Respiratory Organ Aging and Cancer

15

Leah J. Witt and Carolyn J. Presley

Contents

Abstract

Lung aging begins in the third decade, initiating a gradual decline in maximal pulmonary function that continues throughout the remainder of life. Lung aging may mimic obstructive and restrictive lung diseases. Lung parenchyma loses elasticity via alveolar wall and mesenchymal degradation and distortion, similar to emphysema. Muscles of respiration become sarcopenic and weaken, while the

L. J. Witt (✉)
Division of Geriatrics and Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, University of California, San Francisco, San Francisco, CA, USA
e-mail: leah.witt@ucsf.edu

C. J. Presley
Thoracic Oncology/Geriatric Oncology, The Ohio State University Comprehensive Cancer Center, The James Cancer Hospital/Solove Research Institute, Columbus, OH, USA
e-mail: carolyn.presley@osumc.edu

M. Extermann (ed.), *Geriatric Oncology*,
https://doi.org/10.1007/978-3-319-57415-8_63

thorax contorts due to osteoporotic vertebral fractures, all of which manifest as a restrictive lung function pattern. Chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) and their pathogenesis may be related to accelerated cellular aging. Chronic lung disease impacts cardiopulmonary fitness, which can lead to decreased physical exertion and resultant frailty.

Lung cancer incidence also increases with age and is increased in older adults with COPD and IPF. Lung cancer is the leading cancer-related cause of death in the world. Most lung cancer in the USA is attributable to smoking. Globally, indoor air pollution is also a significant risk factor. Approximately 85% of lung cancer is non-small cell lung cancer (NSCLC), and adenocarcinoma is the predominant histologic type. Depending on stage at diagnosis, treatment options can include surgical resection, medical therapy (e.g., chemotherapy, driver mutation-targeted agents, and immunotherapy), and radiation therapy (photon or proton). Best care practices mandate that multidisciplinary teams formulate treatment plans to optimize care. Comprehensive geriatric assessments are useful decision-making tools and may improve survival while limiting treatment toxicity. Surgical resection impacts postoperative lung function, so preoperative evaluations must include pulmonary function testing with additional cardiopulmonary testing as indicated. Early palliative care interventions should be a cornerstone of medical management in advanced lung cancer.

Keywords

Lung aging · Dyspnea · COPD · IPF · Lung cancer

Introduction

Lung function peaks in the third decade of life, and then begins to slowly decline, precipitated by degradation of lung parenchyma, weakening of respiratory muscles, and distortion of the thorax. The natural history of chronic lung disease may mimic chronic obstructive pulmonary disease, due to air trapping (increased residual volume) and decreased forced expiratory volume in one second (FEV_1). However, respiratory muscles weakness and restriction of the thoracic cavity may counteract some of these obstructive changes on pulmonary function testing.

Chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) are prototypical chronic lung diseases of aging. Not only does prevalence and incidence of both diseases rise with age, but the pathogenesis of each overlaps with hallmarks of aging, such as shortened telomeres, defective DNA repair, genomic instability, cellular senescence, stem cell exhaustion, and mitochondrial dysfunction. Emerging evidence suggests that individuals with chronic lung disease experience physiologic aging that outpaces chronologic aging, therefore they are disproportionately burdened with geriatric syndromes such as frailty.

The prevalence of lung cancer is increased with COPD and IPF. Lung cancer is the deadliest of all cancers in the USA and causes substantial morbidity and mortality for aging populations. Given the increasing prevalence of lung cancer with age, understanding lung aging is an important element of caring for these patients. This chapter will discuss lung aging, chronic lung disease, lung cancer screening, and the nuances of caring for geriatric patients with lung cancer.

Recent guidelines recommend initiating low-dose computed tomography (LDCT) lung cancer screening in select at-risk populations with smoking exposures. These new guidelines are altering clinical practice particularly for geriatric patient populations, as screening targets patients between ages 55 and 80 years, and Medicare now pays for annual screening in select populations. Primary care physicians must decide how to incorporate lung cancer screening into their care of geriatric patients and use shared-decision making to determine when to stop screening.

When lung cancer is suspected, a multidisciplinary team including primary care

providers, geriatricians, pulmonologists, oncologists, and thoracic surgeons helps to shape the management plan for geriatric patients. Geriatric populations are heterogeneously resilient to the risks of cancer treatment; some high-risk subgroups are burdened with decreased physical function, disability, multimorbidity, and/or geriatric syndromes (including falls, incontinence, and polypharmacy). It is essential that providers appropriately risk-stratify patients to make the complex decisions required in care planning, so to avoid overtreatment of high-risk groups and undertreatment of resilient groups.

Lung Aging

Lung aging begins in the third decade of life, far earlier than what could be described as a "geriatric" age. Understanding lung aging, therefore, mandates an understanding of the embryologic underpinnings of the respiratory system (Bush 2016). Lung development first begins at week 3 of embryologic development, when the lung bud develops from the foregut (Burri 2006). By week 4, the lung bud has divided into two bronchial buds. Primitive alveolar sacs develop at approximately 16 weeks and proliferate. At 24 weeks, more alveoli have developed and the epithelium is thin enough for respiration, at which time the type 2 pneumocytes begin to produce surfactant. The lungs continue to develop throughout postnatal life, by increasing the size and number of respiratory bronchioles and alveoli until approximately age 8. Lung aging, the gradual decline of maximal lung function, begins just 20 years later (Janssens et al. 1999; Janssens 2005; Meiners et al. 2015).

Aging incites structural and functional changes throughout the respiratory system, including the thorax, muscles of respiration, bronchioles, and alveoli. The elasticity of lung parenchyma deteriorates, impeding bronchiole patency, alveolar integrity, and the alveolar/capillary interface. Muscles of respiration, including the diaphragm, intercostal muscles, and other accessory muscles, gradually lose muscle mass with age (called sarcopenia) and may functionally weaken (Cruz-Jentoft et al. 2010). The thorax, including the spinal column and rib cage, contorts due to osteoporotic vertebral body fractures and resultant kyphosis, hampering the lungs' expansion (Leech et al. 1990).

There are several objective assessments of respiratory organ aging. Such tools include lung volume measurements (by body box plethysmography or single breath helium dilution) **(**Fig. 1a**)**, airflow measurements (by spirometry), gas exchange capability (via diffusing capacity of the lung for carbon monoxide (DLCO)), respiratory muscle strength (by maximal inspiratory and expiratory pressure), exercise testing (6-min walk testing, shuttle walk testing, and cardiopulmonary exercise testing), and oxygenation measures (by arterial blood gas or pulse oximetry) (Table 1). Lung volumes are measured in liters, and these values are reported along with "predicted" values based on height, age, and gender (Quanjer et al. 1993).

Age-related changes in airway and alveolar structure impede air egress, which decreases forced expiratory reserve volume in one second (FEV_1) particularly as compared to the total forced expiratory reserve volume (FVC), consistent with airflow obstruction **(**Fig. 2a–c**)** (Schmidt et al. 1973). These changes mimic chronic obstructive pulmonary disease (COPD). Alveolar distortion impairs gas exchange which decreases the DLCO. Pathologically, enlargement of the alveolar structure with age may appear similar to emphysema, though typically without the same degree of alveolar wall destruction (Janssens et al. 1999).

Lung volume changes with age vary between individuals. Airflow obstruction causes air trapping and an increased residual volume (RV), which is the volume of air remaining in the lungs after maximal exhalation **(**Fig. 1b**)**. Total lung capacity (TLC) may stay constant or shrink due to chest wall restriction from thorax distortion or respiratory muscle weakness (Enright et al. 1994). Therefore, the outcome of pulmonary function testing will vary depending on an individual's burden of aging-related lung function changes.

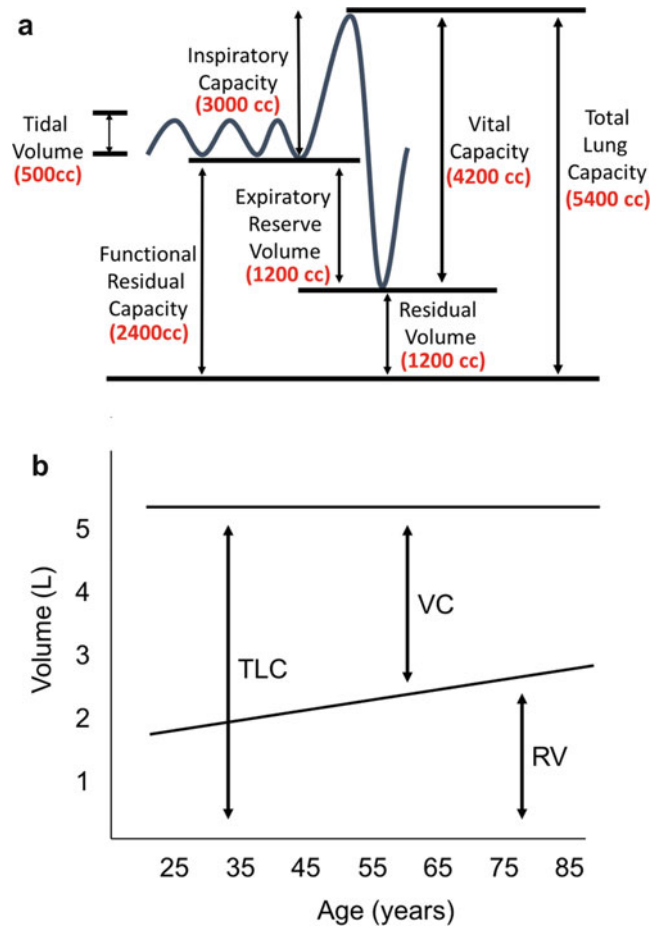

Fig. 1 (**a**) Lung volume measurements and sample volumes. (**b**) Changes seen in spirometry with aging. (Adapted from Janssens 2005)

Table 1 Lung function assessments

Lung volume measurements	TLC, FRC, RV
Spirometry	FEV_1, FVC
Gas exchange	DLCO
Oxygenation	paO_2, SpO_2
Ventilation	pCO_2
Respiratory muscle strength	MIP, MEP
Exercise testing	
Low technology	6-min walk, shuttle walk, stair climb
High technology	Cardiopulmonary exercise testing (VO_2)

TLC total lung capacity, *FRC* functional residual capacity, *RV* residual volume, *FEV_1* forced expiratory volume in 1 second, *FVC* forced expiratory volume, *DLCO* diffusing capacity of the lung for carbon monoxide, *paO_2* partial pressure of oxygen, *SpO_2* pulse oximetry, *pCO_2* partial pressure of carbon dioxide, *MIP* maximal inspiratory pressure, *MEP* maximal expiratory pressure, *VO_2* maximal oxygen consumption

Chronic Lung Diseases and Aging

Chronic lung diseases such as COPD, IPF, combined pulmonary fibrosis and emphysema (CPFE), asthma, and the newly described asthma-COPD overlap syndrome (ACOS) can impact quality of life and mortality of geriatric patients. General primary or specialty pulmonary

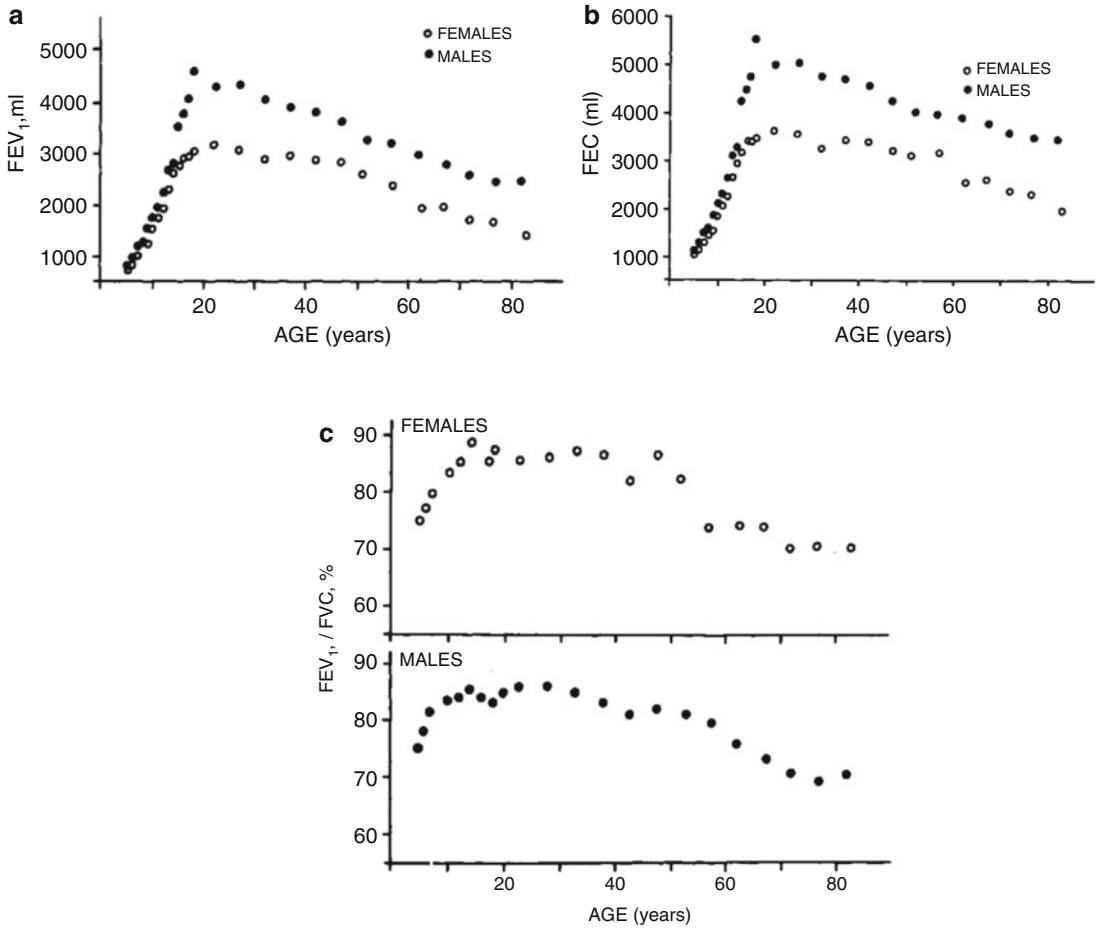

Fig. 2 (**a**) Mean forced expiratory volume in 1 second capacity (FEV_1) values by age 5–94 years. (**b**) Mean forced vital capacity (FVC) values by age 5–94 years. (**c**) Mean FEV_1/FVC values compared by age 5–94 years. (Adapted from Schmidt et al. (1973). Reprinted with permission of the American Thoracic Society. Copyright © 2017 American Thoracic Society. The American Review of Respiratory Disease is an official journal of the American Thoracic Society)

care for patients with chronic lung disease should include an assessment of pulmonary function (as described above), physical function (as measured by low-technology exercise testing and oxygenation), appropriate maintenance and rescue inhaler prescriptions, supplemental oxygen when indicated, and meticulous preventive care (including influenza and pneumococcal vaccination). Pulmonologists are increasingly recognizing the impact of aging on caring for patients with chronic lung disease and incorporating geriatric assessments into their care (Singer et al. 2016; Castriotta et al. 2010; Fried et al. 2012a).

