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

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Abstract

Chronic obstructive pulmonary disease (COPD) and lung cancer are common global causes of morbidity and mortality. Because both diseases share several predisposing risks, the 2 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 lung cancer are identified during screening. Importantly, the presence of COPD has significant implications on prognosis and management of patients with lung cancer. In this monograph, we review the mechanistic linkage between lung cancer and COPD, the impact of lung cancer screening on patients at risk, and the implications of the presence of COPD on the approach to the diagnosis and treatment of lung cancer. This manuscript succinctly reviews the epidemiology and common pathogenetic factors for the concurrence of COPD and lung cancer. Importantly for the clinician, it summarizes the indications, benefits, and complications of lung cancer screening in patients with COPD, and the assessment of risk factors for patients with COPD undergoing consideration of various treatment options for lung cancer.

Abbreviations: chronic obstructive pulmonary disease, COPD; forced expiratory volume in 1 second, FEV1; low-dose computed tomography, LCDT; non-small cell lung cancer, NSCLC; cholinergic receptor nicotinic alpha, CHRNA; computed tomography, CT; diffusion capacity for carbon monoxide, DLCO; the National Lung Screening Trial, NLST; epidermal growth factor receptor, EGFR; anaplastic lymphoma kinase, ALK; inhaled corticosteroid, ICS; chest x-ray, CXR; Nederlands–Leuvens Longkanker Screenings Onderzoek, trial, NELSON; confidence interval, CI; Lung Imaging Reporting and Data System, Lung-RADS; U.S. Preventative Services Task Force, USPSTF; Cancer Interventional Surveillance Modeling Network, CISNET; epidermal growth factor receptor, EGFR; anaplastic lymphoma kinase, ALK; inhaled corticosteroid, ICS; chest x-ray, CXR; Nederlands–Leuvens Longkanker Screenings Onderzoek, trial, NELSON; confidence interval, CI; Lung Imaging Reporting and Data System, Lung-RADS; U.S. Preventative Services Task Force, USPSTF; Cancer Interventional Surveillance Modeling Network, CISNET; high-resolution computed tomography, HRCT; stereotactic body radiotherapy, SBRT; lung cancer, LC; low- and middle-income countries, LMICs; forced vital capacity, FVC; total lung capacity, TLC; radiofrequency ablation, RFA; microwave ablation, MWA; cryoablation, CRYO; programmed death-ligand, PD-L1; congestive heart failure, CHF

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Introduction

Chronic obstructive pulmonary disease (COPD) and lung cancer are common global causes of morbidity and mortality. COPD has a worldwide prevalence of 7% to 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. Lung cancer is one of the most frequently diagnosed cancers worldwide (11.6% of all cancers) and is the most common cancer diagnosed in men and third most common cancer diagnosed in women (Table 1). Lung cancer 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 2018. Tobacco smoking causes lung cancer in 80% of cases, but exposures to biomass fuels, radon, and asbestos also contribute.

Because COPD and lung cancer share similar risks, both diseases may concur in susceptible patients. Lung cancer is an important comorbidity of COPD that contributes to increased mortality. 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. Smokers with COPD have a 6-fold risk of lung cancer compared to smokers without airflow limitation and lung cancer incidence increases as forced expiratory volume in 1 second (FEV₁) declines, regardless of cigarette smoke exposure. Emphysema also increases lung cancer risk. In the Danish Lung Cancer Screening Trial, patients with airflow limitation, emphysema, age >70 years and ≥35 pack-years smoking had a 2-fold greater lung cancer risk.

