended that acetaminophen and/or a nonsteroidal antiinflammatory drug (NSAID) be prescribed unless contraindicated (Grade 1A)**.**

2.13.4. In lung cancer patients with chronic pain who are taking NSAIDs and who are at high risk of gastrointestinal bleeding it is recommended that they take either misoprostol 800 mcg/day, standard dose proton pump inhibitors, or double-dose histamine H2 antagonists (Grade 1A)**.**

2.13.5. In patients with chronic neuropathic pain due to cancer, treatment with an anticonvulsant (eg, pregabalin, gabapentin or carbamazepine) or a tricyclic antidepressant (eg, amitriptyline or imipramine) is recommended (Grade 1A)**.**

2.13.6. In patients with chronic pain due to lung cancer, the use of ketamine, lidocaine 5% plasters, and cannabinoids is not recommended (Grade 1A)**.**

2.13.7. In lung cancer patients with mild to moderate chronic pain (score 3-6 on a VAS or NRS), it is recommended that codeine or dihydrocodeine be added to acetaminophen and/or NSAID (Grade 1C)**.**

2.13.8. In lung cancer patients with severe chronic pain, oral morphine is recommended as first-line treatment (Grade 1C)**.**

2.13.9. In lung cancer patients with severe chronic pain, oxycodone or hydromorphone are recommended as alternatives when there are significant side effects or lack of efficacy with oral morphine (Grade 1A)**.**

2.13.10. In lung cancer patients with severe chronic pain who are able to swallow, transdermal fentanyl is not recommended for first-line use (Grade 1C)**.**

2.13.11. In lung cancer patients with stable, severe, chronic cancer pain who have difficulty swallowing, nausea and vomiting, or other adverse effect from oral medications, transdermal fentanyl is recommended as an alternative to oral morphine (Grade 1B)**.**

2.13.12. In lung cancer patients with severe chronic pain, it is suggested that the prescription

of methadone as an alternative to oral morphine be confined to a specialist in palliative care units with experience in methadone prescription, because of difficulties with dose prediction, adjustment, and drug accumulation (Grade 2C).

2.13.13. In lung cancer patients with severe chronic cancer pain, treatment with systemic strong opioids is recommended (Grade 1C).

Remark: The oral route of administration is recommended on the grounds of convenience and cost.

2.13.14. In lung cancer patients with severe chronic cancer pain treated with systemic strong opioids who cannot swallow or who suffer excessive nausea and vomiting, the parenteral, transcutaneous or transmucosal route of administration is recommended (Grade 1C).

2.13.15. In the management of pain in lung cancer patients unable to take oral opioids, it is suggested that the subcutaneous route to administer continuous infusion of strong opioids, is equally effective as the intravenous route (Grade 2C).

2.13.16. In lung cancer patients with severe chronic cancer pain treated with systemic strong opioids, dose titration using either immediate release or sustained release oral morphine is suggested (Grade 2B).

Remark: The recommended starting dose is oral morphine 30 mg/24 h in patients not previously treated with opioids, and 60 mg/24 h in those already taking an opioid at step 2 of the WHO ladder. Where immediate release oral morphine is used, the four-hourly dose is used to treat episodes of uncontrolled pain and in this context may be used up to hourly. The total dose administered in 24 h is used to calculate ongoing opioid requirements. Where sustained release morphine is used, the total estimated daily dose is prescribed as once-daily or twice-daily oral morphine.

2.13.17. In lung cancer patients with severe chronic cancer pain treated with systemic strong opioids who experience breakthrough pain, parenteral morphine or transmucosal fentanyl citrate are recommended (Grade 1B).

Remark: Oral transmucosal fentanyl citrate, fentanyl buccal tablet and transnasal fentanyl spray are all effective formulations for breakthrough pain.

Remark: In patients with severe chronic cancer pain who experience a lack of effective analgesia, or uncontrollable side effects, or both, it is appropriate to switch to an alternative strong opioid, or route of administration, or both, though evidence of benefit from this approach is lacking.

