Review Article

Chronic Obstructive Pulmonary Disease and Lung Cancer: A Review for Clinicians

Gerard J. Criner, MD1 Alvar Agusti, MD2 Hossein Borghaei, DO3 Joseph Friedberg, MD1 Fernando J. Martinez, MD 4 Curtis Miyamoto, MD5 Claus F. Vogelmeier, MD6 Bartolome R. Celli, MD7,8

Author Affiliations:
1. Department of Thoracic Medicine and Surgery, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, United States
2. Cátedra Salud Respiratoria, University of Barcelona; Respiratory Institute, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Centro de Investigacion Biomedica en Red Enfermedades Respiratorias, Barcelona, Spain
3. Department of Medical Oncology, Fox Chase Cancer Center at Temple University, Philadelphia, Pennsylvania, United States
4. Cornell University School of Medicine, New York, New York, United States
5. Department of Radiation Oncology, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, United States
6. Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Centre Giessen and Marburg, Philippus-University Marburg, German Centre for Lung Research, Marburg, Germany
7. Pulmonary and Critical Care Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, United States.
8. Harvard Medical School, Boston, Massachusetts, United States

Correspondence:
Gerard J. Criner, MD
Department of Thoracic Medicine and Surgery
Lewis Katz School of Medicine
Temple University
745 Parkinson Pavilion
3401 North Broad Street
Philadelphia, PA 19140
Email: Gerard.Criner@tuhs.temple.edu
Phone: 215-707-7979
Fax: 215-707-6867

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) and lung cancer (LC) are common global causes of morbidity and mortality. Because both diseases share several predisposing risks, the two diseases may occur concurrently in susceptible individuals. The diagnosis of COPD has important implications for the diagnostic approach and treatment options if lesions concerning for LC are identified during screening. Importantly, the presence of COPD has significant implications on prognosis and management of patients with LC. In this monograph, we review the mechanistic linkage between LC and COPD, the impact of LC screening in patients at risk, and the implications of the presence of COPD on the approach to the diagnosis and treatment of LC. This manuscript succinctly reviews the epidemiology and common pathogenetic factors for the concurrence of COPD and LC. Importantly for the clinician, it summarizes the indications, benefits, and complications of LC screening in patients with COPD, and the assessment of risk factors for patients with COPD undergoing consideration of various treatment options for LC.
Introduction

Chronic obstructive pulmonary disease (COPD) and lung cancer (LC) are common global causes of morbidity and mortality. COPD has a worldwide prevalence of 7-19% and is the 3rd leading cause of death. Over 65 million people suffer from COPD worldwide; COPD caused 3.23 million deaths in 2019.(1) LC is one of the most frequently diagnosed cancers worldwide (11.6% of all cancers) (2) and is the most common cancer diagnosed in men and third most common cancer diagnosed in women (Table1). LC is the leading cause of all cancer deaths at 1.74 million (18.4%), a number expected to reach 2.45 million patients worldwide by 2030, a 39% increase since 2016. Tobacco smoking causes LC in 80% of cases, but exposures to biomass fuels, radon and asbestos also contribute.

Because COPD and LC share similar risks, both diseases may concur in susceptible patients. Lung cancer is an important comorbidity of COPD that contributes to increased mortality. (3, 4) Conversely COPD is associated with reduced overall survival in patients with lung cancer and COPD compared to those without COPD, especially in those with an emphysematous predominant component.(5) Smokers with COPD have a 6-fold risk of LC compared to smokers without airflow limitation(6) and LC incidence increases as FEV₁ declines regardless of cigarette smoke exposure.(7, 8) Emphysema also increases LC risk.(9) In the Danish LC Screening Trial, patients with airflow limitation, emphysema, age > 70 yrs. and ≥ 35 pack-years smoking had a twofold greater LC risk. (10)

The diagnosis and severity of COPD has important diagnostic and therapeutic implications for the population undergoing low dose chest CT (LDCT) for LC screening. This monograph reviews the mechanistic linkage between LC and COPD, the impact of LC screening and the implications of COPD on the diagnosis and treatment of LC.

Pathobiological factors linking LC and COPD

LC is caused by mutations in oncogenes leading to an uncontrolled proliferation of cells and tumor formation.(11) Pathophysiological links between COPD and LC has been elusive due to heterogeneity in responses to chronic inflammation and lung reparative processes.(12) Possible
common pathobiological processes includes: chronic inflammation, genetic predisposition, epigenetic changes, telomere shortening, protease and anti-protease imbalance, mitochondrial dysfunction, premature aging and aberrant reparative processes. (Figure 1)

Inflammation and cancer are closely linked; most cancerous tissue shows inflammation. (13-15) Tobacco smoking, a shared risk between lung cancer and COPD, is a major factor contributing to lung carcinogenesis since smoking-related inflammation is superimposed upon the presence of tobacco smoke carcinogens. (16) It is also feasible that chronic lung inflammation in COPD predisposes to LC. (17) A reduction in mucociliary clearance may enable carcinogens to reside longer in the lung. (8) The COPD lung microbiome differs from healthy individuals and may induce inflammatory changes that promotes LC development. (18, 19) Cigarette smoke may also induce release of VEGF from epithelial cells causing angiogenesis which facilitates the progression, invasion, and metastasis of lung cancer. (20)