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

Pathobiological Factors Linking Lung Cancer and COPD

Lung cancer is caused by mutations in oncogenes leading to an uncontrolled proliferation of cells and tumor formation. Pathophysiologial links between COPD and lung cancer have been elusive due to heterogeneity in responses to chronic inflammation and lung reparative processes. Possible common pathobiological processes include: 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.\textsuperscript{14-16} 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.\textsuperscript{17} It is also feasible that chronic lung inflammation in COPD predisposes to lung cancer.\textsuperscript{18} A reduction in mucociliary clearance may enable carcinogens to reside longer in the lung.\textsuperscript{8} The COPD lung microbiome differs from healthy individuals and may induce inflammatory changes that promote lung cancer development.\textsuperscript{19,20} Cigarette smoke may also induce release of vascular endothelial growth factor from epithelial cells causing angiogenesis which facilitates the progression, invasion, and metastasis of lung cancer.\textsuperscript{21}

Immune cell composition and function is important in non-small cell lung cancer (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) with increases in CD4+ TH1 as the disease progresses.\textsuperscript{22} Interleukin17 (IL-17) drives protumor inflammatory responses and facilitates tumor growth in animal models.\textsuperscript{22,23} COPD has increased sensitivity of CD8+ tumor-infiltrating T lymphocytes to tumor-mediated immune escape mechanisms suggesting higher sensitivity to PD-1 blockade.\textsuperscript{22} In NSCLC, immune cell composition is heterogenous and varies between adenocarcinomas and squamous cell carcinomas.\textsuperscript{12} In stage I non-squamous NSCLC, a more favorable gene signature for survival (FAIM3) is predominantly expressed in tumor-infiltrating leukocytes.\textsuperscript{24} Patients
Clinical Features of COPD That Increase Lung Cancer 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 lung cancer development. Studies in smokers and nonsmokers report a relationship between severity of airflow limitation and lung cancer risk. In a post hoc subset analysis of the National Lung Screening Trial (NLST), participants with COPD had a 2-fold increase in lung cancer incidence. Others, however, report the opposite relationship, that severity of airflow limitation is inversely related to lung cancer risk. In 2517 patients with COPD followed over 60 months, lung cancer occurred in those with less severe airflow limitation (Global initiative for chronic Obstructive Lung Disease [GOLD] stages 1 and 2), lower body mass index and DLCO <80%. Others report emphysema may be a greater risk factor for lung cancer compared to airflow limitation. The Pamplona International Early Lung Cancer Detection Program and the Pittsburgh Lung Screening Study databases showed that emphysema was independently associated with increased lung cancer risk using a risk stratification score (range 0-10 points). In both cohorts, the risk of lung cancer was 3.5-fold higher in the high (7-10) versus the low (0-6) risk group. Severity of emphysema was related to greater likelihood of developing and dying from lung cancer even after adjustment for age and smoking history. Others report no impact of emphysema severity on lung cancer risk.

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

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 lung cancers arising in emphysematous tissue are more aggressive. Smokers with impaired lung function have shorter doubling times and less indolent lung cancer. Epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements are less prevalent in patients with COPD-associated lung cancers and EGFR mutation is inversely related to the severity of airflow limitation.

Between 10% to 39% of COPD patients are never smokers and some evidence exists for an association between COPD and lung cancer in never smokers. In a population-based cohort of 338,548 Korean citizens, lung cancer incidence in never smokers with COPD was increased compared to never smokers without COPD. The highest risk of lung cancer was in patients who had COPD and had smoked with a 6-fold risk of developing lung cancer compared with never smokers without COPD.

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

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 versus non-ICS use.

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

Other pulmonary diseases may increase lung cancer risk such as a history of tuberculosis, chronic bronchitis, or emphysema. Patients with combined pulmonary emphysema and fibrosis have a higher incidence of lung cancer. Pulmonary fibrosis also increases lung cancer risk.

### Lung Cancer Screening

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

Several studies have demonstrated that lung cancer screening with LDCT reduces mortality by detecting lung cancer at earlier stages. (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 lung cancer, were not powered to show a mortality benefit.

The NLST and the 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 lung cancer-specific and all-cause mortality.

The 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. Participants in the intervention arm underwent 3 annual LDCT screenings and the controls had single view posteroanterior CXRs. Study adherence
was greater than 90%; the rate of positive screening tests was 24.2% with LDCT and 6.9% with CXRs over the 3 rounds. Lung cancer 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 lung cancer deaths per 100,000 person-years compared to 309 deaths per person-years with CXR: a relative mortality reduction from lung cancer of 20% with LDCT. Mortality from any cause was reduced by 6.7% with LDCT compared to the CXR group.

