Lung Cancer: Targets and Therapy

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REVIEW

Chronic obstructive pulmonary disease in patients with lung cancer: prevalence, impact and management challenges

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Abstract: Chronic obstructive pulmonary disease (COPD) and lung cancer share a common etiological factor (cigarette smoking) and usually coexist in everyday clinical practice. The prevalence of COPD among newly diagnosed patients with lung cancer sometimes exceeds 50%. COPD is an independent risk factor (2–4 times higher than non-COPD subjects) for lung cancer development. The presence of emphysema in addition to other factors (e.g., smoking history, age) could be incorporated into risk scores in order to define the most appropriate target group for lung cancer screening using low-dose computed tomography. Clinical management of patients with coexistence of COPD and lung cancer requires a multidisciplinary oncology board that includes a pulmonologist. Detailed evaluation (lung function tests, cardiopulmonary exercise test) and management (inhaled drugs, smoking cessation, pulmonary rehabilitation) of COPD should be taken into account for lung cancer treatment (surgical approach, radiotherapy).

Keywords: lung cancer, COPD, coexistence, risk factor, therapy decisions

Introduction

Chronic obstructive pulmonary disease (COPD) and lung cancer are among the most common causes of death worldwide,[1] and as they have the same etiological factor (cigarette smoking) they usually coexist in everyday clinical practice.[2] Lung cancer is the leading cause of cancer in the USA, even though it is the second in prevalence for both sexes. Recently published worldwide statistics showed that it is also the leading cause of cancer death among men and the second cause of cancer death among women.[3] The 5-year survival rates are quite disappointing (17.9% for the USA), even though there is a statistically significant improvement during the last years (−2.3% in mortality between 2004 and 2013).[4] On the other hand, COPD is a common disease – especially among current/former smokers and the elderly – as it was estimated that 10% of adults >40 years old suffered from clinically important disease (spirometric stage II or higher).[5] According to World Health Organization, COPD is the third leading cause of death worldwide accounting for 3.2 million of deaths in 2015.[6] The aim the present review article is to point out the treatment challenges of patients who suffer from lung cancer and COPD simultaneously.

Prevalence of lung cancer among COPD patients and vice versa

Long-standing, prospective studies of COPD patients evaluating the effect of inhaled drugs on mortality and lung function decline showed that lung cancer was among the

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most common cause of death.[7,8] Several observational studies have concluded that COPD is an independent risk factor for the development of lung cancer.[9–14] The relative risk of lung cancer presence seems to be higher among patients with emphysema compared to those with chronic bronchitis.[9,15] Additionally, the severity of airflow obstruction, as expressed by forced expiratory volume in 1 second (FEV_1), is associated with lung cancer development[16] even though one study came to the opposite conclusion.[11]

Taking into account the common etiological factor (cigarette smoking) and possible interrelated pathogenetic pathways (chronic exposure of bronchoalveolar stem cells to pro-inflammatory cytokines, low respiratory clearance of carcinogenetic substances in patients with COPD, epithelial–mesenchymal transition, abnormal repair, oxidative stress, increased cellular proliferation, genomic and epigenomic changes),[17,18] the percentage of patients with COPD is extremely high among patients with lung cancer. In a retrospective study among patients with newly diagnosed lung cancer, the prevalence of COPD was much higher for men (72.8%) compared to women (52.5%). It is important to notice that this difference remained after adjustment for age and number of pack-years for smoking (odds ratio [OR]: 0.48; 95% CI: 0.28–0.83; p=0.009).[19] Additionally, in a comparative study between newly diagnosed patients with lung cancer and a matched controlled community-based population (according to age, sex and pack-year smoking exposure), the prevalence of COPD in individuals with and without lung cancer was 50% and 8%, respectively (OR: 11.6, p<0.0001). After adjustment for possible etiological variables, the prevalence of COPD in lung cancer cases was sixfold greater than in matched smokers.[20]