Immune cell composition and function is important in non-small cell LC (NSCLC) as well as COPD. COPD severity has been related to CD4+ T cell content and differentiation status (T-helper type -1 cells, TH17, regulator t cells (Treg) with increases in CD4+ TH1 as the disease progresses. (21) IL-17 drives protumor inflammatory responses and facilitate tumor growth in animal models. (22) COPD has increased sensitivity of CD8+ tumor-infiltrating T lymphocytes to tumor mediated immune escape mechanisms suggesting higher sensitivity to PD-1 blockade. (21) In NSCLC, immune cell composition is heterogenous and varies between adenocarcinomas and squamous cell carcinomas. (12) In stage I non-squamous NSCLC a more favorable gene signature for survival (FAIM3 ) was predominantly expressed in tumor-infiltrating leukocytes. (23) Patients with COPD and lung cancer are reported to have a decline in IgG-secreting plasma cell levels but not in other cell types compared to patients with lung cancer but without COPD. (24)

Aging of the lung may represent a common thread between LC and COPD. (25) The failure of organs to repair DNA caused by oxidative stress and telomere shortening drives aging and occurs
in COPD. (26) Cigarette smoking decreases telomere length; LC and COPD are both associated with shortened telomere length. (27-29)

Oxidative stress plays a role in LC and COPD through DNA damage and leads to carcinogenic mutations.(11) (30, 31) In COPD, nitrification of histone deacetylase (HDAC) leads to its inactivation and enhances further inflammation. Oxidants inactivate other proteins making them auto-antigenic and thereby immunoinflammatory. (32)

Extensive exposure to nicotine is also common to patients with COPD and those that develop lung cancer. Nicotine promotes tumor growth by increasing proliferation, angiogenesis, migration, epithelial to mesenchymal transition, and stimulates tumor growth.(33) It is also the principal compound that drives smoking addiction.

Genetic predisposition to LC and COPD has been localized to chromosome 6. (34-36) genome-wide association study (GWAS) studies have implicated loci at cholinergic receptor nicotinic alpha subunit (CHRNA) 3 and CHRNA5 single nucleotide polymorphisms (SNPs) and regions at 4q31, 4q24 and 5q. (37) Genetic polymorphism of IL10 in peripheral blood mononuclear cells (PBMC) was found to be associated with increased rates of COPD and LC.(13, 38)

Epigenetic changes (DNA methylation, micro-RNA expression, covalent histone modifications and nucleosome remodeling) may play roles in COPD and LC.(39, 40) COPD patients with LC have hypermethylation of tumor suppressor and other gene promoters than COPD patients without LC.(11)

**Clinical Features of COPD that increase LC risk**

The presence and severity of airflow limitation and/or emphysema (diagnosed using computerized chest tomography [CT] or diffusing capacity for carbon monoxide [DLCO]) are important risks for LC development.(7, 9, 41-43) Studies in smokers and nonsmokers report a relationship between severity of airflow limitation and LC risk.(7, 41, 44) (Table. 2) In a post hoc subset analysis of the National Lung Screening Trial (NLST), subjects with COPD had a twofold increase in LC incidence. (45) Others, however, report the opposite relationship, that severity of airflow limitation is inversely related to LC risk. (46, 47) In 2,517 patients with COPD followed over 60 months, LC occurred in those with less severe airflow limitation (GOLD stages I and II), lower body mass index (BMI) and DLCO < 80%. (48) Others report emphysema may be a greater risk factor for LC compared to airflow limitation.(9, 42) The Pamplona International Early LC Detection Program and the Pittsburgh Lung Screening Study
databases showed (49) that emphysema was independently associated with increased LC risk using a risk stratification score (range, 0-10 points). In both cohorts, the risk of LC was 3.5-fold higher in the high (7-10) vs. the low (0-6) risk group. Severity of emphysema was related to greater likelihood of developing and dying from LC even after adjustment for age and smoking history. (50) Others report no impact of emphysema severity on LC risk. (44)

The histology and localization of LC is linked to the regional presence and degree of emphysema. Squamous cell carcinoma is more common when COPD and emphysema are present (48, 51). A link exists between LC location and degree of emphysema. (52) A lower emphysema burden is found with central tumors while a greater emphysema burden is associated with peripheral lesions. (51)

The aggressiveness of tumors is associated with the extent of emphysema and presence of COPD. Patients with COPD who develop adenocarcinoma have less invasive characteristics, while LCs arising in emphysematous tissue are more aggressive. (53, 54) Smokers with impaired lung function have shorter doubling times and less indolent LCs. (55-57) EGFR mutations and ALK rearrangements are less prevalent in patients with COPD associated LCs and EGFR mutation is inversely related to the severity of airflow limitation. (58, 59)