NELSON was powered to show a reduction in lung cancer mortality of ≥25% with volume-based LDCT screenings in high-risk male participants at 10 years follow-up. A total of 13,195 men and 2594 women between 50 and 74 years old were randomized to LDCT at baseline and years 1, 3, and 5.5 versus no screening. At the 10 year-follow-up among men, the incidence of lung cancer was 5.58 cases per 100 person years with LDCT and 4.91 cases per 1000 person years in controls; lung cancer mortality was 2.50 versus 3.30 deaths per 1000 person years, respectively. The cumulative rate ratio for lung cancer death at 10 years was 0.76 (95% confidence interval [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 (95% CI, 0.38 to 1.14).

Patient populations in the above 2 trials were predominately White (91% in the 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 2472 to 53,542 and follow-up periods from 5.2 to 10 years. Male predominance existed in both studies (range 56%– 84%). A unique aspect of NELSON was volumetric measurements of nodules and calculations of volume doubling.

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

**Influence of Age, Sex, Smoking Status, and Comorbid Conditions on Computed Tomography Screening Benefits**

Age, sex, smoking status, comorbidities, and other pulmonary conditions may impact prevention of lung cancer death. Sixty-four percent of NLST participants had no pulmonary conditions at baseline, 24.7% had 1 pulmonary condition, and 10.8% had 2 or more conditions. 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 the NLST women participants compared to men and the same benefit was found in NELSON. The German Lung Cancer Screening Intervention also found women had a significant reduction in lung cancer mortality compared to men. Sub-analyses showed that age or smoking status did not impact LDCT to reduce lung cancer 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.

The NLST reported false positive rates of 26.3% at baseline, and 27.2% and 15.9% at rounds 2 and 3, respectively. NELSON reported false positive rates of

**Table 3. Lung Cancer Screening**

| The number needed to prevent 1 lung cancer death was 323 over 6.5 years of follow-up in the NLST and 130 participants screened over 10 years in the NELSON trial. |
| 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 death for every 13 individuals versus 18.5 lung cancer deaths avoided by screening. |
| LDCT screening is cost-effective. |

NLST=National Lung Screening Trial; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek trial; LDCT=low-dose computed tomography; USPSTF=U.S. Preventative Services Task Force
19.8% at baseline and 7.1% at year 1, 9.0% at year 3 (males), and 3.9% at year 5 (males). Needle biopsies for false positive rates in several studies ranged from 0.09%–0.56% and surgical resections from 0.1%–0.5%. Invasive procedures were performed in 1.7% of screened participants in the NLST; number needed to harm, n=59. Use of Lung Reporting and Data System (Lung-RADS) criteria may avoid 23.4% of invasive procedures for false positive results.

**Radiation Risk with Low-Dose Computed Tomography**

Precise risks of developing cancer from cumulative radiation from lung cancer screenings are unknown. Estimates of radiation exposure after 25 years of annual screenings 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. The 2021 U.S. Preventative Services Task Force (USPSTF) recommendation estimates a higher rate of radiation-related lung cancer deaths (29.0 to 42.5 versus 20.6 per 100,000) than the 2013 recommendation but is outweighed by increases in lung cancer deaths prevented and life-years gained for women.

**Cost-effectiveness**

Some critics consider lung cancer screenings to be less cost-effective than smoking cessation. The U.K. LDCT trial compared screening to usual care in 4055 individuals and estimated the cost-effectiveness of screening to be £8466 per quality adjusted life-year gained. Annual screenings might be most cost-effective when eligibility is restricted to high-risk groups.

**Screening Intervals**

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

**Impact of Lung Cancer Screenings on Smoking Cessation**

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

**Psychosocial Harms of Lung Cancer Screenings**

Several studies report 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 lung cancer distress, quality of life improved following negative scans.

