

**Original Research****Lung Cancer in Patients With COPD: Predictors of Surgery and Long-Term Survival Following Lung Resection**

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***Running Head: Lung Cancer in COPD***

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***Abbreviations:*** BMI: body mass index; COPD: chronic obstructive pulmonary disease; FEV<sub>1</sub>: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; NSCLC: non-small cell lung cancer; SBRT: stereotactic body radiotherapy

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## Abstract

**Background:** Lung resection is the preferred treatment option for lung cancer. Patients with chronic obstructive pulmonary disease (COPD) may be denied surgery due to lung function impairment or other comorbidities.

**Research question:** To describe the predictors of lung resection and long-term survival in patients with COPD with early-stage non-small cell lung cancer (NSCLC).

**Study Design and Methods:** Retrospective cohort study of patients with COPD treated for resectable NSCLC between 2009 and 2019 in a tertiary care hospital. The decision to operate or not followed a thorough clinical evaluation. Survival status was obtained from a provincial registry. A multivariable logistic regression analysis was used to determine predictors of surgery. A propensity score technique was used to control for confounding by indication. Hazard ratios (HR) for survival were estimated from a Cox regression model, adjusted for measured baseline confounders and propensity score as covariates.

**Results:** 1307 patients with COPD were included, including 918 who underwent surgery. 147 (38%) of those who did not have surgery were treated with stereotactic body radiotherapy, 86 (22%) with conventional radiotherapy and 156 (40%) did not receive any active treatment. Predictors of surgery included age, FEV<sub>1</sub>, adenocarcinoma versus squamous cell carcinoma, and stage IIA versus stage IA. Propensity score-adjusted survival was significantly reduced with non-surgical versus surgical approaches.

**Interpretation:** Lung resection was associated with better survival in patients with COPD and resectable lung cancer compared to non-surgical approaches.

## Introduction

Lung cancer is the first cause of mortality by cancer with approximately 1,8 millions deaths in 2022<sup>1</sup> surpassing colorectal, pancreatic and breast cancer combined<sup>2</sup>. Surgery for stage I and II non-small cell lung cancer (NSCLC) is still the treatment of choice<sup>3</sup> although advances in radio-oncology with the development of stereotactic body radiotherapy (SBRT) offering the possibility of delivering high dose of radiation in a targeted area is now considered a viable option for many patients unfit for surgery<sup>4</sup>. Although local control may be similar between surgical resection and SBRT, survival is more favorable with the former treatment even when the analysis is limited to patients with operable disease<sup>4,5</sup>, perhaps with the exception of T1N0M0 disease in whom 3-year survival may be similar with both therapies<sup>4</sup>.

Chronic obstructive pulmonary disease (COPD) is found in 50 to 70% of the lung cancer population<sup>6</sup>, smoking being the main shared risk factor for both pathologies<sup>7</sup> but COPD also representing an independent risk factor for lung cancer<sup>8</sup>. COPD is often the main reason for not performing surgery<sup>9</sup>, lung function being recognized as a predictor of mortality and morbidity following lung resection<sup>10</sup>, particularly in those with moderate or severe airflow limitation<sup>11</sup>. A conservative practice toward patients with COPD may be justified considering that higher mortality and morbidity rates have been reported in this situation, particularly if patients were to die of their comorbid conditions and not of lung cancer. However, in one study involving 4,069 patients with stage 1 lung cancer, including 449 treated by SBRT and 3620 by surgical resection, the latter treatment was associated with decreased lung cancer-related death in all scenarios of severity of airflow limitation<sup>12</sup>.

We recently reported our experience with lung resection for lung cancer in patients with COPD<sup>13</sup>. Although 30-day mortality was slightly higher in patients with COPD compared to those with normal lung function (1.3% compared to 0.2%), mortality rate was within the expected range for this type of surgery<sup>10</sup>. This study mainly involved patients with mild to moderate airflow limitation contributing to favorable post-operative outcomes. Alternatively, favorable mortality rates after lung resection in COPD could be related to applying strict and conservative selection criteria before proposing surgery. One downside of using stringent selection criteria for surgery, is the

possibility to deny the best treatment option to marginal patients that could nevertheless tolerate lung resection

COPD is often not the sole comorbid condition as it is frequently associated with advanced age and cardiovascular disease<sup>14-16</sup>. The role of accumulating comorbidities in the treatment decision regarding the treatment of lung cancer in patients with COPD is unclear. Many studies report that lung cancer resection is the best therapeutic approach<sup>4,17,18</sup> but it may not always be the case<sup>19-23</sup>. Secondary analyses of retrospective studies support the view that surgery is advantageous in the majority of clinical situations<sup>12</sup> but these results were obtained in heterogeneous population in which COPD was not universally present and in which the impact of added comorbid conditions in addition to COPD was not addressed. It would be of interest to evaluate the efficacy of surgical compared to non-surgical approaches exclusively in patients with COPD who are affected or not by other comorbid conditions.