10 to 39% of COPD patients are never smokers, some evidence exists for an association between COPD and LC in never smokers. In a population-based cohort of 338,548 Korean citizens, LC incidence in never smokers with COPD was increased compared to never smokers without COPD. (60) The highest risk of LC was in patients who had COPD and had smoked with a sixfold risk of developing LC compared with never smokers without COPD. (60)

Inhaled corticosteroids (ICS) are recommended in select patients with COPD and their impact on LC development has conflicting reports. Data from a British Columbia database (61) suggested a 30% reduction in LC risk with ICS, however, the study lacked key inclusion variables including severity of airflow limitation, presence of emphysema, family history of LC and degree of tobacco exposure. (62) Others report a reduction in LC risk in COPD patients prescribed ICS. (63-67) A more pronounced protective effect of ICS was reported in former compared to current patients.
smokers (64), those with a concurrent diagnosis of asthma(67) or, those prescribed higher ICS dose.(65) A systematic review reported a protective effect of a higher dose of ICS in observational studies but no benefit in randomized trials.(68) An analysis designed to avoid immortal time bias found no effect of ICS on reducing LC risk.(69) Similarly, a large observational study reported no effect of ICS use on LC incidence (11). One study reported increased LC risk in patients prescribed ICS (10)

Large prospective controlled trials conducted in patients with moderate to severe COPD focused on lung function decline, exacerbation reduction or mortality, reported no difference in cancer deaths in patients randomized to ICS vs. non-ICS use. (12-17)

Conflicting results between observational and randomized controlled trials may be due to different patient populations, characterization of LC risk, follow-up time and whether annual LDCT was used to screen for LC. Based on available data, there is no clear evidence that ICS use increases or decreases LC risk.

Other pulmonary diseases may increase LC risk such as a history of tuberculosis, chronic bronchitis and emphysema.(70) Patients with combined pulmonary emphysema and fibrosis have a higher incidence of LC.(71) Pulmonary fibrosis also increases LC risk.(72)

**LC screening**

Prognosis in LC is tightly linked to tumor stage at time of diagnosis, typically too late to allow for surgical treatment. (73, 74) The Mayo Lung Project randomized 4600 male smokers to either CXR and sputum cytology tests every 4 months for 6 years or annually. (75) Twice as many LCs were diagnosed, more surgical procedures were performed, and LC 5-year survival was better in intensively screened patients, however, overall mortality was similar. Other CXR screening studies confirmed lack of mortality benefit.(76, 77)

Several studies have demonstrated that LC screening with LDCT reduces mortality by detecting LC at earlier stages. (10, 78-90) (Table. 3) The beneficial effect on survival is balanced by false positives that increases radiation exposure, morbidity and mortality from unnecessary diagnostic
procedures, patient distress, and medical costs. Many studies, although consistent in showing greater detection of LC, were not powered to show a mortality benefit. (83, 84, 87, 90)

National Lung Screening Trial (NLST) and Dutch–Belgian lung-cancer screening trial (Nederlands–Leuvens Longkanker Screenings Onderzoek [NELSON]) were population based multicentered trials with adequate power to examine the impact of LDCT on LC specific and all-cause mortality. (78, 79)

NLST enrolled 53,454 patients between 55-74 years of age with a history of cigarette smoking ≥30 pack-years, or if former smokers within 15 years of quitting. (78) Participants in the intervention arm underwent 3 annual LDCT screenings, the controls had single view posteroanterior CXR. Study adherence was greater than 90%; the rate of positive screening tests was 24.2 % with LDCT and 6.9% with CXRs over the three rounds. LC incidence was 645 cases per 100,000 person-years in the LDCT group and 572 cases per 100,000 person-years in the CXR group. With LDCT there were 247 LC deaths per 100,000 person-years compared to 309 deaths per person-years with CXR; a relative mortality reduction from LC of 20% with LDCT. Mortality from any cause was reduced by 6.7% with LDCT compared to CXR group.

NELSON was powered to show a reduction in lung-cancer mortality of ≥25% with volume-based, LDCT screening in high-risk male participants at 10 years follow-up. (79) 13,195 men and 2,594 women between 50 and 74 years old were randomized to LDCT at baseline and years 1, 3 and 5.5 vs. no screening. At 10 years follow-up among men, the incidence of LC was 5.58 cases per 100 person-years with LDCT and 4.91 cases per 1000 person years in controls; LC mortality was 2.50 vs. 3.30 deaths per 1000-person years, respectively. The cumulative rate ratio for LC death at 10 years was 0.76 (955 CI, 0.61 to 0.94; p=0.01) with LDCT compared to controls. In women at 10 years follow-up, the rate ratio was 0.67 (955 CI, 0.38 to 1.14).