Dyspnea or shortness of breath is a common complaint in geriatric populations and a frequent reason for referral to pulmonary subspecialists. Dyspnea can occur for a multitude of reasons, including cardiopulmonary impairment (e.g., congestive heart failure), neuromuscular diseases (e.g., amyotropic lateral sclerosis), and psychological distress (e.g., anxiety). Dyspnea complaints should receive a comprehensive evaluation, as detailed in the 2012 American Thoracic Society consensus statement, which includes a thorough history and physical examination to narrow the broad differential diagnosis and

Table 2 Clinical dyspnea scales

mMRC (Mahler and Wells 1988)	Modified Borg dyspnea scale (Borg 1982)
0 – No breathlessness except with strenuous exercise 1 – Breathlessness when walking up a slight hill or hurrying on level ground 2 – Walks slower than people of same age or must stop occasionally due to breathlessness on level ground 3 – Stops for breathlessness after walking 100 yards or a few minutes on level ground 4 – Too breathless to leave the house or breathless when dressing/undressing	*How much difficulty is your breathing causing you right now?* 0 – Not at all 0.5 – Very, very slight 1 – Very slight 2 – Slight 3 – Moderate 4 – Somewhat severe 5 – Severe 7 – Very severe 9 – Very, very severe 10 – Maximal

mMRC: modified Medical Research Council

determine further testing (Parshall et al. 2012). In a study of home-dwelling elderly individuals (aged 70 and older), the prevalence of dyspnea by the modified Medical Research Council scale (mMRC) (Table 2) was 32.3% (95% CI 30.3–34.3%) (Ho et al. 2001).

Dyspnea also appears to be related to mortality. In a cohort study of elderly family practice patients, dyspnea at baseline evaluation was significantly associated with death at 8-year follow-up (Huijnen et al. 2006). Some experts suggest that dyspnea be considered a geriatric syndrome. In an analysis of the 4413 community dwelling people in the Cardiovascular Health Study, moderate to severe dyspnea (Miner et al. 2016) was associated, expectedly, with cardiopulmonary impairments such as low FEV_1 or left ventricular function. Surprisingly, dyspnea was also associated with anxiety/depressive symptoms, inability to perform a chair stand, and grip weakness.

COPD is the third leading cause of death in the USA and fourth in the world (NCHS 2016; WHO 2016). Most patients with COPD have a history of personal or second-hand smoking (GOLD 2017). In countries with significant air pollution, such as from indoor solid-fuel use, COPD causes an even higher burden of mortality. For example, in China, COPD is the second leading cause of death due to high rates of smoking and indoor air pollution (Lin et al. 2008).

COPD is characterized by progressive airflow obstruction, defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria as an FEV_1/FVC ratio $< 70\%$ (actual) and a forced expiratory volume (FEV_1) $< 80\%$ (predicted) (GOLD 2017). Traditionally, COPD staging depended solely on FEV_1 impairment, but now dyspnea symptoms and exacerbation history are included in staging. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) Index can assist in predicting 4-year survival (Celli et al. 2004). Patients may have the chronic bronchitis (mucous production and increased airway resistance) and/or emphysema (impaired gas exchange and increased air trapping) subtypes of COPD.

COPD mimics the natural history of normal lung aging (Macnee 2016; Mercado et al. 2015). An emerging debate is challenging the traditional paradigm of COPD pathogenesis as solely attributable to accelerated lung aging and suggests that a subset of patients may be predisposed to develop COPD due to abnormal lung development but normal lung aging. In 1977, Fletcher and Peto presented what would become the conventional model of COPD pathogenesis. Their epidemiological description of "British disease," so-called due to the high prevalence of COPD in Britain, suggested that gradual age-related lung function decline can be accelerated by smoking in some individuals (Fletcher and Peto 1977).

A 2015 study by Lange and colleagues contested the traditional model as the only path to COPD pathogenesis. In their review of spirometry and outcomes from three large cohort studies, the Framingham Offspring Cohort, the Copenhagen City Heart Study, and the Lovelace Smokers Cohort, the authors showed that some patients

who develop obstructive lung disease may have failed to achieve normal lung function before experiencing normal age-related lung function decline (Lange et al. 2015). Risk factors in childhood and early adolescence, such as parental smoking (particularly intrauterine exposure by the mother), a family history of asthma, and/or a personal history childhood asthma, or respiratory infections, may predispose an individual to obstructive lung disease (Bush 2016).

Clearly, there is heterogeneity within the COPD patient population, and as a result, the rate at which FEV_1 declines in COPD is highly variable between patients. Data from a 2011 study by Vestbo et al., that followed 2163 patients over a 3-year period, found a mean (± standard error) rate of decline of 33 (±2) ml per year (Vestbo et al. 2011). Notably, patient subgroups experienced different rates of decline, with higher rates in current smokers compared to nonsmokers (21 ± 4 ml), those with emphysema compared to those without emphysema (13 ± 4), and those with bronchodilator reversibility compared to those without reversibility (17 ± 4 ml). These findings demonstrate that the clinical course of COPD is variable and difficult to predict.

Caution must be exercised before conferring COPD diagnoses on elderly individuals. Remember that normal lung aging mimics COPD **(**Figs. 2a–c**)**, yet patients may not be symptomatic and medical therapy for COPD has not been studied to "treat" normal lung aging. In a study of 208 asymptomatic never-smoker individuals over age 70 who underwent spirometry, 35% were found to qualify for stage 1 COPD by the GOLD criteria (Hardie et al. 2002). Further evidence from 2025 individuals aged 65–100 years old found airflow limitation in 28.2 per 1000 person-years when using the GOLD criteria (Luoto et al. 2015). The number of patients classified as having airflow limitation decreased to 11.7 per 1000 person-years when an age-dependent predicted lower limit of normal (LLN) value was used instead. Increasingly, experts suggest modifying diagnostic criteria to be based on standard deviations from the median (called spirometric z scores) (Vaz Fragoso et al. 2015) or LLN criteria for older patients.

Idiopathic pulmonary fibrosis (IPF), an interstitial lung disease of unknown etiology, is far less prevalent than COPD though similar aging-related changes are implicated in its pathogenesis. The incidence and prevalence of IPF increases significantly with age, male gender, and history of tobacco use (Raghu et al. 2006). Two-thirds of patients with IPF are over 60 years old at time of presentation, with a mean age at diagnosis of 66 years (Fig. 3).

In IPF, aberrant wound healing and resultant pathogenic fibrosis causes progressive lung destruction. Pulmonary function testing reveals small lung volumes and a restrictive lung disease pattern. There is typically a normal or high FEV_1/FVC ratio due to increased elastic recoil in the lungs. There is no cure for IPF, though two new recently approved medications, pirfenidone and nintedanib, slow the progression of IPF (King Jr et al. 2014, Richeldi et al. 2014). End-stage IPF may be treated with lung transplant. Median survival following diagnosis is 2.5–3.5 years and approximately 40,000 people die per year of IPF just in the USA (Blackwell et al. 2013; Ley et al. 2011), though this data was reported prior to use of antifibrotic agents.

Combined pulmonary fibrosis and emphysema (CPFE) is an increasingly recognized disease state that combines pathogenic features of COPD and IPF. Pulmonary function testing may approach normal due the balanced deficits of lung restriction and obstruction (Jankowich and Rounds 2012). Therefore, the diagnosis is often made radiographically or on pathology. Median survival is slightly higher than IPF, ranging from 2.1 to 8.5 years.

Asthma in the elderly often mimics COPD and is under recognized and undertreated (Skloot et al. 2016). Patients 65 years and older have the highest rates of asthma deaths and second highest rate of asthma hospitalizations as compared to other age groups. Further, the natural history of lung aging, such as decreased elastic recoil, can further exacerbate asthma symptoms making the disease more challenging to treat. The asthma-COPD overlap syndrome (ACOS), like CPFE, identifies a unique subset of older patients with an overlapping asthma and COPD phenotype.

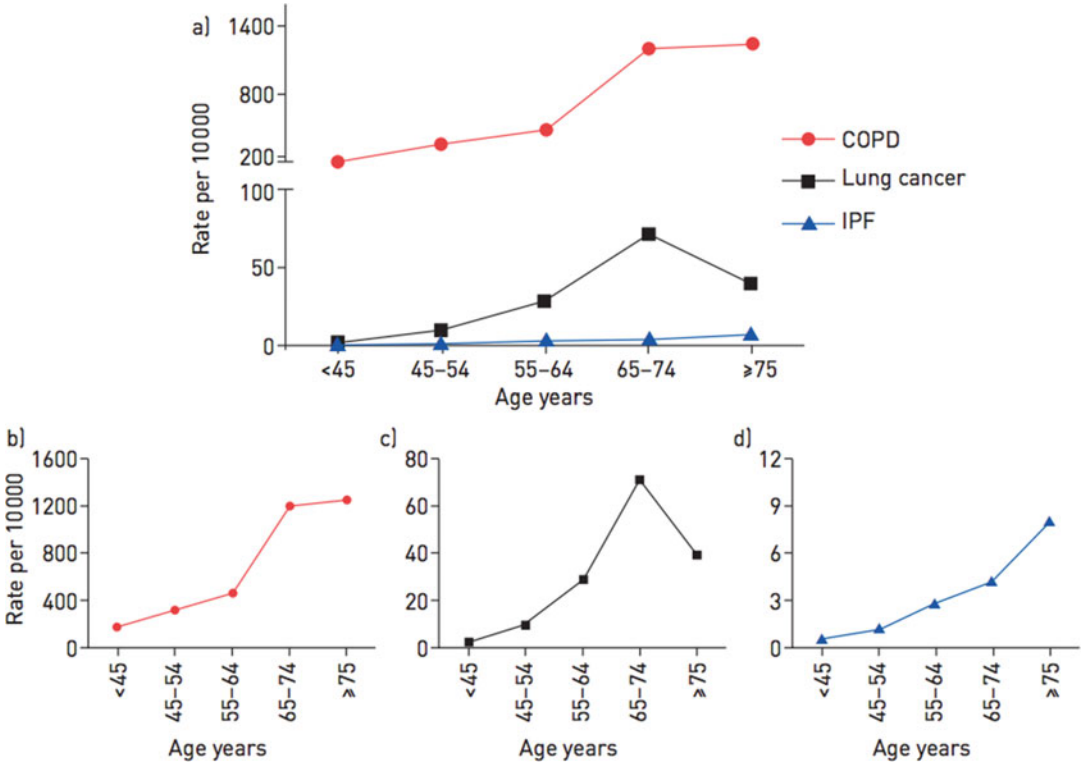

Fig. 3 The all-gender incidence rates of chronic obstructive pulmonary disease (COPD), lung cancer, and idiopathic pulmonary fibrosis (IPF) according to age in the USA. (Reproduced with permission from the European Respiratory Society ©. European Respiratory Journal. 2015;45(3):807–827. https://doi.org/10.1183/09031936.00186914)

(Postma and Rabe 2015). One study estimated the prevalence of ACOS in individuals with COPD at 17.4%, and noted increased dyspnea, wheezing, respiratory-related quality of life by the St. George' Respiratory Questionnaire (SGRQ) and reduced physical activity, as compared to nonoverlap COPD patients (Miravitlles et al. 2013).

Primary care for patients with chronic lung disease can be complex (Fried et al. 2012b). These patients often have multiple comorbidities such as arthritis, osteoporosis, congestive heart failure, and depression (Schnell et al. 2012). One study noted a prevalence of four or more comorbid conditions in over half of patients with moderate to very severe COPD (Vanfleteren et al. 2013). Comorbid conditions such as gastroesophageal reflux and cardiac dysfunction can exacerbate asthma and COPD (Hanania et al. 2011; Le Jemtel et al. 2007). The guideline-based management of multiple comorbid conditions, when taken together, may offer contradictory advice or be financially or logistically impractical to undertake (Boyd et al. 2005).

Chronic Lung Diseases and Frailty

Patients with COPD are more likely to be frail. Frailty is a phenomenon of impaired physiologic reserve and resilience, first described by the Cardiovascular Health Study in 2001, through the creation of the Fried Frailty Phenotype (FFP) (Fried et al. 2001). The FFP is an aggregated score of five assessments: grip strength, walk speed, weight loss, exhaustion, and physical activity level. Fried's original study revealed that a frailty phenotype was significantly associated

with COPD even when adjusted for age. Lahousse et al. confirmed these findings through a study of community-dwelling individuals, finding that those with COPD by spirometry were more likely to be frail by FFP (10.2%) as compared to those without COPD (3.4%) ($p = 0.001$) (Lahousse et al. 2016). Frail patients with COPD had a mortality rate three times that of nonfrail patients with and without COPD. The authors noted that frailty predicted mortality better than FEV_1 or other comorbidities.