An incidence analysis from the UK General Practice Research Database during a 14-year period showed that lung cancer was four to five times more common among patients suffering from COPD in comparison with subjects without COPD, of the same age group and similar risk profile.[10] During the BODE (Body Mass Index, Airflow Obstruction, Dyspnea, Exercise Performance) study, which was designed for identifying prognostic factors for COPD, 2,507 patients were followed-up for a median of 60 months, and 215 of them were diagnosed with lung cancer (incidence density of 16.7 cases per 1,000 person-years).[11] The SYNERGY project aimed to investigate the relationship between previous respiratory diseases among patients with lung cancer. Emphysema was proved to be the strongest risk factor compared with other pulmonary diseases (bronchitis, pneumonia, tuberculosis and asthma) for lung cancer development (OR: 1.5 for men and 1.35 for women).[9] A recent meta-analysis showed that only when emphysema was diagnosed qualitatively by a radiologist there was an increased risk for lung cancer but this association was lost if the diagnosis of emphysema was based on image analysis software.[14] A possible explanation is that emphysema diagnosis by a radiologist probably reflects the most severe cases of the disease, which corresponds to higher burden of chronic inflammation and carcinogenesis.

The impact of COPD on survival of lung cancer patients

A long-standing (1991–2004) retrospective evaluation of >4 million patients enrolled in the UK General Practice Research Database showed that the 3-year survival for lung cancer patients with simultaneous diagnosis of COPD was almost half that of the general population (15% vs 26%; p<0.01).[10] In a sample of 4,447 elderly lung cancer patients, the presence of COPD was associated with a decreased survival (hazard ratio [HR]: 1.14, 95% CI: 1.05–1.25) and the probability of surgical treatment or administration of chemotherapy was also lower.[21] The presence of COPD and its severity have been proved to be significant prognostic factors for non-small-cell lung cancer (NSCLC) patients who underwent surgical treatment.[22,23]

A recent meta-analysis that included 26 studies (2001–2015, only one was prospective, all the others were retrospective) estimated the effect of COPD on overall and disease-free survival among lung cancer patients.[24] The HR was 1.19 (95% CI: 1.10–1.25, p<0.00001) for overall survival and 1.52 (95% CI: 1.04–2.23, p=0.03) for disease-free survival. Studies that focused on patients with emphysema showed similar results even though the outcomes were less consistent because of a limited number of patients. Poorer prognosis was noticed independent of tumor staging, although the association was even stronger in early-stage disease (I–II). A recent, long-standing (30 years of follow-up) observational study from Finland showed that the severity of airway obstruction was associated with all-cause and lung cancer mortality.[25] Sometimes, in the most severe cases of COPD, it is difficult to decide what the exact cause of death was but it is has been proved that the presence of both diseases has a negative effect on survival.

The impact of COPD on lung cancer screening programs

Taking into account the high incidence of lung cancer among patients with COPD, the effectiveness of screening programs might be increased if more subjects of this specific target

group are included. The implementation of objective score scales would probably improve the diagnostic yield of screening programs. Recently, risk stratification scores have been developed in order to specify the target population for screening, and emphysema was included as an important parameter. De Torres et al validated the COPD Lung Cancer Screening Score that was based on age (>60 years), body mass index (<25 kg/m^2), smoking history (>60 pack-years) and presence of emphysema on low-dose computed tomography (LDCT). They found that a score of 7–10 points was associated with a 3.5-fold increase for lung cancer diagnosis.[26] Using a risk prediction model based on clinical parameters and the presence of emphysema, the investigators of the National Lung Screening Trial classified participants into 5 quintiles.[27] They found that subjects in the subgroup with highest risk for lung cancer death (quintiles: 3–5) accounted for almost 90% of the screening-prevented lung cancer deaths, while the number needed to screen in order to prevent one death due to lung cancer was much lower among participants in the upper quintile (number needed to screen: 5,276 vs 161 for Q1 and Q5, respectively). Criteria for participation in screening programs might be that symptomatic smokers regardless of age should undergo spirometry while elderly heavy smokers with or without symptoms should be offered LDCT. Those who are diagnosed with COPD (spirometry) and/or emphysema (LDCT) and achieve increased scores in risk stratification models should be considered as a high-risk group for lung cancer development and more often follow-up might be indicated.[28,29]

Results from observational studies among COPD patients suggest the potential protective role of inhaled corticosteroids (ICS) against lung cancer – particularly at high doses – but small randomized trials did not come to the same conclusions.[30] A recent, retrospective, population-based study showed that treatment with specific statins was related with a significant chemopreventive effect against lung cancer in COPD patients in a dose-dependent manner.[31]