Patient populations in the above two trials were predominately Caucasian (91% in NLST), <5% were African American and 2% were Hispanic. The trials differed in positive screen definitions, number of screening rounds, screening intervals, mean age, and baseline smoking status. Participants numbers ranged from 2,472 to 53,542 ((78, 90) and follow-up periods from 5.2 to 10
years. (79, 91). Male predominance existed in both studies (range 56- 84%). (79, 83) A unique aspect of NELSON was volumetric measurements of nodules and calculations of volume doubling. (79)

The number needed to screen to prevent 1 cancer death was 323 over 6.5 years of follow-up in NLST (78) and 130 participants screened over 10 years follow-up in NELSON. (79)

**Influence of age, sex, smoking status, and comorbid conditions on CT screening benefits**

Age, sex, smoking status, comorbidities and other pulmonary conditions may impact prevention of LC death. (92) Sixty-four percent of NLST participants had no pulmonary conditions at baseline, 24.7% one pulmonary condition and 10.8% two or more conditions. (78) There was no difference in the efficacy of screening according to the number of coexisting pulmonary conditions.

A trend of greater benefit was found in NLST women participants compared to men as did NELSON. The German LC Screening intervention (LUSI) (87) also found women had a significant reduction in LC mortality compared to men. Sub-analyses showed that age or smoking status did not impact LDCT to reduce LC mortality.

**False positive rates**

False positive rates varied across studies due to definitions of positive results, thresholds for nodule size, and use of volume doubling time. (82)

NLST reported false positive rates of 26.3% at baseline, 27.2% and 15.9% at rounds two and three, respectively. (78) NELSON reported false positive rates of 19.8% at baseline and 7.1% year one, 9.0% year 3 (males) and 3.9 % year 5.5 (males). (79) Needle biopsies for false positive rates in several studies ranged from 0.09-0.56% and surgical resections from 0.1-0.5%. (55, 78, 80, 87, 93-102) Invasive procedures were performed in 1.7% of screened participants in NLST; number needed to harm, n=59. (78) Use of LUNG-RADS criteria may avoid 23.4% of invasive procedures for false positive results. (103)
**Radiation risk with LDCT**

Precise risks of developing cancer from cumulative radiation from LC screening are unknown. Estimates of radiation exposure after 25 years of annual screening yields 20.8-32.5 mSv. Estimates of lifetime cancer risk from radiation exposure following 10 annual LDCTs was 0.26-0.81 major cancers for 1000 individuals screened. The 2021 U.S. Preventative Services Task Force (USPSTF) recommendation estimates a higher rate of radiation-related LC deaths (29.0 to 42.5 vs. 20.6 per 100,000) than the 2013 recommendation but is outweighed by increases in LC deaths prevented and life-years gained for women.

**Cost-effectiveness**

Some critics consider LC screening to be less cost-effective than smoking cessation. UK LDCT trial compared screening to usual care in 4,055 individuals and estimated the cost-effectiveness of screening to be £8466 per quality adjusted life-year gained. Annual screening might be most cost-effective when eligibility is restricted to high-risk groups.

**Screening intervals**

The Multicentric Italian Lung Detection (MILD) trial randomized 2376 screening participants to annual (n=1190) or biennial (n=1186) LDCT for median screening periods of 6.2 years and 23,083 person-years follow-up. Biennial LDCT showed similar overall mortality and LC specific mortality at 10 years compared with annual LDCT. Biennial screening saved 44% of follow-up LDCTs in subjects with a negative baseline LDCT and 38% of LDCTs patients without increased occurrence of Stage II-IV LCs.

**Impact of LC screening on smoking cessation**

Several studies found no impact of LDCT screening on smoking cessation, abstinence, smoking relapse, or smoking intensity.

**Psychosocial harms of LC screening**

Several studies report (80, 118-122) no worsening in quality-of-life, anxiety, or other measures of distress in screened patients compared to controls. Although participants in NELSON reported
short term recipients of indeterminant results had increased LC distress, quality of life improved following negative scans.(121)

**USPSTF updated LC screening recommendations**
In 2021, the USPSTF updated its recommendation (123) based on systematic review of the accuracy, benefits and harms associated with LC screening. It assessed if screening benefits vary by subgroup (e.g., race or sex), number or frequency of LDCT scans and whether harms associated with screening and nodule evaluation differs when using International Early LC Action Program (I-ELCAP), LUNG-RADs, or other approaches to reduce false positive rates. USPSTF also commissioned modeling studies from the National Cancer Institute (NCI) Cancer Intervention and Surveillance Modeling Network (CISNET) to provide optimal ages to begin and end screening. USPSTF now recommends annual LDCT screening in adults aged 50-80 years with a 20-pack year smoking history who currently smoke or quit smoking ≤ 15 years. They recommended stopping screening once a person has not smoked for 15 years or develops a health problem that limits life expectancy or ability to undergo lung surgery. The 2021 recommends LDCT screening at a younger age with less smoking burden based on NELSON.(79, 123) Additionally, CISNET analyses supports screening at a younger age with lower smoking burden to address racial disparities.(123-127)

**Implementation of LC screening in clinical practice**
Most cited trials were conducted at large academic medical centers. The transition to community practices, especially those serving minority populations may be different.(78, 128)

Screening solely based on NLST criteria could miss a significant number of LC cases. A retrospective analysis combining emphysema detected by HRCT with NLST criteria detected a higher number of LCs. (129)

Implementation of LC screening has been proposed in high-risk populations such as COPD patients. Combining a screening program in ever smokers with ≥ 10 pack years aged 55-74 years during annual COPD review found a positive LDCT scan in 5% of patients.(130) Although
detected cancers were at an earlier stage, because of lower lung function and more comorbidities, the rates of surgical resections were lower, and stereotactic body radiotherapy (SBRT) higher.