Not surprisingly, frailty is highly prevalent in patients seen in outpatient pulmonary clinics. In 2016, Mittal and colleagues described a frailty prevalence of 18% and prefrailty prevalence of 64% in pulmonary outpatients (Mittal et al. 2016). Fried frailty phenotype assessments can be arduous to complete, so the authors used easily collected ambulatory data such as 100 feet gait speed, as frailty surrogates. They defined slow gait speeds as less than 60 m/min, finding that this was 95% sensitive and 34% specific to predict frailty. Gait speed may be an adequate frailty screening tool in an outpatient pulmonary clinic and could suggest referral to a geriatric clinic.

Spirometric impairment, even without diagnosed lung disease, impacts mortality. Vaz Fragoso and colleagues discovered that, among participants aged 65–80 years in the Cardiovascular Health Study, mortality was highest in those with both frailty and respiratory impairment (adjusted hazard ratio, 3.91, 95% CI, 2.93–5.22) as compared to those with and without frailty and/or respiratory impairment alone (Fragoso et al. 2012).

Sarcopenia, the phenomenon of muscle loss with age, has been described in individuals with COPD. Jones et al. applied the European Working Group on Sarcopenia in Older People (EWGSOP) criteria to 622 outpatients with COPD and found a 14.5% (95% CI 11.8–17.4%) prevalence of sarcopenia, which was associated with age and COPD severity (Jones et al. 2015). In an evaluation of the exercise capacity and muscle strength of 41 patients with COPD, Gosselink et al. found that lung function and peripheral muscle strength were significantly related to exercise capacity in these patients (Gosselink et al. 1996). Pulmonary rehabilitation, a pillar of chronic lung disease management, improves sarcopenia (Jones et al. 2015).

End-stage lung disease can be treated with single or double lung transplant in appropriate candidates, and transplant centers are examining the role of geriatric assessments in further evaluating transplant candidates. While the current lung allocation score incorporates some candidate characteristics (e.g., 6-min walk distance and functional status) accumulating evidence about global functional impairment in patients with severe lung disease suggests the utility of frailty and sarcopenia assessment tools for transplant candidates (Egan et al. 2006). A 2015 study of listed lung transplant candidates showed a high burden of frailty by FFP (28%) and Short Physical Performance Battery (SPPB) (10%) (Singer et al. 2015). Frailty was significantly associated with lung transplant delisting, disability, and death.

Lung Cancer and Aging

Lung Cancer Epidemiology and Risk Factors

Lung cancer is the leading cause of cancer-related deaths for both men and women in the USA. Until recently, lung cancer screening was not standard of care, and most patients presented with late stage disease. As a result, the 5-year survival of all stages of lung cancer from 2006 to 2012 was 17.7% (Howlader et al. 2016). The median age of lung cancer patients at time of diagnosis is 70 years old, and lung cancer is most frequently diagnosed between 65 and 74 years. Men, particularly African American men, face the highest burden of lung cancer diagnoses and death. In the USA, the incidence of lung cancer began to decline in the late 1980s for men, though it did not decline for women until the 2000s (ACS 2016). Lung cancer costs in the last year of life are the highest compared to other types of cancer (Mariotto et al. 2011).

Non-small cell lung cancer (NSCLC) comprises about 85% of all lung cancers (ACS 2016). Adenocarcinoma is the most frequently

identified histologic type of NSCLC and accounts for approximately 40% of all lung cancers. The frequency of adenocarcinoma declines with age, while the frequency of squamous cell carcinoma increases (ACS 2016). In the USA, 80% of lung cancer deaths are attributed to smoking (ACS 2016). Other lung cancer risk factors include second-hand smoke exposure, smoke from indoor burning of coal and wood for cooking and heating, air pollution, radiation therapy (e.g., for Hodgkin lymphoma or breast cancer), and environmental/occupational carcinogens (e.g., radon) (Darby et al. 2005; Pope III et al. 2002; Fontham et al. 1994; Travis et al. 2002).

The pathogenesis of chronic lung diseases such as COPD and IPF have cellular "hallmarks of aging" that overlap with those found in malignant lung cancer cells. Similar pathogenic features include shortened telomeres (Morla et al. 2006), defective DNA repair (Caramori et al. 2011), genomic instability, cellular senescence/stem cell exhaustion (Chilosi et al. 2013), metabolic alterations such as mitochondrial dysfunction (Mora et al. 2017), and epigenetic changes (López-Otín et al. 2013; Mercado et al. 2015; Pardo and Selman 2016; Macnee 2016; Vancheri et al. 2010) (Fig. 4).

Lung cancer is more prevalent in those with COPD and IPF compared to patients without chronic lung disease. In a 2009 study of patients with lung cancer, COPD prevalence by all GOLD stages was significantly higher than age/sex/smoking exposure matched-controls (50% compared to 8%) (Young et al. 2009). COPD appeared to confer a sixfold greater risk of developing lung cancer compared to participants without COPD. Emphysema on computed tomography (CT) scan is an independent risk factor for lung cancer. In a 2007 study of 1166 individuals undergoing lung cancer screening with low radiation-dose CT, the incidence of lung cancer was 25.0 per 1000 person-years in those with emphysema vs. 7.5 per 1000 person-years in those without emphysema (De Torres et al. 2007) (Fig. 5).

Patients with IPF also have higher rates of lung cancer. In a retrospective study of patients with CPFE, IPF, and emphysema, patients with CPFE were found to have the highest risk of lung cancer (adjusted hazard ratio of 4.62, 95% CI 1.58–13.55) as compared the emphysema group (Kwak et al. 2014). The IPF group also had an increased risk of lung cancer as compared to the emphysema group (adjusted HR 4.15, 95% CI 1.03–16.78).

Lung Cancer Screening

Until recently, there was no standardized lung cancer screening practice supported by strong evidence. In 2011, the National Lung Screening Trial Research Team published a randomized, prospective study of 53,454 participants who received either three annual screenings with low-dose computed tomography (LDCT) or single-view posteroanterior chest radiography, from 2003 to 2004 (Team 2011). At the end of the study, the LDCT group had fewer deaths related to lung cancer (247 deaths per 100,000 person-years) versus the chest radiography group (309 deaths per 100,000 person-years). All-cause mortality in the LDCT group was significantly reduced by 6.7% (95% CI 1.2–13.6; $p = 0.02$) as compared to the chest radiography group. A follow-up analysis of the data suggested that LDCT screening could prevent approximately 12,000 lung cancer deaths per year in the USA (Ma et al. 2013).

This data must be interpreted with an understanding of the greatest drawback of increased lung cancer screening: falsely positive tests leading to increased invasive diagnostic procedures and anxiety about test results. The 2011 screening study found a high false positive rate in both the LDCT group (96.4%) and the chest radiography group (94.5%). Further analyses of the same study population have demonstrated higher false positive rates in participants 65 years or older (Medicare-eligible) as compared to those less than 65 (Pinsky et al. 2014). More false-positive screening exams resulted in more invasive procedures to pursue diagnosis. Importantly, participants who underwent invasive procedures experienced a relatively low complication rate in both age groups, that was not significantly different (9.8% in <65 group and 8.5% in ≥ 65 group). However, the older participants had a higher prevalence of cancer and higher positive predictive

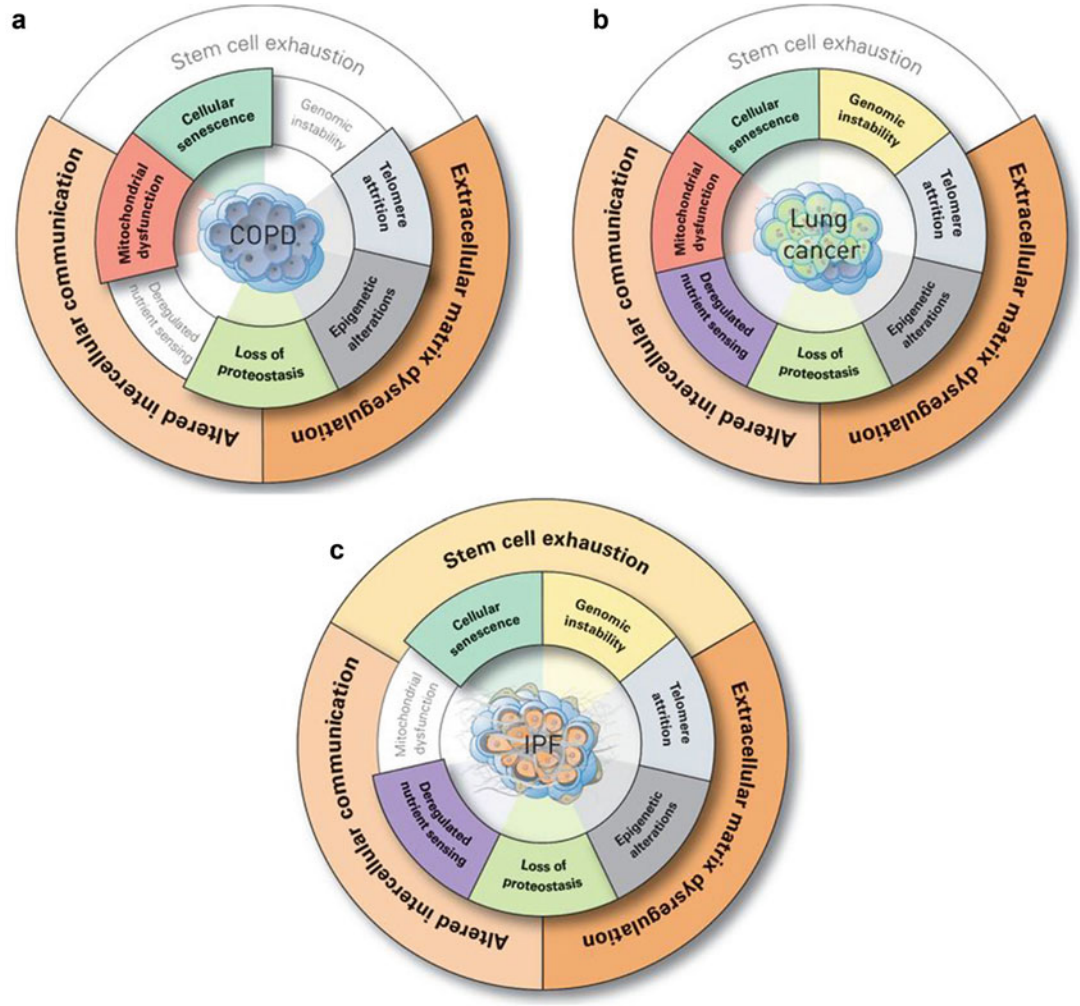

Fig. 4 The predominant hallmarks of aging in (**a**) chronic obstructive lung disease, (**b**) lung cancer, and (**c**) idiopathic pulmonary fibrosis. (Reproduced with permission from the European Respiratory Society ©. European Respiratory Journal. 2015;45(3):807–827. https://doi.org/10.1183/09031936.00186914)

value (4.9% vs. 3.0%) as compared to the group under age 65.

The findings from the National Lung Screening Trial Research Team study led the United States Preventive Task Force (USPSTF) to give a grade B recommendation for annual lung cancer screening by LDCT. This recommendation applies to adults aged 55–80 years with a 30 pack-year smoking history and current smoking behavior, or smoking cessation within the last 15 years. They suggest that screening should continue until a patient has not smoked for 15 years (Moyer 2014).

The intent of the screening practice is to identify early-stage resectable lung cancer. Therefore, annual screening should cease if a patient's life expectancy is limited by comorbidities or the patient is unwilling to have curative lung surgery or radiation treatment. In 2015, the Centers for Medicare and Medicaid Services began covering LDCT lung cancer screening as a preventive service benefit (Medicare and Services 2015).

The American College of Radiology (ACR) has suggested a standard method for evaluating LDCT, called the ACR Lung CT Screening Reporting and Data System (Lung-RADS)

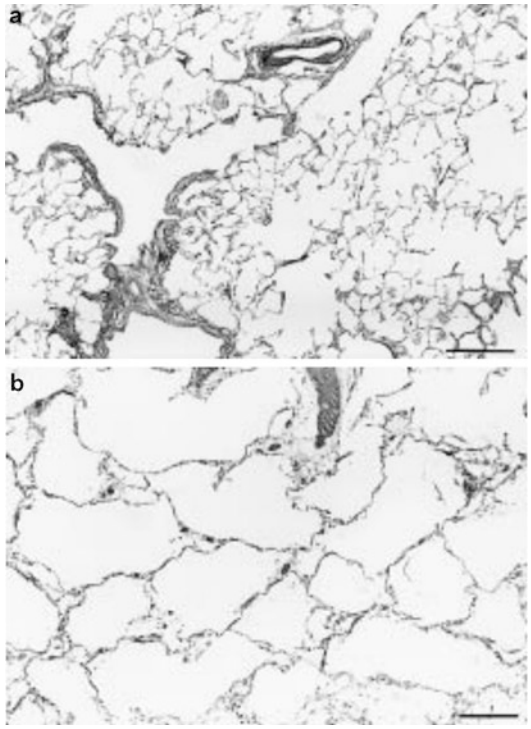

Fig. 5 (**a**) Lung parenchyma from a 29-year-old individual with no history of smoking; (**b**) lung parenchyma from a 100-year-old nonsmoking individual. The alveolar spaces are markedly enlarged as compared to the younger individual in panel a. (Hematoxylin and eosin stain; internal scale bar = 280 mm (**a**); 250 mm (**b**)). (Reproduced with permission from the European Respiratory Society ©. European Respiratory Journal. 1999;13(1):197–205)

(Mckee et al. 2016). Suggested categorization for screening LDCTs along with management recommendations is summarized in Table 3. The ACR's guidelines were retrospectively applied to the National Lung Screening Trial group's method of approaching nodules and demonstrated a decreased false positive rate (12.8% vs. 26.6%) but a lower sensitivity (78.6% vs. 93.8%)(Pinsky et al. 2015).