Management challenges: COPD as a limitation for radiotherapy

Preoperative assessment of pulmonary function by measuring FEV_1 and diffusion capacity (DLco) is considered necessary. Recent guidelines recommend that if predicted postoperative (PPO) FEV_1 and/or PPO DLco are <30% pred., then cardiopulmonary exercise testing is essential in order to calculate the surgical risk and decide about treatment plan.[32,33] Taking into account the above recommendation, patients with severe COPD (preoperative FEV_1 <50% pred.) are defined as high-risk group and surgical treatment of lung cancer is contraindicated in many cases. Stereotactic body radiotherapy (SBRT) is a new treatment option for such patients with early-stage lung cancer.[34] Stereotactic radiotherapy consists of 3–5 fractionations of highly prescribed doses (e.g., total dose of 36–54 Gy in 3–5 fractions) that are directed to small planning target volume. Retrospective and nonrandomized studies that included patients with inoperable disease or those who refused the surgical approach showed that local control, recurrence rates and overall survival are comparable with surgical series.[35–40] A recent pooled analysis of two small randomized trials (58 patients), which closed early because of slow accrual, showed that stereotactic ablative radiotherapy (SART) was associated with increased 3-year survival compared with lobectomy (HR: 0.14, 95% CI: 0.017–1.190, p=0.037) in patients with operable stage I (≤4 cm) NSCLC.[41] We should emphasize that patients with severe COPD, with or without cardiovascular comorbidities, usually die because of cardiopulmonary complications, so the lung cancer-specific rather than overall mortality should be taken into account for the effectiveness of SART.

Palma[42] in a single-institution cohort of 176 patients with severe COPD (FEV_1 <50% pred.) achieved a 3-year overall survival of 47%. Three patients developed radiation pneumonitis of Grade 3 (one patient early <6 weeks after SBRT and two late >6 weeks). They also reviewed two surgical and two SBRT studies among patients with severe COPD (FEV_1 <40%–50% pred.) and found comparable long-term survival rates, with higher 30-day mortality for surgical series. A retrospective study from Japan[43] that compared 74 non-COPD patients with 62 suffering from COPD who underwent SBRT concluded that even though there was no difference in lung cancer-specific survival, the presence of COPD was associated with radiation pneumonitis in the multivariate analysis. On the contrary, Takeda et al[44] evaluating retrospectively 265 lung cancer patients who were treated with SBRT found that radiation pneumonitis was relatively milder among patients with severe COPD. Probably this could be attributed to lower radiation doses that were used for COPD patients. The same authors followed up patients who underwent SBRT using spirometry and found that COPD was not correlated with faster FEV_1 decline.[45] Guckenberger et al[46] evaluated the effect of pulmonary function on the risk of pulmonary toxicity after SBRT. They retrospectively studied more than 400 patients from five international institutions with a wide range of FEV_1 (29%–109% pred.) although there was not a subgroup analysis for COPD patients. They found that radiation-induced pneumonitis was not inversely related

with pulmonary function tests. It was quite interesting that pulmonary function improved more for those with worst pretreatment measurements, an effect that is similar with lung volume reduction surgery (LVRS) for emphysema patients.

Conclusively, patients with early-stage, inoperable lung cancer due to COPD should be carefully evaluated for SBRT and closely followed up for the possibility of radiation pneumonitis. There is no recommended/optimal radiation dose for patients with severe COPD based on spirometric variables or other severity index scores. Even severe COPD is not an absolute contraindication for SBRT. Tumor size, location (peripheral vs central), dose per fraction and total dose are important factors that are related with the severity of radiation pneumonitis. It seems that prolonging the time period of SBRT – with the same number of fractions – might reduce the long-term adverse events, especially dyspnea.[47] Conventional radical radiotherapy should be avoided if possible, because of lower effectiveness rates compared with SBRT based on published data but not head-to-head randomized studies.[36,48]

Management challenges: COPD as a limitation for surgical treatment

Surgical treatment (lobectomy plus mediastinal lymph node dissection) is considered the standard of care and most effective approach for the limited stage NSCLC.[49] Taking into account the effect of COPD on survival[50] and postoperative complications (three times more common compared with non-COPD patients)[51] as well as the recommended absolute contraindications of surgical management based on lung function parameters,[32,33] spirometric evaluation is considered one of the most important steps for preoperative assessment.