Implementation of LC screening is challenging in low- and middle-income countries (LMICs). More than 70% of global smoking related deaths occur in LMICs where > 80% of 1.3 billion smokers reside.(131) Upper middle income countries have the highest incidence of cancer and mortality; LC incidence increased by 465% in China over the past 30 years.(132) Common barriers in LMICs include inadequate transportation and infrastructure (133) and lack of awareness of screening guidelines and need for shared decision making.(134)

Strategies to improve LC screening in LMICs includes: more restricted eligibility criteria (additional inclusion of family history of lung cancer or COPD), biennial screening, intensive smoking cessation, private-public implementation efforts, digital technologies for remote locations and adequate funding.(132)

**Detection of comorbidities during LC screening**

Malignancies, cardiovascular diseases, and COPD share common risks: smoking, obesity, physical inactivity and alcohol abuse are responsible for > 75% of deaths from non-communicable diseases.(135) Patients with comorbid conditions may present with LC at an earlier age.(136-138) The “surveillance hypothesis” purports that patients with coexisting diseases have increased medical visits and more opportunities for cancer detection.(139) The detection of comorbid conditions during annual LC screening, however, has received limited attention.

In 8,637 heavy smokers screened in the Pomeranian Pilot LC Screening Program, 52% had cardiovascular disease (33 %), diabetes (26%) and COPD (21%).(140) A study that performed a “lung health check” during LC screening reported COPD in 57% of patients; 67% did not have a prior diagnosis.(141)

Studies that incorporate spirometry into screening have similarly reported high incidences of previously undiagnosed COPD. In 2,525 screened subjects of which 99.4% performed
spirometry, 37.4% had airflow limitation and 49.7% had no prior COPD diagnosis.(142) The detection of undiagnosed COPD was more likely in males, younger age, lower smoking duration and cigarettes per day and asymptomatic individuals. Screening detected LC was higher in those with airflow limitation with prior diagnosis of COPD (OR 2.80; p=0.002).

**Special considerations using LC screening in COPD patients**

LC screening has benefits and risks that should be discussed during the shared decision-making process especially in patients with COPD and limited lung reserve. Patients with COPD are at increased risk for morbidity and mortality during evaluation of false positive lesions or with LC treatments.

Most patients with COPD are, or have been smokers, and represent the age of patients enrolled into NLST and NELSON and meet 2021 USPSTF recommendations for LC screening. COPD patients should undergo annual LC screening like any other individual based on the screening criteria recommended by the USPSTF. LDCT in COPD patients can identify structural abnormalities that characterize COPD such as emphysema, bronchial inflammation, or mucous plugging. These individuals merit lung function testing to confirm or exclude the diagnosis of COPD and therefore begin treatment.

A secondary analysis of NLST data assessed impact of COPD on patient outcome.(143) Among 24,453 subjects who underwent screening, 30.5% underwent a diagnostic study and 4.2% an invasive procedure of which 0.9% experienced a procedure related complication. Patients with COPD were more likely to undergo an invasive procedure and have a serious complication (OR 1.78, p=0.01).

Because of reduced lung function and comorbid conditions, some suggest that screening COPD patients has limitations due to “competing causes of death”.(144) In an analysis of NLST data, a mortality benefit of LC screening was found in COPD patients with mild to moderate but not severe or very severe disease. (144).
The impact of newer diagnostic techniques to investigate indeterminate lung lesions identified by LDCT is unknown. Positive emission tomography (PET) may help characterize solid lesions for malignant potential and decrease the number of false positive lesions undergoing unnecessary invasive procedures.(145) Navigational bronchoscopy coupled with cone-beam CT imaging and augmented fluoroscopy may help increase the proportion of diagnosed lesions with less morbidity and mortality.(146)

**Assessment of treatment risks for patients with COPD and NSCLC**

The discussion below focuses only on the assessment of risk and treatment of NSCLC. The treatment of small cell lung cancer and other types of malignant lung diseases is outside the purview of this focused review.