Some lung cancers are found incidentally on radiographic imaging obtained for other reasons. The Fleischner Society has published guidelines for managing incidentally discovered pulmonary nodules in nonimmunocompromised patients over 35 years (Macmahon et al. 2017). These recommendations stratify risk by nodule type (solid versus subsolid) and further by size (by average diameter) and pretest probability for lung cancer (Table 4).

The guidelines for management of incidental pulmonary nodules should not be used to interpret lung cancer screening LDCT studies, primarily because the pretest probability for lung cancer is higher in the preselected lung cancer screening group. A predictive calculator tool may assist in estimating a nodule's probability of malignancy (Mcwilliams et al. 2013). Increased risk is ascribed to individuals with older age, female sex, a personal history of emphysema, and a family history of lung cancer. Nodule characteristics that impart additional risk are larger size, spiculation, semisolid components, and upper lobe location.

Lung Cancer Diagnosis

Outside of screening or incidental findings, physicians may infrequently suspect lung cancer based on clinical signs or symptoms. However, patients do not typically develop symptoms suggestive of lung cancer until late in the disease course. Symptoms can include cough, chest pain, hemoptysis, clubbing, weight loss, and fever (Spiro et al. 2007). When lung cancer is suspected based on clinical symptoms, one should proceed to chest radiography or contrast-enhanced CT scanning.

If lung cancer is suspected by imaging, the patient may have either a biopsy to obtain tissue for pathologic evaluation and staging, or if radiographic characteristics strongly suggest an early stage cancer (stage IA), proceed directly to surgical resection for diagnosis and curative management. The most commonly used staging system is the TNM (tumor/node/metastasis) classification produced by the American Joint Committee on Cancer (AJCC), recently updated to an 8th edition in 2017 (Tables 5 and 6) (AJCC 2017).

There are two steps of staging lung cancer. First, patients are clinically staged prior to invasive procedures, to determine the best next step. Clinical staging should begin with contrast-enhanced CT imaging of the chest and upper abdomen and brain imaging (Silvestri et al. 2013).

Table 3 LDCT grading and management

Category	Description	Findings	Recommendation
0	Incomplete	Cannot evaluate (poor study, need prior imaging)	Additional images needed (or compare to prior)
1	Negative	No nodules or nodule(s) with benign calcifications	Annual LDCT
2	Benign appearance/ behavior	*Solid nodule(s)*: < 6 mm or new <4 mm *Part-solid nodule(s)*: <6 mm total on baseline screen *Non-solid nodule(s)*: < 20 mm or ≥ 20 mm and unchanged Category 3 or 4 without change for ≥3 months	
3	Probably benign	*Solid nodule(s)*: ≥6–8 mm at baseline or new 4 mm to <6 mm *Part-solid nodule(s)*: ≥6 mm total, solid component <6 mm or new <6 mm total *Non-solid nodule(s)(ground glass)*: ≥20 mm baseline or new	6 month LDCT
4A	Suspicious	*Solid nodule(s)*: ≥8 – < 15 mm baseline or growing <8 mm or new 6 – <8 mm *Part-solid nodule(s)*: ≥ 6 mm with solid component ≥6–8 mm or new/growing <4 mm solid component *Endobronchial nodule*	3 month LDCT, may use PET/CT if ≥8 mm solid component
4B		*Solid nodule(s)*: ≥ 15 mm or new/growing and ≥8 mm *Part-solid nodule(s)*: Solid component ≥8 mm or new/growing solid component ≥4 mm	Chest CT with or without contrast, PET/CT and/or tissue sampling
S	Significant – other	Add on to 0–4 coding	No specific recommendation
C	Prior lung cancer	Add on to 0–4 coding	

Adapted from https://www.acr.org/Quality-Safety/Resources/LungRADS. For multiple nodules, manage based on largest nodule. For follow-up screening findings, refer to the LUNG-RADS guidelines
LDCT low-dose computed tomography, *PET* positron emission tomography, *CT* computed tomography

Table 4 Fleischner criteria for incidental lung nodules

Low risk	
<4 mm	No follow-up
4–≤6 mm	Repeat in 1 year
6–≤8 mm	Repeat 6–12 months
≥8 mm	Repeat at 3, 9, and 24 months Consider PET/biopsy
High risk	
<4 mm	Repeat in 1 year
4–<6 mm	Repeat in 6–12 months
6–≤8 mm	CT at 3–6 months
≥8 mm	CT at 3,9, and 24 months

Adapted from MacMahon et al. (2017)

The evidence for use of whole body positron emission tomography (PET) or PET/CT scans to stage is mixed, and staging decisions should not be made based on PET/CT scan alone. Staging consensus guidelines suggest synthesizing radiographic data to guide tissue biopsy planning (Travis et al. 2011; Murgu 2015). A PET/CT scan may help guide clinicians to biopsy lymph nodes (via endoscopy or mediastinoscopy) or to proceed directly to surgery for resection and surgical/pathologic staging (Schmidt-Hansen et al. 2014).

Table 5 AJCC TNM staging, seventh edition and eighth edition[a] comparison

7th edition	8th edition	N0	N1	N2	N3
T1 ≤ 1 cm	T1a	IA→**IA1**	IIA→**IIB**	IIIA	IIIB
T1 > 1–2 cm	T1b	IA→**IA2**			
T1 > 2–3 cm	T1c	IA→**IA3**			
T2 > 3–4 cm	T2a	IB			
T2 > 4–5 cm	T2b	IB→IIA			
T2 > 5–7 cm	**T3**	IIA→**IIB**	IIB→**IIIA**	IIIA→**IIIB**	IIIB→**IIIC**
T3 structures	**T3**	IIB	IIIA		
T3 > 7 cm	**T4**	IIB→IIIA			
T3 diaphragm	**T4**				
T4	T4	IIIA		IIIB	IIIB→**IIIC**
M1a	M1a	IV→IVA			
M1b (single)	M1b				
M1c (multiple)	M1c	IV→IVB			

Adapted from Goldstraw et al. (2007, 2016)

AJCC American Joint Committee on Cancer, *TNM* tumor, node, metastasis
[a]The 8th edition will not come into clinical practice until January 2018

Table 6 AJCC 8th edition regional lymph node (N) and distant metastasis (M) definitions

Nx	Cannot assess regional lymph nodes
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or hilar lymph nodes and intrapulmonary nodes, including direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal or hilar lymph nodes, or ipsilateral or contralateral scalene or supraclavicular lymph nodes
M0	No distant metastasis
M1a	Metastasis in a contralateral lobe, pleural or pericardial nodule(s), pleural or pericardial effusion
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases in one or more organs

Adapted from Goldstraw et al. (2016)
AJCC American Joint Committee on Cancer

The second step of lung cancer staging is pathologic staging, either surgical with mediastinal lymph node dissection or nonsurgical lymph node sampling. If Stage IB, II, or III is suspected, the preferred diagnostic and staging modality is endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA), particularly for centrally located lesions or paratracheal lymph node biopsies. The EBUS-TBNA procedure allows for safe, moderately invasive tissue diagnosis, typically under general anesthesia, with on-site cytologic evaluation (Yasufuku et al. 2005). A 2014 study of 451 patients showed that the risk of complication rates among patients $\geq$70 years was similar to patients <70 years (5.1% vs. 8.7%, respectively, $p = 0.13$), in spite of worse performance status in the older patients ($p < 0.001$) (Evison et al. 2014).

If cancer is diagnosed during the EBUS-TBNA procedure, the disease is further staged during the same procedure by obtaining tissue from contralateral lymph nodes that could "up-stage" the

disease and alter treatment plans. If biopsies from the EBUS-TBNA procedure are negative or inconclusive, and clinical suspicion of regionally advanced disease is high, the patient proceeds to mediastinoscopy or thoracoscopy for regional nodal assessment (Rivera et al. 2013). When lesions are peripheral, the yield by bronchoscopy decreases, and alternative diagnostic methods such as CT-guided transthoracic needle aspiration or video-assisted thoracic surgery (VATS) may be useful. If stage IV lung cancer is suspected based on distant metastases, a more readily available metastatic tissue sample may be obtained, such as from pleural fluid or a superficial lymph node. No matter the diagnostic modality, adequate tissue must be obtained for histologic type and molecular analysis.

Non-Small Cell Lung Cancer

Making Treatment Decisions

Lung cancer treatment planning requires a multidisciplinary approach that integrates expert recommendations from medical oncologists, medical and radiation oncologists, pathologists, thoracic surgeons, pulmonologists, primary care doctors, and geriatricians (Spira and Ettinger 2004). Lung cancer stage along with comorbidities, lung function, and physiologic status informs treatment recommendations that can include surgical resection, single agent chemotherapy, doublet chemotherapy, immunotherapy, targeted driver mutation therapies, radiation, and/or palliative care. Oncologic treatment planning for elderly patients with NSCLC is nuanced, as providers must synthesize guideline-based recommendations with patient preferences and assessments of global function (Gajra and Jatoi 2014).

Traditionally, risk-stratification prior to oncologic treatment interrogated patient fitness for treatment using the Eastern Cooperative Oncology Group (ECOG)/World Health Organization (WHO) score, a 0–5 scale of health symptoms and disability, or the Karnofsky method, a 0–100 scale with more discrimination in disability description (Table 7) (Karnofsky et al. 1948; Oken et al. 1982). The Comprehensive Geriatric Assessment (CGA) has, over the over the last several decades, gained popularity as a more comprehensive risk-stratifying tool for elderly patients with cancer (Extermann and Hurria 2007).

The components of a CGA can vary based on the practice of the administering provider, but typically include a thorough assessment of activities of daily living (ADLs), instrumental activities of daily living (IADLs), comorbidities, functional-based assessments (e.g., 6-min walk test and grip strength), mental health, cognition, nutritional status, social support, and medications/polypharmacy (Table 7). In particular, the CGA adds additional risk information to traditional performance status measures, which often miss IADL disability. For example, a 2005 study of 566 elderly patients with advanced NSCLC found that pretreatment assessments of quality of life and IADLs were associated with improved prognosis (Maione et al. 2005). Assessments of ADLs and comorbidities, the central elements of the Karnofsky and ECOG/WHO scores, did not correlate with prognosis.

These studies support the notion that chronologic age alone should not determine treatment planning. Instead, treatment decisions should be made based on physiologic age, using CGAs such as the Elderly Selection on Geriatric Index Assessment (ESOGIA) (Corre et al. 2016). Treatment-related toxicity can be predicted using the Cancer and Aging Research Group tool (CARG) (Hurria et al. 2011) or Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) (Extermann et al. 2012) tools (Table 7).

Early-Stage NSCLC (Stages I and II)

Early stage lung cancer increases in prevalence with age. In 2005, a large retrospective analysis of 14,555 patients with early-stage NSCLC in the Surveillance, Epidemiology, and End Results (SEER) database revealed that the prevalence of stage I NSCLC increased from 79% in patients less than age 65 compared to 87% in patients older than age 75 (Mery et al. 2005). Five-year relative survival for localized lung cancer is 55% (ACS

Table 7 Pretreatment risk assessments

Traditional performance status measures	
ECOG/WHO (Oken et al. 1982)	Karnofsky[a] (Karnofsky et al. 1948)
0 – Asymptomatic 1 – Symptomatic but completely ambulatory 2 – Symptomatic, <50% in bed during the day 3 – Symptomatic, >50% in bed but not bedbound 4 – Bedbound 5 – Death	100 – Normal; no complaints; no evidence of disease 70 – Cares for self; unable to carry on normal activity or do work 50 – Requires considerable assistance and frequent medical care 20 – Very sick: hospital admission necessary; active supportive treatment necessary 0 – Dead
Chemotherapy toxicity tools	
CARG (Hurria et al. 2011)	CRASH (Extermann et al. 2012)
Age/gender/height/weight Cancer type Number and dosage of chemotherapy agents Falls IADL: Medication management ADL: Walking block Subjective assessment Labs: Hemoglobin/creatinine	Chemotherapy risk *Nonhematologic toxicity*: ECOG PS, MMSE, mininutritional assessment *Hematologic toxicity*: IADL, LDH, diastolic BP
Comprehensive geriatric assessments	
Proposed screening tools (Balducci and Extermann 2000)	ESOGIA CGA (Corre et al. 2016)
Mental status Emotional Status ADL/IADL Home Environment Social Support Comorbidity Nutrition Polypharmacy	PS (ECOG) ADL (0-6) IADL (0-4) MMSE Geriatric Syndrome[b] Charlson comorbidity Index GDS5 (0-5)

CARG scoring: http://www.mycarg.org/Chemo_Toxicity_Calculator
CRASH scoring: https://www.moffitt.org/eforms/crashscoreform
ECOG Eastern Cooperative Oncology Group, *WHO* World Health Organization, *CARG* Cancer & Aging Research Group, *CRASH* Chemotherapy Risk Assessment Scale for High-Age Patients, *ADL* activities of daily living, *IADL* instrumental activities of daily living, *MMSE* Mini-Mental State Examination, *BP* blood pressure, *LDH* lactate dehydrogenase, *GDS5* Geriatric Depression Scale 5, *PS* performance status, *ESOGIA* elderly selection on geriatric index assessment, *CGA* comprehensive geriatric assessment
[a]Abbreviated
[b]Confirmed dementia, repeated falls, or urinary or fecal incontinence

2016), but true pathologic stage I NSCLC may have five-year survival of approximately 80% (Cerfolio and Bryant 2009). However, lung cancer is infrequently diagnosed at a localized stage (16%) (ACS 2016), which is the basis for more aggressive lung cancer screening.

Surgery is the first-line treatment for early-stage lung cancer (stages I and II) (Table 8). If a patient has a potentially resectable lung cancer, multidisciplinary teams perform presurgical risk assessments, to identify patients at high-risk for surgical complications. While age has historically been used as a crude risk-stratification method, recent surgical guidelines by American (Brunelli et al. 2013) and European (Brunelli et al. 2009) societies recommend against using age cut-offs to make surgical decisions. In fact, approximately one-third of lung-resection candidates are over 70 years old. Instead, if a patient has potentially surgically resectable cancer, the patient should be further risk-stratified with appropriate preoperative testing including lung function assessments (Table 1) and evaluation of other comorbidities (Table 7).