Even though previous guidelines of British Thoracic Society[52] recommend that no further respiratory function tests are required for a lobectomy if the post-bronchodilator FEV_1 is >1.5 L and for a pneumonectomy if the post-bronchodilator FEV_1 is >2.0 L, most recent reports agree that both FEV_1 and DLco are necessary as well as calculation of PPO values. Guidelines agree that preoperative FEV_1 + preoperative DLco both >80% pred., preoperative VO_2max >75% pred. or >20 mL/kg/min and PPO FEV_1 + PPO DLco both >60% pred. are considered safe cutoff points for pulmonary resection up to pneumonectomy. On the contrary, if preoperative or PPO VO_2max is <35% pred. or <10 mL/kg/min then the patient is considered as high-risk and alternative therapeutic option should be considered (SBRT or chemotherapy plus radiotherapy).[32,33] Also, patients with either or both PPO FEV_1 and DLco <30% pred. are considered as high-risk group and cardiopulmonary exercise testing is indicated for more detailed evaluation. Measurement of arterial blood gases is considered a routine in everyday clinical practice for patients with severe COPD or based on oximetry values, but hypercapnia[53] or hypoxemia[54] is not considered as absolute contraindications.

There are some treatment strategies (preoperatively and the choice of the surgical approach) that could decrease the risk of postoperative pulmonary complications. Even though it is well known that long-term bronchodilators and ICS reduce symptoms and prevent exacerbations of COPD,[55] there are no large-scale, randomized trials about the effect of inhaled drugs on the postoperative complications and survival. Optimizing treatment for COPD before lung cancer resection is considered the standard of care.[56] A recent study about the effect of perioperative administration of ICS showed no association (advantageous or deleterious) with respiratory postoperative complications.[57] Regarding smoking abstinence, it should be of at least 4–8 weeks before surgery in order to reduce significantly the incidence of pulmonary postoperative complications[58,59] but FEV_1 1 year after operation was not different between those who quitted smoking > or <1 month before surgery.[60] Concerning pulmonary rehabilitation, a study that included 27 COPD patients with marginal lung function for resection (FEV_1: 1.14±0.7 L, VO_2max <15 mL/kg/min) who underwent an intense pulmonary rehabilitation program of 4–6 weeks (6 days/week) showed significant improvements in PaO_2, FEV_1 and VO_2max, and eventually all of them were capable for lobectomy.[61] A review on this topic that included small case series concluded that preoperative pulmonary rehabilitation could increase exercise capacity, as expressed by VO_2max, but the effect on pulmonary postoperative complications is not quite clear.[62]

The choices of surgical approach (video-assisted thoracoscopic surgery [VATS] vs open thoracotomy and lobectomy vs sigmentectomy) as well as performing LVRS simultaneously are important treatment decisions that should be discussed in a multidisciplinary oncology board. A matched controlled propensity analysis of 182 COPD patients who underwent VATS or open thoracotomy lobectomy showed that the former was associated with a lower incidence of pulmonary complications, shorter operation time and shorter length of hospital stay.[63] A recent review about the comparison of VATS versus thoracotomy lobectomy among patients with limited lung function reserves (PPO FEV_1 <40%–60% pred.) ascertained the lower incidence for pulmonary postoperative complications, length of hospital stay and better long-term survival.[64] LVRS has been proved to be an effective

treatment approach for COPD as it improves exercise capacity, lung function and survival, especially among patients with heterogeneous upper-lobe emphysema and low exercise capacity.[65,66] Single-center studies showed that patients with lung cancer and severe emphysema (preoperative FEV_1: 29%–44% pred.) who underwent lobectomy alone (the specific pulmonary lobe had the worst emphysema score) or lung cancer resection plus LVRS improved their lung function postoperatively.[67,68] There is some evidence that the presence of airway obstruction preoperatively is related with better preservation of postoperative lung function than healthy subjects, even among the elderly.[69,70] Bronchopleural fistula and prolonged hospitalization due to inability of early chest tube removal after lung cancer surgery are a quite common complications for COPD patients.[71]

There is no data concerning the effectiveness and adverse events of chemotherapy among COPD patients with lung cancer. There is evidence that epidermal growth factor receptor mutations are detected less commonly among patients with concomitant emphysema.[72,73]

Conclusions

Lung cancer and COPD usually coexist in everyday clinical practice. COPD is an independent risk factor for the development of lung cancer. COPD is a negative prognostic factor for lung cancer patients. The presence of COPD may alter the treatment plan (radiotherapy, surgical approach) for lung cancer.

Disclosure

The authors report no conflicts of interest in this work.

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