**Pulmonary risk**

Standard treatment for Stage I NSCLC is lobectomy with systematic mediastinal lymph node examination.(147) (Table. 4) Approximately 25% of patients are not candidates for curative lobectomy due to frailty (e.g., the presence of fatigue, low activity, weakness, weight loss, and slowness of gait), pulmonary or non-pulmonary comorbidities. The presence of COPD is associated with an increased need for tracheostomy, pneumonia and decreased disease-free and overall survival in patients undergoing lobectomy with lymph node dissection in Stage IA LC.(148)

Preoperative evaluation should include spirometry to measure FEV1, and the measurement of DLCO if there is diffuse disease or dyspnea disproportionate to the level of FEV1 reduction. (149) (Table.4) If FEV1 or DLCO is less than 80%, then an estimation of postoperative pulmonary reserve should be done by either the anatomic method (e.g., number of segments or lobes to be removed) or lung perfusion scanning.(149) An estimated FEV1 or DLCO ≤ 40% is associated with increased perioperative complications including death. Further assessment using cardiopulmonary exercise testing is recommended, VO2 max<15 ml/kg/min indicates an increased risk of perioperative complications. Alternative types of testing using stair climbing, shuttle walk, or 6-minute walk may be used if exercise testing is not available.(149-153)
HRCT imaging can estimate perioperative risk. Regression based FVC and FEV₁ derived from HRCT data correlated with physiologically measured FVC and FEV₁ suggesting that HRCT could be used to estimate preoperative pulmonary function in patients unable to perform spirometry.(154)

**Non-pulmonary risk**

The high-risk group for LC surgery has been defined by male sex, older age, lower FEV₁, lower DLCO, poor performance status, obesity, renal disease, diabetes, malnutrition, frailty, steroid use, and coronary heart disease.(155-157) In patients ≥ 75 years of age who underwent lobectomy, performance status, coronary heart disease, history of stroke, restrictive lung disease, male sex and interstitial pneumonia were associated with increased postoperative complications.(158-162) Air trapping measured by RV/TLC prolong operative hospitalization.(163)

Nutritional status influences postoperative reoccurrence and death, especially those with more severe airflow limitation. (164) Sarcopenia predicts postoperative complications and survival following LC surgery. (161)

Current smoking may adversely affect surgical outcomes (e.g., prolonged air leak, pneumonia, tracheostomy, and atelectasis) with reduced relapse free survival in GOLD stage 2/3 patients.(165)

**LC surgical therapies and reduced lung function**

Anatomical lung resection can be performed in selected high risk patients based on preoperative lung function without increased morbidity and mortality (166) (Table. 5). Assessment of the COPD patient’s fitness for surgery should be thoroughly discussed in multidisciplinary fashion. In some patients, the operative risk of death exceeds the risk of LC death.(166)

The frequent occurrence of LC in older COPD patients with other pulmonary and comorbid conditions has prompted exploration of therapies other than curative resection.(167)
Lobectomy via video-assisted thoracoscopic surgery (VATS) in high risk patients (e.g., age > 75 yrs., FEV₁ < 50% predicted, DLCO < 50% predicted, history of coronary heart disease) has a low, but not negligible incidence of major complications. Survival benefits may not be greater in patients > 71 years of age compared to palliative resection.

The most common surgical approaches for limited resection are segmentectomy or wedge resection. Segmentectomy includes lymph node dissection whereas wedge resection consists of lung tumor removal with surrounding normal lung parenchyma. Segmentectomy has been reported to be superior to wedge resection in overall survival and LC specific survival in patients with Stage IA NSCLC, especially when resected tumors are ≤ 2 cm in size and lymphadenectomy is performed. Perioperative complications are lower with sub lobar resection compared to lobectomy in older patients and FEV₁ < 85%. In tumors 2-5 cm in size, sub lobar resection is inferior to lobectomy, and sub lobar resection may be inferior to lobectomy even for Stage IA tumors. Differences in patient populations, extent of lymph node dissection and margin size around the resected tumor may all affect outcomes. Reduced lymphadenectomy during sub lobar resection results in inferior survival outcomes compared with lobectomy; an increased number of resected lymph nodes resected may be more important than the extent of lung resection.

Only using calculation of postoperative FEV₁ to predict postoperative lung function may be misleading in patients with emphysema. In patients with predicted postoperative FEV₁ < 40% who underwent lobectomy for NSCLC in an emphysematous lobe, no significant reduction in postoperative FEV₁ was observed.

**Thermal ablation**

Thermal ablation is an alternative local therapy for NSCLC. Radiofrequency ablation (RFA), microwave ablation (MWA) and cryoablation (CRYO) have been used in patients with NSCLC. Tumor location has bearing on ablation choice; in the middle and outer thirds of the lung, CRYO, MWA or RFA are all possible considerations, while in the central lung zone, CRYO is preferred for lesions abutting airways or along the pleura or chest wall.
literature reports percutaneous image guided RFA. In 51 patients with inoperable Stage IA NSCLC, overall survival rate was 86.3% year one and 69.8% year two. Local control and recurrence free rates were 68.9% and 59.8% at years one and two, respectively.(186) Recurrence rate was worse for tumors > 2 cm in size. Several studies have reported minimal to no significant decline in lung function at one- and three-months post ablation.(186, 191, 197, 198) Reduced lung function post RFA treatment has been infrequently attributed to pleuritis or ablation volume.(198) Follow-ups at one and two years post RFA reported no decline in lung function or DLCO.(186, 197).(186) FVC increased in some subjects possibly due to remodeled emphysematous tissue and decreased hyperinflation.(186) Most studies report success with tumor sizes <3 cm, preferably <2 cm. Pneumothorax, pleural effusion and tumor track seeding may be complications(197).(188) MWA ablation produces larger ablation zones with reduced time compared to RFA and MWA. CRYO is safer to use in patients with pacemakers. Bronchoscopic approaches with thermal ablation are undergoing feasibility trials.(200)