Table 8 Suggested non-small cell lung cancer treatment by clinical stage[a]

Stage I and IIA (Local): Lungs only, without lymph node extension
Surgical resection with mediastinal lymph node dissection (if clinical stage IA, may proceed directly to resection for diagnosis, staging, and curative intent surgery)
+/− adjuvant chemotherapy
SABR +/− chemotherapy if inoperable
Stage IIB–IIIA (N0–1) (Regional): Lung and nearby lymph nodes
Preoperative mediastinal staging to determine eligibility for surgical resection
Adjuvant chemotherapy
SABR +/− chemotherapy if inoperable
Stage IIIA(N2)–IIIB (Locally advanced): Extension to central ipsilateral lymph nodes **or** to central contralateral lymph nodes/above clavicle
Role of surgery and neoadjuvant chemotherapy controversial, consider resection if noninvasive tumor and N2 disease eradicated with induction chemotherapy
N3: Definitive chemotherapy and radiation
Stage IV (Metastatic): Extension to both lungs, pleural space, or extrapulmonary site
Early palliative care
Targeted therapies if indicated (ALK, EGFR, ROS1, PD-L1)
Chemotherapy
Immune checkpoint inhibitors
Radiation targeting metastases
Stereotactic radiosurgery for limited brain metastases

Adapted from AJCC seventh edition staging (Goldstraw et al. 2007) and NCCN Clinical Practice Guidelines in Oncology (Version 5.2017): https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Consult guidelines for addition, nuanced detail

SABR sterotactic ablative therapy

[a]Recommend consultation with multidisciplinary team including medical oncologist, thoracic surgeon, radiologist, pathologist, and geriatrician. Treatment plan may be altered by discrepancy between pathologic stage and clinical stage or patient risk-assessment/treatment tolerability

Surgical resection of lung cancer will impact lung function, so presurgical evaluations must include an objective assessment of pulmonary function to calculate predicted postoperative (ppo) FEV_1 and DLCO, which is based on the number of functional segments to be removed (Brunelli et al. 2013). Regardless of lung disease, all patients should have a DLCO assessment in addition to spirometry, because ppoDLCO is strongly correlated with pulmonary complications, even in patients without COPD (Ferguson et al. 2009). Further, testing of a patient's exercise tolerance is pursued if questions remain about a patient's ability to tolerate the surgery, including low technology exercise testing such as 6-min walk testing, shuttle walk or stair climbing, and high technology exercise testing such as cardiopulmonary exercise testing (Table 9).

Interrogating preoperative lung function and calculating ppo lung function is essential to a careful assessment of projected surgical morbidity and mortality. Ferguson et al. demonstrated that, in 854 patients who underwent major lung resection, ppoFEV1 and ppoDLCO were significantly associated with mortality (HR 1.06, 95% CI 1.01–1.12, $p = 0.03$; HR 1.06, 95% CI 1.01–1.12, $p = 0.02$, respectively) (Ferguson et al. 2014). Additionally, the morbidity and mortality (including noncancer mortality) associated with a low ppoDLCO increases with age (Eguchi et al. 2016).

Frailty is an independent risk factor for postoperative complications, length of hospital stay, and discharge to skilled or assisted living facilities in older patients (Makary et al. 2010). Frailty in patients referred for lung cancer surgical resection is under recognized. A 2017 study by Beckert et al. found, in a prospective cohort study of 125 patients referred to an academic thoracic surgical clinic for thoracic surgical procedures, that

Table 9 Presurgical cardiopulmonary assessments

PPO lung function	Further testing	Risk assessment
$FEV_1 > 60\%$ and DLCO >60%	Not indicated	**Low risk**
FEV_1 or DLCO 30–60% predicted	"Low technology" exercise test (e.g., stair climbing or shuttle walk)	**Low risk** if stair climbing altitude >22 m or shuttle walk distance >400 m
FEV_1 and/or DLCO <30% predicted	"High technology" exercise test (e.g., cardiopulmonary exercise test)	**Low risk** if VO2 peak >20 ml/kg/min (or 75% predicted) **High risk** if VO2 peak <10 ml/kg/min (or 35% predicted)

Adapted from Brunelli et al. (2013)
PPO postoperative lung function, *FEV_1* forced expiratory volume in 1 second, *DLCO* diffusing capacity of the lung for carbon monoxide, *VO2* peak oxygen consumption

12% were frail and 57% were prefrail based on an adapted Fried's phenotypic frailty assessment (Beckert et al. 2017).

Various presurgical assessments of physical robustness have been explored in an effort to achieve greater precision in presurgical risk stratification. Tsiouris et al. created an 11-item modified frailty index (mFI) adapted from the Canadian Study of Health and Aging Frailty Index, a 70-item scale that predicts survival using preoperative data from the National Surgical Quality Improvement Program (NSQIP) (Tsiouris et al. 2013). Items in this index included functional status and co-morbidities (e.g., diabetes, COPD, and cardiovascular disease). The authors found that morbidity and mortality increased as mFI increased in patients who had undergone an open lobectomy. This study suggests that an objective approach to assessing preoperative frailty may improve upon single-organ assessments.

Sublobar resection may not improve long-term survival when compared to lobectomy; however, this has not been demonstrated prospectively. In 2014, Shirvani et al. retrospectively analyzed patients with early-stage NSCLC undergoing curative surgical therapy (mean age 75 years, $n = 9093$) in the SEER database. Most (79.3%) patients underwent lobectomy, while 16.5% underwent sublobar resection and 4.2% underwent stereotactic ablative radiotherapy (SABR) (Shirvani et al. 2014). Unadjusted 90-day mortality was highest for patients who underwent lobectomy (4.0%) as compared to the other two groups (sublobar resection, 3.7%, $p = 0.79$; SABR, 1.3%, $p = 0.008$). However, 3-year unadjusted mortality was lowest for patients who underwent lobectomy (25.0%) as compared to the other two groups (sublobar resection, 35.3%, $p < 0.001$; SABR, 45.1%, $p < 0.001$). Propensity score matching between sublobar resection and lobectomy groups demonstrated worse survival for the sublobar resection groups.

When comorbidities or patient preferences contraindicate surgical resection of an early stage tumor, other options include observation/best supportive therapy or SABR (Table 8). Median survival without surgical resection in patients with early stage disease is poor, with one estimate suggesting survival of 14.2 ± 2.37 months (Mcgarry et al. 2002). In Shirvani et al.'s study, a propensity score-matched analysis of SABR and lobectomy groups, showed a similar overall survival, suggesting that SABR is indicated in patients who cannot tolerate surgical risk (Shirvani et al. 2014). Further, a pooled analysis of two small randomized trials comparing SABR to surgical resection suggests that the two treatments may be equally effective, and that SABR may be preferred in individuals with multiple comorbidities (Chang et al. 2015). In 55 patients with T1 or T2 tumors, stereotactic body radiation therapy without resection had a 3-year local control rate of 90.6% (95% CI, 76.0–96.5%) and a local-regional control rate of 87.2% (95% CI, 71.0–94.7%). The median survival was 48.1 months, with a 55.8% survival rate at 3 years (Timmerman et al. 2010).

Adjuvant therapy with postoperative cisplatin-based doublet chemotherapy for stage

IIA to IIIA is standard of care (Pisters et al. 2007). A 2004 study of 1867 patients treated with cisplatin-based adjuvant chemotherapy following surgical resection showed 44.5% survival at 5 years as compared to 40.4% in the observation group ($p < 0.03$) (Group 2004). Cuffe et al. examined the Ontario Cancer Registry to assess the benefit of adjuvant chemotherapy on older age groups (<70, 70–74, 75–79, and ≥80) (Cuffe et al. 2012). This analysis found benefit of adjuvant chemotherapy in all age groups except for those ≥80 years. The main concerns with using cisplatin-based doublet therapy in older adults are the adverse side effects of renal and ototoxicity, requiring intravenous hydration pre- and postinfusion. It is also highly emetogenic, requiring adequate antiemetic support. Risk stratification taking organ function, social support, transportation, and medication management into account prior to selection of cisplatin is mandatory to prevent severe toxicity. Carboplatin is often substituted for cisplatin for high-risk older adults.

Locally Advanced NSCLC (Stage III)

Concurrent chemoradiation is indicated for curative-intent treatment of locally advanced NSCLC: stage IIIA medically inoperable or stage IIIB (Bezjak et al. 2015). However, for more frail, high-risk older adults, sequential chemotherapy followed by radiation is also an option. The 5-year relative survival rate for regionally advanced lung cancer is 28% and for distant metastatic lung cancer is 4% (ACS 2016). Surgical resection and neoadjuvant chemotherapy are controversial in patients with stage III, N2 cancers. In some centers, patients with adequate performance status and acceptable surgical risk proceed to surgery if the tumor is noninvasive and the N2 disease is completely resectable. Other centers recommend presurgical eradication of N2 disease with induction chemotherapy before proceeding to surgery (Van Meerbeeck et al. 2007; Albain et al. 2009).

There is limited strong, prospective evidence to guide surveillance of patients who have undergone curative intent therapy. Current guidelines suggest that patients who have undergone surgical resection of NSCLC have a follow-up chest CT every 6 months for 2 years, then yearly (Colt et al. 2013). When surveillance becomes yearly for the curative-intent cohort, it mimics the screening suggested for eligible patients in the new lung cancer screening guidelines (Table 3). Just as is suggested in the screening cohort, providers should reevaluate patient wishes to continue surveillance when comorbidities or functional status alter patient preferences to undergo further cancer work-up or therapy, if disease recurrence is identified on imaging.

Metastatic NSCLC (Stage IV)

Most lung cancer is diagnosed at an advanced, metastatic state of disease. Currently, the treatment for advanced NSCLC is expanding rapidly and includes targeted treatments and immunotherapy in addition to traditional chemotherapy, the original mainstay of treatment for advanced disease. All metastatic lung cancer biopsy specimens should undergo molecular marker testing for the EGFR mutation, anaplastic lymphoma kinase (ALK) rearrangement, or ROS1 translocation (Lindeman et al. 2013), to determine if driver mutation-targeted therapies can be used. In a small study of 32 patients (median age 80 with NSLC and the EGFR mutation) treated with the EGFR tyrosine kinase inhibitor erlotinib, this drug was well-tolerated and had similar efficacy (56.3% response rate) as compared to a prior study of a mixed-age cohort (58.1% response rate) (Rosell et al. 2012; Inoue et al. 2015). The most frequent adverse event was skin-related toxicity. A separate study of erlotinib versus placebo in 731 patients compared outcomes based on age (<70 years or ≥70 years). The older age group had similar survival as compared to the younger group but experienced more severe (grade 3/4) toxicity. For ALK positive tumors, ALK tyrosine kinase inhibitors (e.g., crizotinib or ceritinib) are superior to standard chemotherapy (Solomon et al. 2014; Shaw et al. 2014). Tumors with the

ROS1 rearrangement should be treated with crizotinib (Bergethon et al. 2012).

Immunotherapy utilizing checkpoint inhibitors such as programmed death-1 (PD-1) inhibitors is beginning to emerge as an important pillar of treatment in NSCLC. PD-1 inhibitors have a survival benefit as compared to first-line platinum-based doublet chemotherapy or second-line chemotherapy after treatment failure with doublet therapy. Two pivotal studies in 2015 demonstrated increased overall survival in patients treated with the PD-1 inhibitor nivolumab, as compared to docetaxel, in previously treated, advanced squamous-cell NSCLC regardless of PD-L1 expression (Brahmer et al. 2015) and previously treated, advanced nonsquamous NSCLC (Borghaei et al. 2015). Reck et al., in 2016, then demonstrated superiority of the PD-1 inhibitor pembrolizumab as compared to platinum-based chemotherapy, in untreated NSCLC (both squamous and non-squamous), in which at least half of the tumor cells were PD-L1 positive but ALK and EGFR negative (Reck et al. 2016). Progression-free survival was 10.3 months in the pembrolizumab group as compared to 6.0 months in the chemotherapy group. Importantly, overall survival was significantly longer in the group treated with pembrolizumab (HR 0.6, 95% CI 0.41–0.89, $p = 0.005$). Six-month survival was 80.2% for those treated with pembrolizumab compared to 72.4% in the chemotherapy group. Additionally, there were fewer treatment-related adverse events in the pembrolizumab group. Though promising, these results have yet to be replicated in large population-based studies. As clinical trials include younger, healthier adults, evidence of improved overall survival and decreased toxicity among frail older adults is needed.

Cytotoxic platinum-based chemotherapy is the first-line treatment for the majority of advanced NSCLC without a molecular mutation with a targeted therapy (Table 8). Standard chemotherapy consists of two agent (doublet) therapy with a platinum agent (e.g., cisplatin or carboplatin) plus a second agent (e.g., docetaxel, paclitaxel, gemcitabine, etoposide, irinotecan, or vinorelbine) (Masters et al. 2015). Several studies have shown efficacy of chemotherapy treatment in elderly patients with lung cancer. A 2011 multicenter study of 451 patients aged 70–89 years with locally advanced or metastatic NSCLC and good performance status (WHO performance status 0–2) found that platinum-based doublet chemotherapy improved survival (10.6 months) compared to monotherapy (6.2 months) with vinorelbine or gemcitabine (Quoix et al. 2011). The patients who underwent doublet chemotherapy experienced significantly more side effects, particularly cytopenias and neuropathy.

Histologic subtyping of NSCLC helps determine the preferred first-line cytotoxic chemotherapy agents. A study by Scagliotti and colleagues in 2008 found a significant survival benefit for patients with squamous cell carcinoma treated with cisplatin/gemcitabine (10.8 months) versus cisplatin/pemetrexed (9.4 months) (Scagliotti et al. 2008). In patients with adenocarcinoma, treatment with cisplatin/pemetrexed is preferred (12.6 months compared to 10.9 months). High-grade cytopenias were significantly higher with cisplatin/pemetrexed treatment.