Accordingly, the objectives of this study were to: (1) compare the characteristics of patients with COPD who underwent surgical resection for early-stage NSCLC compared to a non-surgical approach; (2) describe the predictors of lung resection in this population; (3) evaluate the impact of surgery on long-term survival and (4) determine, when feasible, the mortality causes in this population.

## Methods

### Study design and population

We conducted a retrospective study of patients who were diagnosed with resectable (stage I and II) NSCLC and treated at the *Institut universitaire de cardiologie et de pneumologie de Québec* (IUCPQ), a tertiary-care hospital and main thoracic oncology centre in eastern Québec, Canada between January 1<sup>st</sup> 2009 and December 31<sup>st</sup>, 2019. Data about patients who underwent lung resection was prospectively collected in the institutional biobank database after written consent was obtained. Data on patients who did not have surgery was collected in a clinical database of medically-treated patients with lung cancer in our institution. The study was approved by the institutional ethic committee (project CER 21184).

To be included in this study, patients needed to be 18 years old or older and have an airflow limitation caused by COPD as defined by a forced expiratory volume in 1 second (FEV<sub>1</sub>) to forced vital capacity (FVC) ratio < 0.70 in the presence of a smoking history of at least 10 pack-years. Spirometry was done according to published guidelines<sup>24</sup>. Airflow limitation was stratified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria<sup>25</sup>. Patients were included at the first occurrence of lung cancer. Patients were excluded if they had no spirometry available, normal lung function on pulmonary testing or abnormal spirometry not caused by COPD. They were also excluded if they had stage 3 or 4 lung cancer at diagnosis or if the final histologic pathology showed any other histopathology than NSCLC.

Patients were evaluated by a pulmonologist with specific training in lung oncology and/or a thoracic surgeon who considered medical history, comorbidities, functional status, respiratory function tests, disease extent, feasibility of complete surgical resection, as well as individual's preferences in order to reach a therapeutic decision. In our centre, the lung oncology group works as a team in such a way that investigation and therapeutic decisions are practically standardized. Nevertheless, no therapeutic algorithm was used to determine operability and final decision relied on the integration of the clinical and paraclinical data and clinician's judgment in conjunction with the patient input. We run a weekly tumor board but stage 1 and 2 lung cancer cases are generally

not presented when therapeutic decision is straightforward although individual cases could be discussed at the request of the treating physician to reach a decision. Treatment offered included surgical resection (most commonly through video-assisted thoracoscopic surgery [VATS] and including lymph node dissection and sampling), SBRT (4-5 fractions, 48-50 grays), conventional radiotherapy (20-30 fractions, 50-60 grays) or therapeutic abstention. SBRT became available in 2010 but patients had to travel to another region; since 2014 it is available in our area, facilitating access to therapy.

### Data collection

For patients who underwent lung resection, the following information was extracted from the institutional biobank's database: age, sex, body mass index (BMI), smoking history, spirometry, extent of lung resection, type of surgery, histopathological diagnosis and pathologic TNM staging based on staging criteria of the American Joint Committee on Cancer, 8<sup>th</sup> edition<sup>26</sup>. Two authors (AT, CLe) also reviewed medical files to confirm the diagnosis of COPD and to collect information on comorbidities, including coronary artery disease, diabetes, renal insufficiency, peripheral artery disease, hypertension, and dyslipidemia. We also collected information about medication including the use of beta-blockers, antihypertensive, hypolipidemics, oral hypoglycemics and inhaled therapy including bronchodilators and inhaled corticosteroids. For the non-surgical group, the same data was obtained from medical chart review and the clinical database. For these individuals, lung cancer staging was based on clinical TNM, 8<sup>th</sup> edition<sup>27</sup>. Survival status was calculated from the time of surgery or, for the non-surgical patients, from the first medical visit for lung cancer, censored on December 31<sup>st</sup> 2019 from the medical file or from the *Régie de l'assurance maladie du Québec*, a provincial organization to which all deaths occurring in the province of Québec are reported. Mortality causes could be obtained for patients treated between 2009 and 2012 from the *Institut de la statistique du Québec*.