**U.S. Preventative Services Task Force Updated Lung Cancer Screening Recommendations**

In 2021, the USPSTF updated its recommendation based on a systematic review of the accuracy, benefits, and harms associated with lung cancer screening. It assessed if screening benefits vary by subgroup (e.g., race or sex), or number or frequency of LDCT scans, and whether harms associated with screening and nodule evaluation differs when using the International Early Lung Cancer Action Program, Lung-RADS, or other approaches to reduce false positive rates. USPSTF also commissioned modeling studies from the National Cancer Institute’s 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 recommendations advise LDCT screening at a younger age with less smoking burden, based on results from NELSON. Additionally, CISNET analyses supports screening at a younger age with lower smoking burden to address racial disparities.

**Implementation of Lung Cancer Screening in Clinical Practice**

Most cited trials were conducted at large academic medical centers. The transition to community practices,
Detection of Comorbidities During Lung Cancer 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. Patients with comorbid conditions may present with lung cancer at an earlier age. The “surveillance hypothesis” purports that patients with coexisting diseases have increased medical visits and more opportunities for cancer detection. The detection of comorbid conditions during an annual lung cancer screening, however, has received limited attention.

Implementation of lung cancer screening in LMICs has been proposed in high-risk populations such as COPD patients. Combining a screening program in ever smokers with ≥10 pack years and aged 55–74 years with their annual COPD review found a positive LDCT scan in 5% of patients. 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.

Strategies to improve lung cancer screening in LMICs include 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.

Special Considerations Using Lung Cancer Screening in COPD Patients

Lung cancer 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 lung cancer treatments.

Most patients with COPD are, or have been, smokers and represent the age of patients enrolled into the NLST and NELSON and meet 2021 USPSTF recommendations for lung cancer screening. COPD patients should undergo annual lung cancer 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. Among 24,453 individuals who underwent screening, 50.5% 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.”

In an analysis of NLST data, a mortality benefit of lung cancer screening was found in COPD patients with mild to moderate but not severe or very severe disease.

The impact of newer diagnostic techniques to investigate indeterminate lung lesions identified by LDCT is unknown. Positive emission tomography may help characterize solid lesions for malignant potential and decrease the number of false positive lesions undergoing unnecessary invasive procedures. Navigational bronchoscopy coupled with cone-beam CT imaging and augmented fluoroscopy may help increase the proportion of diagnosed lesions with less morbidity and mortality.

### Assessment of Treatment Risks for Patients with COPD and Non-small Cell Lung Cancer

**Note:** 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. 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) and 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 lung cancer.

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. 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. An estimated FEV₁ or DLCO≤40% is associated with increased perioperative complications including death. Further assessment using cardiopulmonary exercise testing is recommended; VO₂ max<15ml/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.

HRCT imaging can estimate perioperative risk. Regression based forced vital capacity (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.

#### Non-pulmonary Risk

The high-risk group for lung cancer 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. 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. Air trapping measured by residual volume/total lung capacity (TLC), prolongs operative hospitalization.

Nutritional status influences postoperative reoccurrence and death, especially in those with more severe airflow limitation. Sarcopenia predicts postoperative complications and survival following lung cancer surgery.
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.166

### Lung Cancer 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 mortality167 (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 lung cancer death.167

The frequent occurrence of lung cancer in older COPD patients with other pulmonary and comorbid conditions has prompted exploration of therapies other than curative resection.168

Lobectomy via video-assisted thoracoscopic surgery in high-risk patients (e.g., age>75 years, FEV1<50% predicted, DLCO<50% predicted, history of coronary heart disease) has a low, but not negligible incidence of major complications.169 Survival benefits may not be greater in patients >71 years of age compared to palliative resection.170

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 lung cancer-specific survival in patients with Stage IA NSCLC,171-174 especially when resected tumors are ≤2 cm in size and lymphadenectomy is performed. Perioperative complications are lower with sublobar resection175-179 compared to lobectomy in older patients and patients with FEV1<85%. In tumors 2-5 cm in size, sublobar resection is inferior to lobectomy,180 and sublobar resection may be inferior to lobectomy even for Stage IA tumors.181 Differences in patient populations, the extent of lymph node dissection, and the margin size around the resected tumor may all affect outcomes.182,183 Reduced lymphadenectomy during sublobar resection results in inferior survival outcomes compared with lobectomy; an increased number of lymph nodes resected may be more important than the extent of lung resection.184,185