Bevacizumab, an antibody that inhibits vascular epithelial growth factor A (VEGF-A), improves survival in patients with metastatic non-squamous NSCLC, in combination with platinum-based doublet therapy (Sandler et al. 2006). Data supporting its efficacy in elderly patients has been inconclusive, and increased adverse events (including death) appear to be significantly higher (Ramalingam et al. 2008). Therefore, the increased risk in older populations may outweigh potential benefits. Bevacizumab is not used in squamous cell lung cancer due to the increased risk of serious hemorrhagic events.

Even when patients cannot have surgical resection either due to advanced disease, risk stratification by performance status and CGA remains important, as chemoradiation therapies carry risk of serious toxicities. Elderly patients are a potentially vulnerable patient population to experience treatment-related toxicities, and oncologists have struggled with both overtreatment and undertreatment when caring for individuals with NSCLC (Presley et al. 2016). A 2010 retrospective study of the SEER Medicare database

revealed that many elderly patients with advanced NSCLC do not receive chemotherapy in spite of survival benefits in those who do (Davidoff et al. 2010).

The first evidence that undertreatment impairs patient quality of life came in 1999, when the Vinorelbine Italian Study Group presented data that, in patients over age 70 with stage IV or IIIB NSCLC ineligible for radiotherapy with good performance status, treatment with six 21-day cycles of vinorelbine (a vinca alkaloid) significantly improved survival (Group 1999).Cognitive function was better in the vinorelbine group, and they reported less pain and dyspnea. They did report worse constipation, nausea/vomiting, hair loss, and peripheral neuropathy.

Elderly patients are an at-risk group with potentially more comorbidities and functional impairments that can impact chemoradiation tolerance. Hurria et al. found that 53% of older adults experienced at least one grade 3–5 toxicity during the course of treatment across cancer types and stages (Hurria et al. 2011). A 2015 retrospective study of the SEER registry demonstrated a significant burden of toxicity on elderly patients (70 years or older) with advanced NSCLC undergoing therapy (Kale et al. 2017). Patients with stage IIIB had a nearly sixfold increase in toxicities with chemoradiation compared to those who received no treatment. The most common toxicity was esophagitis. Stage IV patients had a nearly fourfold increase in toxicities with chemotherapy, most commonly neutropenia. This study was limited by the lack of analysis by chemotherapy agent or doublet versus singlet therapy.

Rarely, chemotherapy agents and radiation therapy can cause toxicity to the lungs directly, which can include pneumonitis or acute respiratory distress syndrome (Read et al. 2002; Parashar et al. 2011). Pulmonologists crowd source and catalog treatment-related lung toxicity at www.pneumotox.com (Camus et al. 2013). Checkpoint inhibitor-related pneumonitis is an uncommon but highly morbid complication of use that is rising in prevalence with increased use of these agents. Pneumonitis is estimated to occur in 5% of patients, with onset ranging from 9 days to 19.2 months following treatment (Naidoo et al. 2017).

Improvements in risk stratification, to limit toxicities while maximizing therapy benefit, are ongoing. A 2016 study by Corre et al. assigned patients with advanced NSCLC (median age 77 years, n = 494) to chemotherapy regimens based either on performance status or CGA (Corre et al. 2016). In the standard arm, patients were assigned based on performance status; if PS $\leq$ 2 and age $\leq$ 75, patients received carboplatin-based doublet chemotherapy, and if PS =2 or age > 75 they received docetaxel. In the CGA group, "fit" patients received carboplatin-based doublet, "vulnerable" patients received docetaxel, and "frail" patients received best supportive care. In summary, patients assigned to treatment based on CGA experienced significantly less treatment toxicity, with similar overall survival and treatment failure free survival.

Joint decision-making with patients is important. Discussions should include careful counseling about expected toxicities including the likelihood of functional or cognitive impairment. Projected toxicities may influence a patient's advanced care planning more than risk of death (Fried et al. 2002). Treatment-related toxicities in older patients receiving chemotherapy can be predicted using the CRASH (Extermann et al. 2012) or CARG (Hurria et al. 2011) calculators (Table 7). Risk calculators for both targeted treatments and immune checkpoint inhibitors are needed.

Finally, palliative care should be a cornerstone of caring for patients with metastatic (stage IV) lung cancer (Table 8). In addition to improving symptom control, palliative care can also increase survival. A revolutionary study by Temel and colleagues in 2010 demonstrated that, in patients with metastatic NSCLC, an early palliative care intervention led to increased median survival compared to standard care (11.6 vs. 8.9 months p = 0.02 (Temel et al. 2010). On average, patients who received early palliative care had received less aggressive care than the standard treatment group (33% vs. 54%, p = 0.05) and noted better quality of life and less depression and anxiety. The

palliative care intervention consisted of guideline-based visits with a dedicated palliative care team, including board-certified palliative care advanced practice nurses and physicians, who met with the patient at least monthly and attended particularly to "physical and psychosocial symptoms."

Lung cancer-related symptoms are wide-ranging and can be debilitating. A frequent lung cancer symptom is dyspnea due to cancer-related etiologies that include pneumonia, pulmonary emboli, metastatic pleural effusions, or superior vena cava syndrome. Care teams can track dyspnea symptoms using clinical dyspnea scales (Table 2). Other symptoms include sequelae of metastases (e.g., bone pain and neurologic impairment), depression, anxiety, insomnia, and fatigue (Simoff et al. 2013). Rarely, airway-esophageal fistulas and paraneoplastic syndromes can occur. Palliative care teams experienced in treating these symptoms are invaluable partners in patient care.

Other Lung Malignancies

Small Cell Lung Cancer

Small cell lung cancer (SCLC) is an aggressive neuroendocrine malignancy comprising about 15% of all lung cancers (ACS 2016). Unlike NSCLC, the malignant cells are characterized by rapid growth and initial sensitivity to chemotherapy and radiation that later becomes resistant to treatment (Rudin et al. 2015). It is strongly associated with a history of smoking. Classic staging for SCLC uses the Veterans Administration system of limited or extensive stage disease, though the AJCC TNM staging system is recommended due to improved prognostic discriminatory power (Micke et al. 2002; Jett et al. 2013). In limited stage disease, the cancer is localized to the ipsilateral hemithorax and regional lymph nodes. Extensive disease includes any spread beyond, such as distant metastases. Staging should be performed radiographically (head MRI/CT and PET) as well as invasively (EBUS or mediastinoscopy) if patients are being considered for curative intent surgical resection.

In stage I disease, which is uncommon, adjuvant chemotherapy should be administered following surgical resection. In limited stage disease, early chemotherapy with radiotherapy is recommended. The foundation of treatment is combination chemotherapy, typically including a platinum agent (e.g., carboplatin or cisplatin) (Rudin et al. 2015). Whether a patient has limited or extensive stage disease, prophylactic cranial irradiation is indicated. However for older adults, cranial irradiation can cause acute, subacute, and long-term impairments to cognition, a particularly pertinent side effect for elderly populations (Robbins et al. 2012).

A 2011 retrospective study of chemotherapy tolerability in the Netherlands looked at 368 patients with limited stage SCLC and 577 with extensive stage SCLC, all 75 years old or older (Janssen-Heijnen et al. 2010). Many patients (48%) did not receive chemotherapy for a wide range of reasons, including poor performance status or patient preference. Up to 75% of all patients undergoing chemotherapy developed a serious toxicity and two-thirds could not complete treatment. Survival is extremely limited without chemotherapy treatment, so even patients with impaired performance status are typically treated (Pelayo Alvarez et al. 2009).

Other Neuroendocrine Tumors, Mesothelioma, and Pulmonary Metastases

Less common malignancies of the respiratory system include malignant mesothelioma and other lung neuroendrocrine tumors such as carcinoid (bronchial neuroendocrine) tumors and large cell neuroendocrine carcinoma. Large cell neuroendocrine carcinoma, like small cell lung cancer, has a poor prognosis and 5-year survival across all stages is approximately 35.3% (Fasano et al. 2015). Treatment can include surgical resection in early stage disease, with adjuvant chemotherapy.

Bronchial neuroendocrine (carcinoid) tumors are indolent tumors that have increased in incidence since the 1980s. Age 60 or greater strongly

predicts mortality (Perez et al. 2007). Localized disease is typically managed with surgical resection and data on adjuvant chemotherapy is mixed. Metastatic disease is treated with first with a somatostatin analog, with everolimus as second-line therapy. Cytotoxic chemotherapy if everolimus fails to control disease. A complication of carcinoid tumors is carcinoid syndrome, which can be treated with somatostatin analogs (e.g., octreotide) (Pavel et al. 2011).

Mesothelioma is an asbestos-associated malignancy, that presents insidiously (Van Zandwijk et al. 2013). The average age of diagnosis is over age 60, implying a disproportionate burden of disease on elderly patients. The average overall survival is 7 months. Malignant mesothelioma is typically treated with two-agent platinum-based chemotherapy. Surgical debulking can palliate symptoms. Radiotherapy is a cornerstone of palliative treatment, both to control symptoms and prevent relapse following surgery. Pleurodesis can be useful to manage recurrent malignant effusions.

The lung and pleural space is a frequent site of metastatic disease from non-lung primary cancers, including breast, colon, ovarian, bladder, and melanoma (Nguyen et al. 2009). In addition to chemotherapy or radiation to treat these metastatic lesions (Rusthoven et al. 2009), further palliative management may be indicated. Interventional pulmonologists can assist with palliative management using stent placement or laser therapy to treat endobronchial lesions or bronchial compression from surrounding tumor (Cavaliere et al. 1996). Pleurodesis or long-term indwelling pleural catheters may be used to manage malignant pleural effusions (Van Meter et al. 2011).

Conclusion

Maximal pulmonary function declines with aging, beginning in the third decade of life (Table 10). The natural history of lung aging involves progressive decline in lung elasticity leading to increased lung volumes and an obstructive spirometric pattern. Respiratory muscle weakness and changes to the architecture of the thorax can concomitantly cause a restrictive pulmonary function pattern. When evaluating pulmonary function testing in the geriatric patient, one must consider the natural history of lung changes so as to avoid overdiagnosis of lung disease.

Chronic obstructive pulmonary disease has been described as a disease of accelerated aging, though recent evidence indicates that a subset of affected patients has abnormal lung development with normal lung aging. Both COPD and IPF share pathogenic cellular features in common with lung cancer, including telomere attrition, defective DNA repair, genomic instability, cellular senescence, stem cell exhaustion, and mitochondrial dysfunction.

Lung cancer is the deadliest malignancy in the USA, and its prevalence increases with age. Non-small cell lung cancer is the most common of lung cancer and adenocarcinoma is the most common histologic type. Depending on the stage at diagnosis, treatment options for NSCLC can include surgical resection, single agent chemotherapy, doublet chemotherapy, immunotherapy, targeted driver mutation therapies, and/or radiation.

For early-stage NSCLC that amenable to surgical resection, patients must have presurgical pulmonary function testing with calculation of predicted postoperative lung function. Depending

Table 10 Key points

Lung aging begins in the third decade of life
COPD, IPF, and lung cancer share pathogenic cellular features, including telomere
Attrition, defective DNA repair, genomic instability, and cellular senescence
Lung cancer is the deadliest of all malignancies
Screening for lung cancer is recommended for high-risk patients (age 55–80 with $\geq$30 pack-year smoking history)
Comprehensive geriatric assessments prior to treatment limit toxicities and may improve survival
Early palliative care should be initiated for all patients with stage IV lung cancer

on the FEV_1 and/or DLCO, patients may require "low technology" (e.g., stair climbing or shuttle walk) or "high technology" (e.g., cardiopulmonary exercise testing) to determine their cardiopulmonary fitness for surgery. Frailty is under recognized, and frail patients have more surgical complications. Adjuvant chemotherapy can improve outcomes.

First-line treatment for advanced NSCLC is driver mutation-targeted therapy if eligible, against ALK, EGFR, ROS1, and/or PDL-1. Most patients do not have these mutations, so doublet platinum-based therapy is their first line treatment. Single-agent or no chemotherapy is reserved for patients with poor performance status or high-risk as determined by a Comprehensive Geriatric Assessment. In metastatic NSCLC, palliative care must be a cornerstone of best supportive care. Given the profound burden of lung cancer on geriatric patients, pretreatment global functioning should be evaluated for risk-stratification and to guide treatment decisions. Traditional risk-stratification relied on assessing performance status with either Karnofsky or ECOG/WHO tools. Variations of the Comprehensive Geriatric Assessment are gaining ground as methods for risk-stratifying patients prior to cancer treatment. Risk stratification based on CGA can lead to decreased treatment toxicity with similar or improved survival.

Avoiding undertreatment in fit elderly patients and overtreatment in vulnerable subgroups remains the shared goal of clinical partnerships between primary care providers, geriatricians, medical oncologists, thoracic surgeons, and pulmonologists. As evidence accumulates about how best to assess pretreatment global fitness, physicians must adopt a shared-decision making strategy, incorporating patient preferences into treatment decisions.

Cross-References

- ▶ Lung Cancer in Older Adults: Local Treatment
- ▶ Lung Cancer in Older Adults: Systemic Treatment

Acknowledgments Funding support for LW is provided by the NIH funded Research Training in Respiratory Biology grant at the University of Chicago (T32 HL007605). Funding support for CP is provided by the Robert Wood Johnson Foundation/Veteran's Health Administration Clinical Scholars Program, The Conquer Cancer Foundation, and Yale University SPORE in lung cancer grant P50CA196530.

References

ACS. Cancer facts & figures 2016. Atlanta: American Cancer Society; 2016.

AJCC 2017. AJCC cancer staging manual, Springer: New York.

Albain KS, Swann RS, Rusch VW, Turrisi AT, Shepherd FA, Smith C, Chen Y, Livingston RB, Feins RH, Gandara DR. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374:379–86.

Balducci L, Extermann M. Management of cancer in the older person: a practical approach. Oncologist. 2000;5:224–37.