### Statistical analyses

Continuous variables were expressed as mean  $\pm$  standard deviation (SD). Categorical variables were presented as absolute and relative frequencies and were analyzed using Fisher's exact test.

To handle the missing data for BMI, smoking status and renal insufficiency, we used a multiple imputations (MI) procedure, in which 100 datasets of plausible values for missing data were imported. A fully conditional specification method using the predictive mean matching technique that assumes the existence of a joint distribution for all variables and ensures that imputed values are plausible was performed for continuous variables. The discriminant function method was used for dichotomous variables. We tested the adequacy of the iterations (convergence) by visual inspection of trace plots for different chains which showed no apparent trends for the imputed values between the imputation models. The imputation procedure and the subsequent analyses were performed according to the Rubin's protocol. Univariate logistic regressions were performed to determine predictors of surgery. Continuous variables were checked for the assumption of linearity in the logit using graphical representations. It was found that the relationships between age, BMI, FEV<sub>1</sub> (% predicted) and the odds of having surgical resection were not linear with significant changing risks along the range of these variables. Knots in these relationships were determined using a nonlinear logistic regression model that maximized the likelihood function. Variables with a probability value < 0.20 in the univariate regressions were candidates for the multivariable logistic regression model building. The variable selection was performed using a forward approach. The Akaike's information criterion and Schwarz's Bayesian criterion were used to compare candidate models. After model building, the Hosmer-Lemeshow test was performed to assess the goodness-of-fit of the model. The overall survival analysis used the Nelson-Aalen estimator for the survival curve and compared with the log-rank test. A Cox regression statistical model adjusted for the propensity score was performed. The propensity score was defined as the likelihood of undergoing surgery assigned to each patient and was computed from the multivariable logistic regression model. Using the same model building strategy mentioned previously, the retained variables were age, FEV<sub>1</sub>, sex, BMI, active smoking status, coronary artery disease, renal failure, peripheral artery disease, FVC, FEV<sub>1</sub>/FVC, adenocarcinoma, squamous cell carcinoma, lung cancer stage IB and IIA. Statistical significance was present with a two-tailed p value < 0.05. Analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, U.S.A.).



## RESULTS

### Patient's characteristics

The flow of patients is presented in **Figure 1**. Between January 1<sup>st</sup> 2009 and December 31<sup>st</sup> 2019, 2 347 patients with COPD were evaluated for NSCLC. From this number, 1 423 patients underwent lung resection for stage I and II NSCLC, including 918 who met the inclusion criteria for this study. VATS was done in 82% of surgical patients. In the same period, 924 patients were not considered as surgical candidates among whom 389 met the inclusion criteria for this study. The non-surgical group included patients who underwent SBRT (n = 147), conventional external beam radiotherapy (n = 86) and therapeutic abstention (n = 156). A preference not to receive active therapy was expressed by 22 patients among the 156 patients who did not receive active treatment. For the remaining ones, this therapeutic choice was based on the integration of the clinical and paraclinical information by the clinician. Histologically-proven cancer was documented in all but 68 patients who all belonged to the non-surgical group.

Patient's characteristics are shown in **Table 1**. The study population included 613 (47%) women with a majority of ex-smokers. Mean FEV<sub>1</sub> averaged  $73 \pm 20$  % predicted value, including 178 patients with GOLD 3+ (FEV<sub>1</sub> < 50% predicted). The most frequently encountered lung cancer stage was stage IA, with a predominance of adenocarcinomas. In comparison to patients in the non-surgical group, patients who had surgery were younger and the proportion of female was greater. Also, the proportion of current smokers and the prevalence of comorbid conditions were lower than in the non-surgically treated group. Consistent with this, operated patients took fewer medications. Patients in the non-surgical group had a lower FEV<sub>1</sub>, the proportion of GOLD stage 3 and 4 was larger and they were more frequently using inhaled medication. There were more adenocarcinomas in the surgically treated group which also had a lower prevalence of stage IIB than in the non-surgical group. Lymph node status was similar in both groups. The 30-day mortality was 0.4% (95% CI: 0.02 to 1.20%) in the surgical group; no death was recorded during this period in the non-surgical group.

### Predictors of surgical treatment



In the univariate analyses, multiple factors were associated with the probability of having surgical treatment, including age, sex, BMI, active smoking, comorbid status, FEV<sub>1</sub> (% predicted), tumor histology and stage (**Table 2**). In the multivariate analysis, the main negative predictor of surgery was age, particularly in individuals aged 75 years and older where each 1-year increment in age associated with a 32% reduction in the odds of being operated. FEV<sub>1</sub> was the second most important factor notably when less than 40% predicted where each 1% predicted increase in FEV<sub>1</sub> was associated with a 27% increase in the probability of having surgery. Over 40% of predicted, the relationship was weaker, each 1% predicted increment in FEV<sub>1</sub> predicting a 5% increase in the odds of being operated. Being diagnosed with an adenocarcinoma versus squamous cell carcinoma (OR = 1.81, 95% CI: 1.27 to 2.57), and stage IB (OR = 2.05, 95% CI: 1.36 to 3.09), stage IIA (OR = 4.41, 95% CI: 2.12 to 9.18) were all associated with an increased likelihood of undergoing surgery. In turn, active smoking was a strong factor predicting a non-surgical approach (OR: 0.39, CI 0.27 to 0.56). The presence of coronary artery disease, BMI above 35 kg/m<sup>2</sup> and renal insufficiency were also associated with a non-surgical approach (ORs ranging from 0.18 to 0.80).

## Survival

During the follow-up period, 192 patients (21.0%) in the surgically-treated group and 229 (58.9%) in the non-surgically treated group died. Median survival was 2.7 years (95% CI: 2.3 to 3.3 years). Multivariate Cox models for survival are shown in **Figure 2**. Propensity score-adjusted survival was significantly reduced with therapeutic abstention (HR = 0.18, 95% CI: 0.14 to 0.25) and conventional radiotherapy (HR = 0.24, 95% CI: 0.17 to 0.33) compared to surgically-treated individuals. Survival was also reduced in SBRT-treated patients compared to surgically-treated patients but this did not reach statistical significance (HR = 0.84, 95% CI: 0.55 to 1.26). Conventional radiotherapy was associated with poorer survival compared to SBRT (HR = 0.28, 95% CI: 0.19 to 0.43).

## Mortality causes

The causes of mortality could be ascertained from death certificate for the entire cohort (**Table 3**). The distribution of mortality causes differed between the two groups; excess in mortality due to lung cancer, cardiovascular diseases and chronic respiratory diseases were noted in the non-surgical group compared to surgically-treated patients ( $p = 0.001$ ). Exploring the causes of mortality according to each type of non-surgical treatment revealed an excess lung cancer mortality with conventional radiotherapy and therapeutic abstention but not with SBRT.

## Discussion

In this study, patients with COPD undergoing lung resection for resectable lung cancer had superior survival compared to those for whom a non-surgical therapeutic approach was selected. This observation persisted even after adjusting for confounding by indication with the exception of those who were treated with SBRT for which the numerical advantage of surgery did not reach statistical significance. In the multivariate analysis, age, sex, smoking status, FEV<sub>1</sub>, BMI, histological diagnosis and lung cancer stage were predictors of surgical resection. We noted an excess of cancer and non-cancer mortality in the non-operated group compared to the surgically treated group. Our study contributes to the literature by virtue of its large, well-characterized study population, which includes spirometric confirmation of COPD and the ascertainment of mortality causes in the study population.

Although not a universal finding<sup>19-23</sup>, these results are consistent with the general notion that surgical resection is the treatment of choice in early-stage non-small cell lung cancer<sup>4,17,18</sup>. In the present study, surgery was clearly superior to conventional radiotherapy and therapeutic abstinence. When considering the low mortality rate in the surgical group (0.4%), it is possible that expanding the surgical indications to a broader patient population could help improved survival in individuals with COPD who are diagnosed with resectable lung cancer while keeping the postoperative complication rate in an acceptable range. Lung cancer being a leading cause of mortality in COPD<sup>28</sup>, selecting the best treatment option for this disease is paramount to optimize survival. The present study results provide a strong argument not to refuse lung cancer surgery solely on the presence of COPD and may also help clinicians to engage a balanced and informed discussion with patients with COPD regarding the available therapeutic options for lung cancer and their relative risks and benefits.