Airway Obstruction

4.1.1. In lung cancer patients with inoperable disease and symptomatic airway obstruction, therapeutic bronchoscopy employing mechanical debridement, brachytherapy, tumor ablation or airway stent placement is recommended for improvement in dyspnea, cough, hemoptysis and overall quality of life (QOL) (Grade 1C).

Symptom Management for Cough

5.4.1. In all lung cancer patients with troublesome cough, evaluation for other treatable causes of cough in addition to cancer-related etiologies is recommended (Grade 1C).

5.4.2. In all lung cancer patients with troublesome cough without a treatable cause, it is recommended that opioids be used to suppress the cough (Grade 1B).

5.4.3. In all lung cancer patients with troublesome cough attributed to chemotherapy or radiation-induced pneumonitis, anti-inflammatory therapy with corticosteroids is recommended (Grade 1C).

Remark: Macrolides can be considered as steroid-sparing agents.

Palliation of Bone Metastasis

6.7.1. In patients with lung cancer who have pain due to bone metastases, external radiation therapy is recommended for pain relief (Grade 1A).

Remark: A single fraction of 8 Gy is equally effective for immediate relief of pain and more cost-effective than higher fractionated doses of external radiation therapy.

6.7.2. In patients with lung cancer who have painful bone metastases, bisphosphonates are recommended in addition to external beam radiation therapy for pain relief (Grade 1A).

6.7.3. In patients with lung cancer who have painful bone metastases to long and/or weight bearing bones and a solitary well-defined lytic lesion circumferentially involving > 50% of the cortex and an expected survival > 4 weeks with satisfactory health status, surgical fixation is recommended to minimize the potential for a fracture (Grade 1C).

Remark: Intramedullary nailing is the preferred approach, especially for the femur or the humerus.

Remark: Radiotherapy should follow the orthopedic management 2-4 weeks later.

6.7.4. In patients with lung cancer who have vertebral compression fractures causing pain, vertebral augmentation procedures are recommended to reduce pain (Grade 1A)**.**

Palliation of Brain Metastasis

7.6.1. In patients with lung cancer who have symptomatic brain metastases, dexamethasone at 16 mg/day is recommended during the course of definitive therapy with a rapid taper as allowed by neurologic symptoms (Grade 1B)**.**

7.6.2. In lung cancer patients with significant brain edema, neurologic symptoms, or large space occupying brain metastasis (>3 cm), surgical resection is recommended if they are surgical candidates (Grade1B)**.**

7.6.3. In lung cancer patients with 1 to 3 brain metastases, stereotactic radiosurgery alone is the recommended initial therapy (Grade 1A)**.**

Remark: With a low burden of disease, the benefit gained by delaying whole brain radiation therapy outweighs the potential risk.

7.6.4. In patients with 5 or more brain metastases, whole brain radiation is the recommended therapy (Grade 1A)**.**

Palliation of Spinal Cord Compression

8.4.1. In patients with lung cancer that have new onset of back pain, sagittal T1-weighted MRI of the entire spine is recommended (Grade 1C)**.**

8.4.2. In patients with lung cancer and epidural spinal cord metastases, who are not symptomatic, prompt treatment with high-dose dexamethasone and radiotherapy is recommended (Grade 1B)**.**

8.4.3. In lung cancer patients with symptomatic, radiographically confirmed epidural spinal cord compression and good performance status, it is recommended that neurosurgical consultation be sought and, if appropriate, surgery should be performed immediately and followed by radiation therapy (Grade 1B)**.**

Palliation of Superior Vena Cava Syndrome

9.1.1. In patients with superior vena cava (SVC) obstruction from suspected lung cancer, definitive diagnosis by histologic or cytologic methods is recommended before treatment is started (Grade 1C)**.**

9.1.2. In patients with symptomatic SVC obstruction due to small cell lung cancer (SCLC), chemotherapy is recommended (Grade 1C)**.**

9.1.3. In patients with symptomatic SVC obstruction due to non-small cell lung cancer (NSCLC), radiation therapy and /or stent insertion are recommended (Grade 1C)**.**

Remark: When using stenting for the management of SVC obstruction, consideration of necessary anticoagulation as it relates to future management of the patient must be considered.