**Stereotactic Body Radiation Therapy (SBRT)**

SBRT or stereotactic ablative radiation therapy (SABR) delivers high doses of precisely focused radiation therapy to malignancies. It is standard care for patients who either refuse or have contraindications to definitive surgery.(167) Treatment of tumor sizes of up to 5 cm has become routine.(201) Optimally, tumors should be > 1cm from the chest wall although this is not an absolute contraindication. Central (within 2 cm of the proximal bronchial tree and/or abutting the mediastinal pleural) and ultra-central tumors (abutting the proximal bronchial tree) were considered high risk, subsequent studies demonstrate no increased toxicities using five fraction treatment regimens.(202)

SBRT in early-stage NSCLC has shown favorable outcomes in quality of life, high local control rates and reduced treatment related complications. SBRT has increased more than twofold from 2008 to 2013 (6.7 to 16.3%).(203) A study in patients treated with inoperable NSCLC reported a 55.8% 3-year overall survival with 90.6% local control rate.(204) Higher maximum doses further improved local control and overall survival.(205)
Studies comparing local control rate and overall survival between surgery and SBRT have shown surgery to be equivalent or superior to SBRT. A review that compared SBRT to sub lobar resection in high risk patients for lobectomy reported similar one-year survivals; however overall 3-year survival was higher with sub lobar resection compared to SBRT. (206) A metaanalysis of 11,540 high-risk elderly patients with Stage I NSCLC reported that sub lobar resection compared to conventional fraction radiation therapy or SBRT significantly improved survival without differences in treatment failure or complications.(207) Fatigue, pneumonitis, and chest wall pain were reported with SBRT but mortality at 30 days was 0%. Sub lobar resection had morbidity between 7.3-33.7% with a 30-day mortality of 1-2.6%.(206) Multiple attempts to perform multicentered randomized trials to evaluate surgical resection and SBRT have been aborted due to low patient accrual.(208, 209) Several trials comparing SBRT with surgical resection are currently ongoing.(208)

SBRT has also been used for salvage after prior surgery or radiation therapy. Median survivals of 23 (95% CI 15-31) and 50 months (95% CI 35-65) and overall, 5-year survivals of 26.2% and 42.4% were reported for patients with prior radiation therapy and surgery, respectively.

COPD and treatment outcomes in advanced NSCLC

The identification of several driver mutations has led to the development of targeted therapies and immune checkpoint inhibitors that provide viable options to traditional chemotherapy. Although for some patients without driver mutations, the combination of chemotherapy and a checkpoint inhibitor is considered standard care, patients with high PD-L1 expressing tumors may be treated with a single agent checkpoint inhibitor. Given the clinical efficacy of targeted therapies and immunotherapy, emphasis has been placed on offering treatment even to patients with multiple comorbidities.

The impact of COPD on treatment response with chemotherapeutic agents has received limited attention. COPD has been reported to negatively impact overall survival in stage IV NSCLC and current smokers treated with conventional chemotherapy.(210) However, others have shown no negative impact of COPD in patients treated with platinum-based chemotherapy or tyrosine kinase inhibitors.(211) COPD patients have reduced ventilatory reserve and may have
comorbidities such as CHF or renal failure. The use of cisplatin in patients with renal dysfunction is problematic and generally avoided. Pemetrexed, a drug commonly used as a component of a platinum doublet chemotherapy backbone in patients with adenocarcinoma of lung requires creatinine clearances ≥45 ml/min. Chemotherapies such as etoposide and vinorelbine can cause cardiotoxicity and may aggravate CHF. Etoposide is used to treat small cell LC and less commonly in NSCLC.

Molecular testing of NSCLC tumors allows identification of patients with driver mutations that could be treated with targeted agents. The likelihood of finding molecular changes is higher in never smokers, however, available data clearly indicates that smokers could also have a targetable alteration. Targeted therapies exist for a number of genetic alterations such as epidermal growth factor receptor (EGFR) mutations, c-ROS oncogene 1 (ROS1) fusions, anaplastic lymphoma kinase (ALK) translocations and other subtypes. Drugs used in these settings are largely well tolerated oral agents with fewer side effects than conventional chemotherapies. Rash and diarrhea are among the most common adverse events. Pneumonitis and interstitial lung disease have been reported in some patients treated with these agents and with EGFR tyrosine kinase inhibitors (TKI).