Beckert AK, Huisingh-Scheetz M, Thompson K, Celauro AD, Williams J, Pachwicewicz P, Ferguson MK. Screening for frailty in thoracic surgical patients. Ann Thorac Surg. 2017;103:956–61.

Bergethon K, Shaw AT, Ignatius Ou S-H, Katayama R, Lovly CM, Mcdonald NT, Massion PP, Siwak-Tapp C, Gonzalez A, Fang R. Ros1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol. 2012;30:863–70.

Bezjak A, Temin S, Franklin G, Giaccone G, Govindan R, Johnson ML, Rimner A, Schneider BJ, Strawn J, Azzoli CG. Definitive and adjuvant radiotherapy in locally advanced non–small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline endorsement of the American Society for Radiation Oncology evidence-based clinical practice guideline. J Clin Oncol. 2015;33:2100–5.

Blackwell TS, Tager AM, Borok Z, Moore BB, Schwartz DA, Anstrom KJ, Bar-Joseph Z, Bitterman P, Blackburn MR, Bradford W, Brown KK, Chapman HA, Collard HR, Cosgrove GP, Deterding R, Doyle R, Flaherty KR, Garcia CK, Hagood JS, Henke CA, Herzog E, Hogaboam CM, Horowitz JC, King TE, Loyd JE, Lawson WE, Marsh CB, Noble PW, Noth I, Sheppard D, Olsson J, Ortiz LA, O'riordan TG, Oury TD, Raghu G, Roman J, Sime PJ, Sisson TH, Tschumperlin D, Violette SM, Weaver TE, Wells RG, White ES, Kaminski N, Martinez FJ, Wynn TA, Thannickal VJ, Eu JP. Future directions in idiopathic pulmonary fibrosis research. An NHLBI workshop report. Am J Respir Crit Care Med. 2013;189:214–22.

Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14:377–81.

Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med. 2015;373:1627–39.

Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA. 2005;294:716–24.

Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. N Engl J Med. 2015;373:123–35.

Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier J-P, Varela G, Licker M, Ferguson M, Faivre-Finn C, Huber RM. Ers/Ests clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J. 2009;34:17–41.

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: American College of Chest Physicians evidence-based clinical practice guidelines. Chest J. 2013;143:E166s–90s.

Burri PH. Structural aspects of postnatal lung development–alveolar formation and growth. Neonatology. 2006;89:313–22.

Bush A. Lung development and aging. Ann Am Thorac Soc. 2016;13:S438–46.

Camus P, Bonniaud P, Camus C, Foucher P, Jacquet L. Pneumotox – an updated time-saving web resource. Eur Respir J. 2013;42:5043.

Caramori G, Adcock IM, Casolari P, Ito K, Jazrawi E, Tsaprouni L, Villetti G, Civelli M, Carnini C, Chung KF. Unbalanced oxidant-induced DNA damage and repair in COPD: a link towards lung cancer. Thorax. 2011;2010:156448.

Castriotta RJ, Eldadah BA, Foster WM, Halter JB, Hazzard WR, Kiley JP, King TE, Horne FM, Nayfield SG, Reynolds HY. Workshop on idiopathic pulmonary fibrosis in older adults. Chest J. 2010;138:693–703.

Cavaliere S, Venuta F, Foccoli P, Toninelli C, La Face B. Endoscopic treatment of malignant airway obstructions in 2,008 patients. Chest. 1996;110:1536–42.

Celli BR, Cote CG, Marin JM, Casanova C, Montes De Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1005–12.

Cerfolio RJ, Bryant AS. Survival of patients with true pathologic stage I non-small cell lung cancer. Ann Thorac Surg. 2009;88:917–23.

Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, Groen HJ, Mcrae SE, Widder J, Feng L. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2015;16:630–7.

Chilosi M, Carloni A, Rossi A, Poletti V. Premature lung aging and cellular senescence in the pathogenesis of idiopathic pulmonary fibrosis and COPD/emphysema. Transl Res. 2013;162:156–73.

Colt HG, Murgu SD, Korst RJ, Slatore CG, Unger M, Quadrelli S. Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. Chest J. 2013;143:E437s–54s.

Corre R, Greillier L, Le Caër H, Audigier-Valette C, Baize N, Bérard H, Falchero L, Monnet I, Dansin E, Vergnenègre A. Use of a comprehensive geriatric assessment for the management of elderly patients with advanced non–small-cell lung cancer: the phase III randomized ESOGIA-GFPC-GECP 08-02 study. J Clin Oncol. 2016;34:1476–83.

Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel J-P, Rolland Y, Schneider SM. Sarcopenia: European consensus on definition and diagnosis report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412–23.

Cuffe S, Booth CM, Peng Y, Darling GE, Li G, Kong W, Mackillop WJ, Shepherd FA. Adjuvant chemotherapy for non–small-cell lung cancer in the elderly: a population-based study in Ontario, Canada. J Clin Oncol. 2012;30:1813–21.

Darby S, Hill D, Auvinen A, Barros-Dios J, Baysson H, Bochicchio F, Deo H, Falk R, Forastiere F, Hakama M. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ. 2005;330:223.

Davidoff AJ, Tang M, Seal B, Edelman MJ. Chemotherapy and survival benefit in elderly patients with advanced non–small-cell lung cancer. J Clin Oncol. 2010;28:2191–7.

De Torres JP, Bastarrika G, Wisnivesky JP, Alcaide AB, Campo A, Seijo LM, Pueyo JC, Villanueva A, Lozano MAD, Montes U. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. Chest J. 2007;132:1932–8.

Egan TM, Murray S, Bustami R, Shearon T, Mccullough KP, Edwards L, Coke M, Garrity E, Sweet S, Heiney D. Development of the new lung allocation system in the United States. Am J Transplant. 2006;6:1212–27.

Eguchi T, Bains S, Lee M-C, Tan KS, Hristov B, Buitrago DH, Bains MS, Downey RJ, Huang J, Isbell JM. Impact of increasing age on cause-specific mortality and morbidity in patients with stage I non–small-cell lung cancer: a competing risks analysis. J Clin Oncol. 2016;35(3):281–90.

Enright PL, Kronmal RA, Manolio TA, Schenker MB, Hyatt R. Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular Health Study Research Group. Am J Respir Crit Care Med. 1994;149:430–8.

Evison M, Crosbie PA, Martin J, Bishop P, Doran H, Joseph L, Chaturvedi A, Barber PV, Booton R. EBUS-TBNA in elderly patients with lung cancer: safety and performance outcomes. J Thorac Oncol. 2014;9:370–6.

Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol. 2007;25:1824–31.

Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, Defelice J, Levine RM, Lubiner ET, Reyes P, Schreiber FJ. Predicting the risk of chemotherapy toxicity in older patients: the chemotherapy risk assessment scale for high-age patients (Crash) score. Cancer. 2012;118:3377–86.

Fasano M, Della Corte CM, Papaccio F, Ciardiello F, Morgillo F. Pulmonary large-cell neuroendocrine carcinoma: from epidemiology to therapy. J Thorac Oncol. 2015;10:1133–41.

Ferguson MK, Gaissert HA, Grab JD, Sheng S. Pulmonary complications after lung resection in the absence of chronic obstructive pulmonary disease: the predictive role of diffusing capacity. J Thorac Cardiovasc Surg. 2009;138:1297–302.

Ferguson MK, Watson S, Johnson E, Vigneswaran WT. Predicted postoperative lung function is associated with all-cause long-term mortality after major lung resection for cancer. Eur J Cardiothorac Surg. 2014;45:660–4.

Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1:1645–8.

Fontham ET, Correa P, Reynolds P, Wu-Williams A, Buffler PA, Greenberg RS, Chen VW, Alterman T, Boyd P, Austin DF. Environmental tobacco smoke and lung cancer in nonsmoking women: a multicenter study. JAMA. 1994;271:1752–9.

Fragoso CAV, Enright PL, Mcavay G, Van Ness PH, Gill TM. Frailty and respiratory impairment in older persons. Am J Med. 2012;125:79–86.

Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G. Frailty in older adults evidence for a phenotype. J Gerontol Ser A Biol Med Sci. 2001;56:M146–57.

Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. N Engl J Med. 2002;346:1061–6.

Fried TR, Fragoso CAV, Rabow MW. Caring for the older person with chronic obstructive pulmonary disease. JAMA. 2012a;308:1254–63.

Fried TR, Vaz Fragoso CA, Rabow MW. Caring for the older person with chronic obstructive pulmonary disease: "I was worried that he didn't have much room to decline". JAMA. 2012b;308:1254. https://doi.org/10.1001/Jama.2012.12422.

Gajra A, Jatoi A. Non–small-cell lung cancer in elderly patients: a discussion of treatment options. J Clin Oncol. 2014;32:2562–9.

GOLD. Global initiative for chronic obstructive lung disease (GOLD). 2017.

Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, Postmus PE, Rusch V, Sobin L, Committee, I. A. F. T. S. O. L. C. I. S. The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol. 2007;2:706–14.

Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, Nicholson AG, Groome P, Mitchell A, Bolejack V. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol. 2016;11:39–51.

Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. Am J Respir Crit Care Med. 1996;153:976–80.

Group, E. L. C. V. I. S. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. J Natl Cancer Inst. 1999;91:66–72.

Group, I. A. L. C. T. C. Cisplatin-based adjuvant chemotherapy in patients with completely resected non–small-cell lung cancer. N Engl J Med. 2004;2004:351–60.

Hanania NA, King MJ, Braman SS, Saltoun C, Wise RA, Enright P, Falsey AR, Mathur SK, Ramsdell JW, Rogers L. Asthma in the elderly: current understanding and future research needs – a report of a National Institute on Aging (NIA) workshop. J Allergy Clin Immunol. 2011;128:S4–S24.

Hardie J, Buist AS, Vollmer W, Ellingsen I, Bakke P, Mørkve O. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. Eur Respir J. 2002;20:1117–22.

Ho SF, O'mahony MS, Steward JA, Breay P, Buchalter M, Burr ML. Dyspnoea and quality of life in older people at home. Age Ageing. 2001;30:155–9.

Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, Cl K, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA, editors. SEER cancer statistics review, 1975–2013. Bethesda: National Cancer Institute; 2016.

Huijnen B, Van Der Horst F, Van Amelsvoort L, Wesseling G, Lansbergen M, Aarts P, Nicolson N, Knottnerus A. Dyspnea in elderly family practice patients. Occurrence, severity, quality of life and mortality over an 8-year period. Fam Pract. 2006;23:34–9.

Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, Lichtman SM, Gajra A, Bhatia S, Katheria V. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011;29:3457–65.

Inoue Y, Inui N, Asada K, Karayama M, Matsuda H, Yokomura K, Koshimizu N, Imokawa S, Yamada T, Shirai T. Phase II study of erlotinib in elderly patients with non-small cell lung cancer harboring epidermal growth factor receptor mutations. Cancer Chemother Pharmacol. 2015;76:155–61.

Jankowich MD, Rounds SI. Combined pulmonary fibrosis and emphysema syndrome: a review. Chest J. 2012;141:222–31.

Janssen-Heijnen M, Maas H, Van De Schans S, Coebergh J, Groen H. Chemotherapy in elderly small-cell lung cancer patients: yes we can, but should we do it? Ann Oncol. 2010;22(4):821–826.

Janssens J-P. Aging of the respiratory system: impact on pulmonary function tests and adaptation to exertion. Clin Chest Med. 2005;26:469–84.

Janssens J-P, Pache J-C, Nicod L. Physiological changes in respiratory function associated with ageing. Eur Respir J. 1999;13:197–205.

Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. Chest J. 2013;143:E400s–19s.

Jones SE, Maddocks M, Kon SS, Canavan JL, Nolan CM, Clark AL, Polkey MI, Man WD. Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. Thorax. 2015;70:213–8.

Kale MS, Mhango G, Gomez JE, Sigel K, Smith CB, Bonomi M, Wisnivesky JP. Treatment toxicity in elderly patients with advanced non-small cell lung cancer. Am J Clin Oncol. 2017;40(5):470–476.

Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma. With particular reference to bronchogenic carcinoma. Cancer. 1948;1:634–56.

King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2083–92.

Kwak N, Park C-M, Lee J, Park YS, Lee S-M, Yim J-J, Yoo C-G, Kim YW, Han SK, Lee C-H. Lung cancer risk among patients with combined pulmonary fibrosis and emphysema. Respir Med. 2014;108:524–30.

Lahousse L, Ziere G, Verlinden VJ, Zillikens MC, Uitterlinden AG, Rivadeneira F, Tiemeier H, Joos GF, Hofman A, Ikram MA. Risk of frailty in elderly with COPD: a population-based study. J Gerontol Ser A Biol Med Sci. 2016;71:689–95.

Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, Guerra S, Marott JL, Martinez FD, Martinez-Camblor P. Lung-function trajectories leading to chronic obstructive pulmonary disease. N Engl J Med. 2015;373:111–22.

Le Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. J Am Coll Cardiol. 2007;49:171–80.

Leech JA, Dulberg C, Kellie S, Pattee L, Gay J. Relationship of lung function to severity of osteoporosis in women. Am Rev Respir Dis. 1990;141:68.

Ley B, Collard HR, King TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;183:431–40.

Lin H-H, Murray M, Cohen T, Colijn C, Ezzati M. Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: a time-based, multiple risk factor, modelling study. Lancet. 2008;372:1473–83.

Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, Jenkins RB, Kwiatkowski DJ, Saldivar J-S, Squire J. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. J Thorac Oncol. 2013;8:823–59.

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153:1194–217.

Luoto JA, Elmståhl S, Wollmer P, Pihlsgård M. Incidence of airflow limitation in subjects 65–100 years of age. Eur Respir J. 2015. http://erj.ersjournals.com/content/erj/early/2015/12/17/13993003.00635-2015.full.pdf

Ma J, Ward EM, Smith R, Jemal A. Annual number of lung cancer deaths potentially avertable by screening in the United States. Cancer. 2013;119:1381–5.

Macmahon H, Naidich DP, Goo JM, Lee KS, Leung AN, Mayo JR, Mehta AC, Ohno Y, Powell CA, Prokop M. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology. 2017;284:228–43.