9.1.4. In patients with SCLC or NSCLC with SVC obstruction who fail to respond to chemotherapy or radiation therapy, vascular stents are recommended (Grade 1C)**.**

Management of Hemoptysis

10.1.1. In all lung cancer patients with large volume hemoptysis, securing the airway with a single-lumen endotracheal tube is recommended. Bronchoscopy is recommended to identify the source of bleeding, followed by endobronchial management options such as argon plasma coagulation, Nd:YAG laser, and electrocautery for visible central airway lesions (Grade 1C)**.**

10.1.2. In all lung cancer patients with non-large volume hemoptysis, bronchoscopy is recommended to identify the source of bleeding. For visible central airway lesions, endobronchial management options are recommended. For distal or parenchymal lesions, external beam radiotherapy is recommended (Grade 1C)**.**

Remark: If these measures are unsuccessful, consideration should be given to bronchial artery embolization to temporize the bleeding. Most reports of bronchial artery embolization are limited by the few cases of lung cancer managed in almost all studies.

Management of Airway-Esophageal Fistulas

11.1.1 In patients with tracheoesophageal fistulas, double stenting of the esophagus and airway or esophageal stenting is recommended with self-expanding metallic stents (Grade 1B)**.**

Remark: When primary esophageal stenting is to be used, airway compromise must be considered prior to placing the stent. If a concern exists, an airway stent should be placed prior to esophageal stenting.

Management of Malignant Pleural Effusions

12.4.1. In patients with a symptomatic recurrent malignant pleural effusion (MPE) with documented re-expandable lung, tunneled pleural catheters or chemical pleurodesis are recommended (Grade 1C)**.**

Remark: In patients with a limited life span, serial thoracentesis can be considered.

12.4.2. In patients with a symptomatic recurrent MPE with lung trapping, tunneled catheters are recommended for symptomatic relief and improvement in QOL (Grade 1C)**.**

12.4.3. In lung cancer patients with a suspected MPE and in whom the diagnosis of stage IV disease is not confirmed, thoracoscopy is recommended instead of a tunneled catheter due to its diagnostic as well as therapeutic benefit (Grade 1C)**.**

12.4.4. In patients with a MPE, graded talc is the pleural sclerosant that is recommended due to its efficacy and safety profile (Grade 1C)**.**

12.4.5. In lung cancer patients with a malignant effusion, thoracoscopy with talc poudrage is recommended instead of talc slurry through a bedside chest tube for pleurodesis (if there are no contraindications to thoracoscopy) (Grade 1C)**.**

Management of Depression, Fatigue, Anorexia, and Insomnia

14.1.1. In patients recently diagnosed with lung cancer, it is recommended that comprehensive biopsychosocial assessment be performed soon after the diagnosis is made and at key transition points (completion of treatment, disease progression, and new symptom onset) thereafter for the remainder of life (Grade 1C)**.**

14.1.2. In lung cancer patients that identify psychologic and physical symptoms causing distress or interfering with their QOL, it is recommended that these symptoms are addressed by appropriately trained individuals (Grade 1C)**.**

14.1.3. In lung cancer patients with depression, anxiety, excessive daytime sedation and fatigue, medications such as antidepressants, anxiolytics and psychostimulants are recommended to decrease the morbidity associated with these symptoms (Grade 1C)**.**

14.1.4. In lung cancer patients with psychologic symptoms, a comprehensive symptom management plan is recommended. This should include non-pharmacologic interventions integrated with medication management, which may be offered as a single treatment modality (Grade 1C)**.**

14.1.5. In lung cancer patients with insomnia, sedating antidepressants (which target both sleep and mood) are recommended over sedative-hypnotics (which only improve sleep) (Grade 1C)**.**

14.1.6. In lung cancer patients with the subjective experience of breathlessness, interventions specifically designed to manage this symptom using psychologic coping and physical adaptation are recommended (Grade 1C)**.**

Remark: Targeted interventions for breathlessness, more effectively decrease distress and improve satisfaction with care than usual care provided during medical follow-up office visits.