Immune checkpoint inhibitors have transformed NSCLC treatment and are used as sole first line agents, or combination with other chemotherapeutic agents. Although checkpoint inhibitors are more effective and less toxic compared to conventional chemotherapy, side effects may develop secondary to their mechanisms of action. Immune check point inhibitors may promote T cell attack on normal cells expressing self-antigens in the skin, thyroid, digestive tract, lungs, and joints. Some data suggests a higher sensitivity to immune checkpoint inhibition in COPD patients with NSCLC. COPD was associated with significantly longer overall and progression-free survival in patients treated with palliative pembrolizumab.

Pneumonitis is a common side effect of checkpoint inhibition therapy followed by sarcoid like granulomatosis, tuberculous or other infections. Pneumonitis occurs in <0.5% to 10% of all patients when immune checkpoint therapy is combined with chemotherapy or nivolumab and CTLA-4 combinations. In an analysis of 11,921 NSCLC patients receiving immune
checkpoint inhibition, deaths related to adverse respiratory events was about 0.2%; pneumonitis was the cause in 0.1% of deaths.(217)

Although patients with a diagnosis of LC and COPD are commonly encountered in everyday clinical practice, the treatment options for LC are rarely significantly altered due to the presence of COPD.

Summary and conclusions
COPD and LC are worldwide highly prevalent causes of morbidity and mortality; their combined presence poses important challenges to diagnosis, treatment, and prognosis. Shared risks and mechanistic factors may play roles in the higher association of LC in patients with COPD and provide opportunities for novel target identification for the prevention and treatment of LC. LDCT is a major advancement for earlier diagnosis and treatment of LC, however, its use requires special considerations in patients with reduced lung function due to COPD because of false positive or indeterminate lesions that may require invasive procedures. LC screening provides an opportunity to assess patients for the presence of COPD that may allow identification and earlier treatment of patients not yet diagnosed. Finally, the presence of COPD has important implications for the management of LC.

Figure Legends
Figure 1. Interaction of genetic features with environmental exposure to predispose patients to develop lung cancer, COPD, interstitial lung disease or a combination of the above. Reprinted with permission from reference (219)
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Table 1. Overall Key points

- Lung cancer is the most common cause of cancer death worldwide
- Lung cancer is projected to afflict 2.45 million individuals by 2030
- Tobacco smoking is the major cause of lung cancer in 80% of cases, but biomass fuel, radon, and asbestos exposure are important causative agents in many cases.
- Presence of emphysema, particularly associated with COPD, increases up to 6-fold the risk of lung cancer compared to smokers without emphysema or airflow obstruction
- Low dose chest CT (LDCT) can reduce mortality by 20% in multiple large clinical trials
- LDCT programs offers an opportunity to diagnose unrecognized emphysema
- The presence of COPD has important implications for the use of invasive procedures to diagnose and manage indeterminate lung nodules and lung cancer lesions

Table 2. Factors That Increase the Risk of Lung Cancer

- Older age > 50
- Smoking history > 20 pack years
- Presence of airflow obstruction
- Presence and extent of emphysema
- Lower BMI
- History of cancer
- Familial history of lung cancer
- Biomass fuel, radon, or asbestos exposure
- History of tuberculosis or pulmonary fibrosis
Table 3. Lung Cancer Screening

- The number needed to prevent one lung cancer death was 323 over 6.5 years of follow-up in NLST and 130 participants screened over 10 years in NELSON
- Women may have a greater mortality benefit with lung cancer screening than men
- Age and the presence and number of comorbid conditions have no impact on the benefits of lung cancer screening
- False positive rates with LDCT range from 19.8 to 26.3 % at baseline in the NLST and NELSON trials, respectively
- Lifetime estimates of radiation-related lung cancer deaths vary by eligibility criteria. The USPTF estimates 1 radiation related lung cancer deaths for every 13 subjects vs. 18.5 lung cancer deaths avoided by screening
- LDCT screening is cost-effective

Table 4. Assessing Surgical Risk for NSCLC Treatment in Patients with COPD

- Spirometry
- RV/TLC
- Diffusion Capacity
- 6-minute walk, stair climbing, symptom limited cardiopulmonary exercise tests
- HRCT
- Lung perfusion imaging
- Assess frailty
- Nutritional status
- Presence and extent of comorbidities
- Current smoking status

RV/TLC, Residual volume/ Total Lung Capacity. DLco, Single breath diffusion capacity for carbon monoxide. HRCT, high resolution computerized chest tomography.
Table 5. NSCLC Therapies in Patients with COPD

- Lobectomy via video assisted thorascopic surgery
- Sub-lobar resection
- SBRT
- Ablation
  - Radiofrequency ablation
  - Microwave
  - Cryoablation
- Medical therapies
  - Non-mutation directed therapy
  - Targeted therapy
  - Immune checkpoint inhibitors
Figure 1: