# Survival After Surgical Resection for Lung Cancer in Patients With Chronic Obstructive Pulmonary Disease

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*Background.* **The best curable therapy for lung cancer is surgical resection. Chronic obstructive pulmonary disease (COPD) may influence survival, and lung function is crucial in the preoperative assessment. We hypothesized that COPD would influence survival after lung cancer resection.**

*Methods.* **During the period 2003 to 2013, 688 patients were operated on for stage I and II non-small cell lung cancer and prospectively registered. Spirometry was performed, and COPD categorized according to the definition by the Global Initiative for Chronic Obstructive Lung Disease. An explanatory strategy was used to investigate the relationship between severe COPD and survival.**

*Results.* **COPD was present in 455 patients (66.1%) and was severe in 51 (7.4%) and mild to moderate in 404 (58.7%), whereas 233 patients (33.9%) had normal lung function. Cumulative survival was similar in patients with normal lung function and patients with mild to moderate COPD. Patients with severe COPD had significantly reduced cumulative survival after 2 and 5 years of 63.5% (95% confidence interval [CI], 48.4% to 75.2%) and 41.8% (95% CI, 26.5% to 56.3%), respectively, compared with nonsevere COPD at 81.7% (95% CI, 77.4% to 85.2%) and 61.3% (95% CI, 55.3% to 66.6%), respectively. Severe COPD was associated with a 69% increased risk of mortality (adjusted hazard ratio, 1.69; 95% CI, 1.12 to 2.55).**

*Conclusions.* **With careful preoperative selection, surgical resection may safely be offered to lung cancer patients with severe COPD. However, these patients have decreased long-term overall survival. Similar survival between patients with normal lung function and mild to moderate COPD suggests that similar indications for lung cancer operations may be applied.**

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Lung cancer is the leading cause of cancer death worldwide, accounting for approximately 1.4 million deaths annually [1]. With 1.6 million new cases each year, it is also the most commonly diagnosed cancer in the world. In Norway, 3,019 new cases of lung cancer were diagnosed in 2014 [2].

The best curable therapy for localized lung cancer (stages I and II) is complete surgical resection [3, 4]. However, comorbidities, such as chronic obstructive pulmonary disease (COPD), may influence the results. Lung function is therefore a crucial factor in the assessment for surgical intervention, and patients with severely reduced lung function may be rejected for surgical treatment. The relationship between COPD and postoperative survival has been studied in several retrospective studies, but most of the larger studies do not grade the severity of airway obstruction [5–7].

A retrospective study by Zhai and colleagues [6] showed that early-stage lung cancer patients with COPD had poorer survival than patients without COPD. COPD was defined by clinical assessment, and lung function was not evaluated in most patients. In a registry study of 61,170 patients, Putila and colleagues [7] found that COPD was an independent predictor for reduced survival after resection for lung cancer. That study linked data collected from the Surveillance Epidemiology and End-Results cancer registry with medical records from the Medicare database. COPD was not stratified by severity, and lung function data were not reported. Some additional retrospective studies have recently been published, suggesting that COPD worsens the prognosis for post-surgical survival for non-small cell lung cancer (NSCLC) [8–10].

Lack of lung function data will cause a misclassification problem related to the diagnosis and severity of COPD. Studies specifically designed to investigate the influence of spirometry-verified COPD on survival after resection for lung cancer are needed. We hypothesized that COPD, based on objective lung function measurements, would influence survival after resection for NSCLC.

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**Abbreviations and Acronyms**

| | |
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| BMI | = body mass index |
| CI | = confidence interval |
| COPD | = chronic obstructive pulmonary disease |
| DLco | = diffusion capacity of the lung for carbon monoxide |
| ECOG | = Eastern Cooperative Oncology Group |
| $FEV_1$ | = forced expiratory volume in 1 second |
| FVC | = forced vital capacity |
| GOLD | = Global Initiative for Chronic Obstructive Lung Disease |
| IRR | = incidence rate ratio |
| NOS | = not otherwise specified |
| NSCLC | = non-small cell lung cancer |
| VATS | = video-assisted thoracoscopy |

## Patients and Methods

The Regional Committee for Medical and Health Research Ethics approved this study. Written consent was obtained from all patients.