14.1.7. In lung cancer patients with psychologic distress, it is suggested that one of several psychologic interventions have demonstrated benefit (including psycho-education, deep breathing, progressive muscle relaxation, guided imagery, cognitive behavioral therapy and supportive psychotherapy) (Grade 2C)**.**

Remark: There is limited evidence to support selection of one intervention over another based on characteristics of the target symptom, patient, or disease status.

Remark: We suggest that psychologic interventions to relieve distress are chosen based on patient preference, available skill-set of the health care team, and the available evidence from lung cancer studies.

14.1.8. It is suggested that educational programs responsible for preparing health care professionals to care for persons with cancer should include specific training in psychologic and physical symptom management of symptoms that are frequently associated with cancer diagnosis, treatment and survivorship (Grade 2C)**.**

14.1.9. It is suggested that health care systems providing care to persons with cancer should develop and support integrated programs in psychologic and physical symptom management which are accessible to all (Grade 2C)**.**

24.0 Palliative and End-of-Life Care in Lung Cancer

Although many effective treatments are available even for patients with incurable lung cancer, at some

point the focus becomes how best to manage end-of-life issues. It is best when this issue is incorporated from the outset into the management of patients with incurable disease rather than avoided until death is imminent. Furthermore, palliative care should be integrated with active cancer treatment in these patients. Although many clinicians consider end-of-life conversations difficult, several tools are available that have demonstrated value in facilitating a productive and rewarding discussion.

Summary of Recommendations: Palliative and End-of-Life Care in Lung Cancer

2.4.1. For patients with stage IV lung cancer and/or a high symptom burden, it is suggested that palliative care combined with standard oncology care be introduced early in the treatment course (Grade 2B)**.**

3.3.1. It is recommended that all physicians caring for patients with lung cancer should begin conversations about the patient's prognosis and goals of care at the time of the diagnosis, and continue these throughout the course of the illness (Grade 1B)**.**

3.3.2. It is recommended that all physicians caring for patients with advanced lung cancer should initiate conversations about the goals of care; the pros and cons of life-sustaining treatment and end-of-life care options (Grade 1B)**.**

Acknowledgments

Author contributions: Dr Detterbeck had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Dr Detterbeck: contributed to writing and revising this article.
Dr Lewis: contributed to reviewing drafts, providing comments, and approving the final article.
Ms Diekemper: contributed to reviewing drafts, providing comments, and approving the final article.
Dr Addrizio-Harris: contributed to reviewing drafts, providing comments, and approving the final article.
Dr Alberts: contributed to reviewing drafts, providing comments, and approving the final article.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Role of Sponsors: The American College of Chest Physicians was solely responsible for the development of these guidelines. The remaining supporters played no role in the development process. External supporting organizations cannot recommend panelists or topics, nor are they allowed prepublication access to the manuscripts and recommendations. Further details on the Conflict of Interest Policy are available online at http://chestnet.org.
Endorsements: This guideline is endorsed by the European Society of Thoracic Surgeons, Oncology Nursing Society, American Association for Bronchology and Interventional Pulmonology, and the Society of Thoracic Surgeons.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10-29.
2. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5)(suppl):e93S-e120S.
3. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013; 143(5)(suppl):e166S-e190S.
4. Ramnath N, Dilling TJ, Harris LJ. 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-e340S.
5. Colt HG, Murgu SD, Korst RJ, Slatore CG, Unger M, Quadrelli S. Follow-up and surveillance of the lung cancer patient after curative-intent therapy: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5)(suppl):e437S-e454S.