Macnee W. Is chronic obstructive pulmonary disease an accelerated aging disease? Ann Am Thorac Soc. 2016;13:S429–37.

Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest. 1988;93:580–6.

Maione P, Perrone F, Gallo C, Manzione L, Piantedosi F, Barbera S, Cigolari S, Rosetti F, Piazza E, Robbiati SF. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non—small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol. 2005;23:6865–72.

Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, Takenaga R, Devgan L, Holzmueller CG, Tian J. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 2010;210:901–8.

Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. J Natl Cancer Inst. 2011;103:117–28.

Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S Jr, Brahmer JR, Ellis PM, Gajra A, Rackear N, Schiller JH. Systemic therapy for stage IV non–small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2015;33:3488–515.

Mcgarry RC, Song G, Des Rosiers P, Timmerman R. Observation-only management of early stage, medically inoperable lung cancer: poor outcome. Chest. 2002;121:1155–8.

Mckee BJ, Regis SM, Mckee AB, Flacke S, Wald C. Performance of ACR lung-RADS in a clinical CT lung screening program. J Am Coll Radiol. 2016;13: R25–9.

Mcwilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, Yasufuku K, Martel S, Laberge F, Gingras M. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med. 2013;369:910–9.

Medicare CF & Services M. Decision memo for screening for lung cancer with low dose computed tomography (LDCT) (CAG-00439n). 2015.

Meiners S, Eickelberg O, Königshoff M. Hallmarks of the ageing lung. Eur Respir J. 2015;45(3):807–27.

Mercado N, Ito K, Barnes PJ. Accelerated ageing of the lung in COPD: new concepts. Thorax. 2015;70(5):482–9.

Mery CM, Pappas AN, Bueno R, Colson YL, Linden P, Sugarbaker DJ, Jaklitsch MT. Similar long-term survival of elderly patients with non-small cell lung cancer treated with lobectomy or wedge resection within the surveillance, epidemiology, and end results database. Chest J. 2005;128:237–45.

Micke P, Faldum A, Metz T, Beeh K-M, Bittinger F, Hengstler J-G, Buhl R. Staging small cell lung cancer: veterans administration lung study group versus international association for the study of lung cancer – what limits limited disease? Lung Cancer. 2002;37:271–6.

Miner B, Tinetti ME, Van Ness PH, Han L, Leo-Summers L, Newman AB, Lee PJ, Vaz Fragoso CA. Dyspnea in community-dwelling older persons: a multifactorial geriatric health condition. J Am Geriatr Soc. 2016;64:2042–50.

Miravitlles M, Soriano JB, Ancochea J, Munoz L, Duran-Tauleria E, Sánchez G, Sobradillo V, García-Río F. Characterisation of the overlap COPD – asthma phenotype. Focus on physical activity and health status. Respir Med. 2013;107:1053–60.

Mittal N, Raj R, Islam EA, Nugent K. The frequency of frailty in ambulatory patients with chronic lung diseases. J Prim Care Community Health. 2016;7:10–5.

Mora AL, Bueno M, Rojas M. Mitochondria in the spotlight of aging and idiopathic pulmonary fibrosis. J Clin Investig. 2017;127:405.

Morla M, Busquets X, Pons J, Sauleda J, Macnee W, Agusti A. Telomere shortening in smokers with and without COPD. Eur Respir J. 2006;27:525–8.

Moyer VA. Screening for lung cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160:330–8.

Murgu SD. Diagnosing and staging lung cancer involving the mediastinum. Chest J. 2015;147:1401–12.

Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, Chaft JE, Segal NH, Callahan MK, Lesokhin AM, Rosenberg J. Pneumonitis in patients treated with anti–programmed death-1/programmed death ligand 1 therapy. J Clin Oncol. 2017;35(7):709.

NCHS. Health, United States, 2015: with special feature on racial and ethnic health disparities. Hyattsville: National Center For Health Statistics; 2016.

Nguyen DX, Bos PD, Massagué J. Metastasis: from dissemination to organ-specific colonization. Nat Rev Cancer. 2009;9:274–84.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, Mcfadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649–56.

Parashar B, Edwards A, Mehta R, Pasmantier M, Wernicke AG, Sabbas A, Kerestez RS, Nori D, Chao KC. Chemotherapy significantly increases the risk of radiation pneumonitis in radiation therapy of advanced lung cancer. Am J Clin Oncol. 2011;34:160–4.

Pardo A, Selman M. Lung fibroblasts, aging, and idiopathic pulmonary fibrosis. Ann Am Thorac Soc. 2016;13:S417–21.

Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, Gift AG, Harver A, Lareau SC. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med. 2012;185(4):435–52.

Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, Klimovsky J, Lebwohl D, Jehl V, Wolin EM. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011;378:2005–12.

Pelayo Alvarez M, Gallego Rubio Ó, Bonfill Cosp X, Agra Varela Y. Chemotherapy versus best supportive care for extensive small cell lung cancer. Cochrane Database Syst Rev. 2009;4:CD001990.

Perez EA, Koniaris LG, Snell SE, Gutierrez JC, Sumner WE, Lee DJ, Hodgson NC, Livingstone AS, Franceschi D. 7201 carcinoids: increasing incidence overall and disproportionate mortality in the elderly. World J Surg. 2007;31:1022–30.

Pinsky PF, Gierada DS, Hocking W, Patz EF, Kramer BS. National Lung Screening Trial findings by age: Medicare-eligible versus under-65 population. Ann Intern Med. 2014;161:627–33.

Pinsky PF, Gierada DS, Black W, Munden R, Nath H, Aberle D, Kazerooni E. Performance of lung-RADS in the National Lung Screening Trial: a retrospective assessment performance of Lung-RADS in the NLST. Ann Intern Med. 2015;162:485–91.

Pisters KM, Evans WK, Azzoli CG, Kris MG, Smith CA, Desch CE, Somerfield MR, Brouwers MC, Darling G, Ellis PM. Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIA resectable non–small-cell lung cancer guideline. J Clin Oncol. 2007;25:5506–18.

Pope III CA, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA. 2002;287:1132–41.

Postma DS, Rabe KF. The asthma–COPD overlap syndrome. N Engl J Med. 2015;373:1241–9.

Presley CJ, Gross CP, Lilenbaum RC. Optimizing treatment risk and benefit for elderly patients with advanced non–small-cell lung cancer: the right treatment for the right patient. J Clin Oncol. 2016;34:1438–42.

Quanjer PH, Tammeling G, Cotes J, Pedersen O, Peslin R, Yernault J. Lung volumes and forced ventilatory flows. European Respiratory Society. Rev Mal Respir. 1993.

Quoix E, Zalcman G, Oster J-P, Westeel V, Pichon E, Lavolé A, Dauba J, Debieuvre D, Souquet P-J, Bigay-Game L. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet. 2011;378:1079–88.

Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006;174:810–6.

Ramalingam SS, Dahlberg SE, Langer CJ, Gray R, Belani CP, Brahmer JR, Sandler AB, Schiller JH, Johnson DH. Outcomes for elderly, advanced-stage non–small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of eastern cooperative oncology group trial 4599. J Clin Oncol. 2008;26:60–5.

Read WL, Mortimer JE, Picus J. Severe interstitial pneumonitis associated with docetaxel administration. Cancer. 2002;94:847–53.

Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med. 2016;375:1823–33.

Richeldi L, Du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82.

Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. Chest J. 2013;143:E142s–65s.

Robbins M, Greene-Schloesser D, Peiffer AM, Shaw E, Chan MD, Wheeler KT. Radiation-induced brain injury: a review. Front Oncol. 2012;2:73.

Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13:239–46.

Rudin CM, Ismaila N, Hann CL, Malhotra N, Movsas B, Norris K, Pietanza MC, Ramalingam SS, Turrisi III AT, Giaccone G. Treatment of small-cell lung cancer: American Society of Clinical Oncology endorsement of the American College of Chest Physicians guideline. J Clin Oncol. 2015;33:4106–11.

Rusthoven KE, Kavanagh BD, Burri SH, Chen C, Cardenes H, Chidel MA, Pugh TJ, Kane M, Gaspar LE, Schefter TE. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol. 2009;27:1579–84.

Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. N Engl J Med. 2006;355:2542–50.

Scagliotti GV, Parikh P, Von Pawel J, Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non–small-cell lung cancer. J Clin Oncol. 2008;26:3543–51.

Schmidt CD, Dickman ML, Gardner RM, Brough FK. Spirometric standards for healthy elderly men and women 1–3: 532 subjects, ages 55 through 94 years. Am Rev Respir Dis. 1973;108:933–9.

Schmidt-Hansen M, Baldwin DR, Hasler E, Zamora J, Abraira V, Roqué I Figuls M. PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer. Cochrane Database Syst Rev. 2014;11:CD009519.

Schnell K, Weiss CO, Lee T, Krishnan JA, Leff B, Wolff JL, Boyd C. The prevalence of clinically-relevant comorbid conditions in patients with physician-diagnosed COPD: a cross-sectional study using data from NHANES 1999–2008. BMC Pulm Med. 2012;12:26.

Shaw AT, Kim D-W, Mehra R, Tan DS, Felip E, Chow LQ, Camidge DR, Vansteenkiste J, Sharma S, De Pas T. Ceritinib in ALK-rearranged non–small-cell lung cancer. N Engl J Med. 2014;370:1189–97.

Shirvani SM, Jiang J, Chang JY, Welsh J, Likhacheva A, Buchholz TA, Swisher SG, Smith BD. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non–small cell lung cancers in the elderly. JAMA Surg. 2014;149:1244–53.

Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, Harris LJ, Detterbeck FC. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. Chest J. 2013;143:E211s–50s.

Simoff MJ, Lally B, Slade MG, Goldberg WG, Lee P, Michaud GC, Wahidi MM, Chawla M. Symptom management in patients with lung cancer: diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. Chest J. 2013;143:E455s–97s.

Singer JP, Diamond JM, Gries CJ, Mcdonnough J, Blanc PD, Shah R, Dean MY, Hersh B, Wolters PJ, Tokman S, Arcasoy SM, Ramphal K, Greenland JR, Smith N, Heffernan P, Shah L, Shrestha P, Golden JA, Blumenthal NP, Huang D, Sonett J, Hays S, Oyster M, Katz PP, Robbins H, Brown M, Leard LE, Kukreja J, Bacchetta M, Bush E, D'ovidio F,

Rushefski M, Raza K, Christie JD, Lederer DJ. Frailty phenotypes, disability, and outcomes in adult candidates for lung transplantation. Am J Respir Crit Care Med. 2015;192:1325–34.

Singer JP, Lederer DJ, Baldwin MR. Frailty in pulmonary and critical care medicine. Ann Am Thorac Soc. 2016;13:1394–404.

Skloot GS, Busse PJ, Braman SS, Kovacs EJ, Dixon AE, Vaz Fragoso CA, Scichilone N, Prakash Y, Pabelick CM, Mathur SK. An official American Thoracic Society workshop report: evaluation and management of asthma in the elderly. Ann Am Thorac Soc. 2016;13:2064–77.

Solomon BJ, Mok T, Kim D-W, Wu Y-L, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014;371:2167–77.

Spira A, Ettinger DS. Multidisciplinary management of lung cancer. N Engl J Med. 2004;350:379–92.

Spiro SG, Gould MK, Colice GL. Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes: ACCP evidenced-based clinical practice guidelines. Chest J. 2007;132:149s–60s.

Team, N. L. S. T. R. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;2011:395–409.

Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF. Early palliative care for patients with metastatic non–small-cell lung cancer. N Engl J Med. 2010;363:733–42.

Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Bezjak A, Videtic G, Johnstone D. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010;303:1070–6.

Travis LB, Gospodarowicz M, Curtis RE, Clarke EA, Andersson M, Glimelius B, Joensuu T, Lynch CF, Van Leeuwen FE, Holowaty E. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst. 2002;94:182–92.

Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, Beer DG, Powell CA, Riely GJ, Van Schil PE. International association for the study of lung cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol. 2011;6:244–85.

Tsiouris A, Hammoud ZT, Velanovich V, Hodari A, Borgi J, Rubinfeld I. A modified frailty index to assess morbidity and mortality after lobectomy. J Surg Res. 2013;183:40–6.

Van Meerbeeck JP, Kramer GW, Van Schil PE, Legrand C, Smit EF, Schramel F, Tjan-Heijnen VC, Biesma B, Debruyne C, Van Zandwijk N. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non–small-cell lung cancer. J Natl Cancer Inst. 2007;99:442–50.

Van Meter ME, Mckee KY, Kohlwes RJ. Efficacy and safety of tunneled pleural catheters in adults with malignant pleural effusions: a systematic review. J Gen Intern Med. 2011;26:70–6.

Van Zandwijk N, Clarke C, Henderson D, Musk AW, Fong K, Nowak A, Loeragan R, Mccaughan B, Boyer M, Feigen M. Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. J Thorac Dis. 2013;5:E254–307.

Vancheri C, Failla M, Crimi N, Raghu G. Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology. Eur Respir J. 2010;35:496–504.

Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, Van Empel VP, Bruijnzeel PL, Rutten EP, Op't Roodt J, Wouters EF, Franssen FM. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;187:728–35.

Vaz Fragoso CA, Mcavay G, Van Ness PH, Casaburi R, Jensen RL, Macintyre N, Gill TM, Yaggi HK, Concato J. Phenotype of normal spirometry in an aging population. Am J Respir Crit Care Med. 2015;192:817–25.

Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, Calverley PM, Celli B, Coxson HO, Crim C. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med. 2011;365:1184–92.

WHO. Global health estimates 2015: deaths by cause, age, sex, by country and by region, 2000–2015. Geneva: World Health Organization; 2016.

Yasufuku K, Chiyo M, Koh E, Moriya Y, Iyoda A, Sekine Y, Shibuya K, Iizasa T, Fujisawa T. Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. Lung Cancer. 2005;50:347–54.

Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble G. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Eur Respir J. 2009;34:380–6.