### *Patients*

During a 10-year period (2003 to 2013), all patients surgically treated for lung cancer were prospectively registered in the hospital's lung cancer database. We excluded patients with small cell lung cancer and carcinoid tumors (Fig 1). The study population comprised 688 patients with histologically confirmed NSCLC (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and carcinoma, not otherwise specified) according to guidelines [11]. Demographic characteristics of the patients are described in Table 1.

Birth date and death date were provided from the National Registry in Norway. Other data were collected from the referral letter, the patient records, and a standardized, self-constructed questionnaire about smoking and former diseases that each patient completed on admittance. Results from the various tests and examinations (eg, radiology and pathology), were consecutively recorded. No data were registered on disease recurrence or specific causes of death.

Patients were referred from hospitals in the southern parts of Norway (population approximately 1.2 million) to our high-volume tertiary university center, which surgically serves about one-quarter of all lung cancer patients in Norway. Before referral, the patients underwent primary assessment in accordance with national guidelines in their local hospital. Patients presumed to have potentially operable tumors were referred to the weekly multidisciplinary team meeting in our hospital. We have no record of patients who were found not eligible for surgical intervention during the primary assessment in their local hospitals.

All patients were referred back to their respective local hospitals approximately 1 week after the operation, after removal of thoracic drainage and appropriate postoperative control of pain and possible infections. Systematic dissection or lymph node sampling was performed according to international guidelines [3]. In line with internal hospital routines, all patients were treated with preoperative and postoperative prophylactic antibiotics.

### *Spirometry*

Spirometry was performed according to the American Thoracic Society/European Respiratory Society guidelines using the Vmax V6200 automated system (SensorMedics, Yorba Linda, CA) [12]. The reference values recommended by European Respiratory Society were used [13]. Registered variables were forced vital capacity (FVC), forced expiratory volume in 1 second ($FEV_1$), and the ratio $FEV_1$/FVC. Gas diffusing variables were the diffusing capacity of lung for carbon monoxide (DLco) and DLco divided by alveolar volume. FVC, $FEV_1$, and DLco were reported in absolute values and as percentage of predicted. Predicted postoperative values for $FEV_1$ and DLco were calculated using the formulas described in the European Respiratory Society guidelines [4].

Airflow limitation was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines as a postbronchodilator $FEV_1$/FVC of less than 0.7 as a confirmation of persistent airflow limitation [14]. The severity of airflow limitation is classified in four classes: mild ($FEV_1 \geq 80\%$ predicted), moderate ($FEV_1$ 50% to <80% predicted), severe ($FEV_1$ 30% to <50%), and very severe ($FEV_1 < 30\%$) airway obstruction.

### *TNM Classification*

All tumors were staged using the Seventh Edition of the International TNM classification [15]. The pathological TNM was used to describe the distribution of the tumor using the postoperative tissue specimen. All patients treated before the introduction of the Seventh Edition were manually reassessed to be comparable.

### *Statistical Analysis*

We used the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines in reporting our cohort study [16]. An explanatory strategy was used to investigate the relationship between severe COPD and survival [17]. All other variables were of interest only as possible confounders or effect modifiers of this association. COPD as an exposure variable was initially categorized in three groups according to the GOLD guidelines. Severe COPD ($FEV_1 < 50\%$ of predicted), mild to moderate COPD ($FEV_1 \geq 50\%$ predicted), and normal lung function. Owing to the similarities in survival rate and a nonsignificant difference in hazard ratios in patients with mild and moderate COPD and patients with normal lung function, these two groups were merged and compared with the severe COPD group in the final survival analysis.

For stratified analysis, age and number of pack-years of smoking were dichotomized according to their respective median values. The Eastern Cooperative Oncology Group