Only using a 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.186

### Thermal Ablation

Thermal ablation is an alternative local therapy for NSCLC.187-194 Radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation (CRYO) have been used in patients with NSCLC.187,191-200 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. Most literature reports percutaneous image guided RFA. In 51 patients with inoperable Stage IA NSCLC, overall survival rate was 86.3% year 1 and 69.8% year 2. Local control and recurrence free rates were 68.9% and 59.8% at years 1 and 2, respectively.187 Recurrence rate was worse for tumors >2 cm in size. Several studies have reported minimal to no significant decline in lung function at 1 and 3 months post ablation.187,191,198,199 Reduced lung function post RFA treatment has been infrequently attributed to pleuritis or ablation volume.199 Follow-ups at 1 and 2 years post RFA reported no decline in lung function or DLCO.187,198 FVC increased in some
individuals possibly due to remodeled emphysematous tissue and decreased hyperinflation. Most studies report success with tumor sizes <3cm, preferably <2 cm. Pneumothorax, pleural effusion, and tumor track seeding may be complications. 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.

### Stereotactic Body Radiation Therapy

SBRT or stereotactic ablative radiation therapy 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. Treatment of tumor sizes of up to 5cm has become routine. Optimally, tumors should be > 1cm from the chest wall although this is not an absolute contraindication. Central (within 2cm 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 5 fraction treatment regimens.

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 2-fold from 2008 to 2013 (6.7% to 16.3%). A study in patients treated with inoperable NSCLC reported a 55.8%, 3-year overall survival with 90.6% local control rate. Higher maximum doses further improved local control and overall survival.

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 sublobar resection in high-risk patients for lobectomy reported similar 1-year survivals. However, overall, 3-year survival was higher with sublobar resection compared to SBRT. A metaanalysis of 11,540 high-risk elderly patients with Stage I NSCLC reported that sublobar resection compared to conventional fraction radiation therapy or SBRT significantly improved survival without differences in treatment failure or complications. Fatigue, pneumonitis, and chest wall pain were reported with SBRT but mortality at 30 days was 0%. Sublobar resection had morbidity between 7.3%–33.7% with a 30-day mortality of 1%–2.6.

Multiple attempts to perform multicentered randomized trials to evaluate surgical resection and SBRT have been aborted due to low patient accrual. Several trials comparing SBRT with surgical resection are currently ongoing.

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 Non-Small Cell Lung Cancer

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. However, others have shown no negative impact of COPD in patients treated with platinum-based chemotherapy or tyrosine kinase inhibitors. COPD patients have reduced ventilatory reserve and may have comorbidities such as congestive heart failure (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 ≥45ml/min. Chemotherapies such as etoposide and vinorelbine can cause cardiotoxicity and may aggravate CHF. Etoposide is used to treat small cell lung cancer 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 EGFR mutations, c-ROS oncogene 1 fusions, 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.

Immune checkpoint inhibitors have transformed NSCLC treatment and are used as sole first-line agents, or in 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 checkpoint inhibitors may promote T-cell attack on normal cells expressing self-antigens in the skin, thyroid, digestive tract, lungs, and joints. Some data suggest 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, or 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 cytotoxic T-lymphocyte-associated protein 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.

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

**Summary and Conclusions**

COPD and lung cancer are highly prevalent causes of morbidity and mortality, worldwide. Their combined presence poses important challenges to diagnosis, treatment, and prognosis. Shared risks and mechanistic factors may play roles in the higher association of lung cancer in patients with COPD and provide opportunities for novel target identification for the prevention and treatment of lung cancer. LDCT is a major advancement for earlier diagnosis and treatment of lung cancer, 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. Lung cancer 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 lung cancer.

**Declaration of Interest**

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