Like others<sup>12</sup>, we found a tendency for better outcomes following surgery versus SBRT. Nevertheless, SBRT is a viable option for high-risk patients, particularly in patients with stage T1N0M0 cancer where there is not clear survival advantage of one therapy versus the other<sup>4</sup>. In our cohort, SBRT also provided a survival advantage compared to conventional radiotherapy, a

finding that is concordant with the result of a meta-analysis of 2 randomized trials and 15 cohort studies conducted in stage 1 non-small cell lung cancer<sup>29</sup>.

It remains unclear whether less favorable outcomes associated with the non-surgical approaches are due to cancer progression or complications from severe comorbidities that underlie the decision for non-operation. To address this question, we had access to the mortality causes of the entire cohort (table 3). We also explored the causes of mortality according to each type of non-surgical treatment. The results are concordant with an excess lung cancer mortality with conventional radiotherapy and therapeutic abstention but not with SBRT. This observation further reinforces the benefit of lung resection even in patients with comorbid condition such as COPD while supporting the notion that SBRT is an adequate alternative to surgery.

We found older age, particularly above 75 years, being female or a current smoker, having a low FEV<sub>1</sub>, and a higher BMI were predictors of medical treatment instead of lung resection. This suggests that these risk factors are integrated by clinicians when therapeutic decisions are made despite the absence of a formal algorithm to guide therapeutic choice. Remarkably, several of these predictors of a non-surgical approach have been previously identified to also predict major morbidity and mortality following lung resection. For example, a report based on the General Thoracic Surgery Database comprising data from 27,844 lung resections, identified advancing age, current smoking, and low FEV<sub>1</sub> as risk factors for post-operative mortality and complications<sup>30</sup>. At variance with our findings, being male predicted of poor post-operative outcome. Reasons for this discrepancy with our results are uncertain but may be related to the specificity of the present study population which exclusively involved patients with COPD, a disease for which being female is associated with worse outcome<sup>31</sup>. In our study, age, particularly above the age of 75 years predicted that a conservative approach was often the preferred treatment option. Frailty has been reported to be a better predictor of postoperative mortality following lobectomy than age alone<sup>32</sup>. Although not currently systematically done in clinical practice, the integration of several variables in predictive models could help predict more accurately postoperative outcomes in patients who are considered marginal candidates for lung resection.

## Limitations

This was a retrospective study done in a single center which may limit the generalizability of the data. Relying on clinical data available in medical charts may have led to some misdiagnoses in individuals in whom airflow limitation is due to other diseases such as asthma. Some variables that are considered relevant to risk stratification before lung surgery such as diffusion capacity and functional status<sup>30</sup> were not widely available for the medical chart review. Propensity score matching reduces but does not eliminate potential unbalance between experimental groups in non-randomized trials. Thus, we cannot exclude the possibility that the treatment effect of surgery might have been overestimated due to unaccounted confounding variables. It might be surprising that only 60% of patients were treated with inhaled medication despite having COPD. COPD undertreatment is common<sup>33</sup> providing an opportunity to optimize lung function and to reduce postoperative complications<sup>34</sup>, possibly allowing more patients to become eligible to surgery. Since this investigation was not done in the context of a research project, no treatment algorithm was proposed to determine which treatment would be offered; we rather relied on the clinical judgment of pulmonologists and thoracic surgeons and this might have influenced treatment decision compared to a pre-established standardized decision tree. Nevertheless, the similarity in the predictors on a non-surgical approach and the risk factors for post-operative mortality and morbidity supports the adequacy of the clinical decision process. We used the clinical staging for the non-operated group rather than the pathologic staging which was applied for the operated group. This may have led to underestimating tumor burden in the non-surgical patient in whom positive N1 or N2 node stations that are occasionally discovered during surgery could have been missed despite thorough clinical evaluation. The extent of this effect is difficult to quantify but it may have potentially contributed to more cancer mortality in this group compared to the surgically treated group. Lastly, 156 patients did not receive active treatment which may appear surprising. The decision to opt for therapeutic abstention was based on the integration of the clinical and paraclinical information by the clinician, also considering patient's preference. Following the introduction of SBRT in our area in 2014, a safer and more effective approach than conventional radiotherapy, there was a progressive decline in the proportion of patient who did not receive active treatment; between 2012 and 2019, we observed a 60% reduction in the number of patients who did not receive active treatment.

## Conclusion

Patients with COPD with a resectable NSCLC who did not undergo lung resection had a higher mortality compared to those who underwent surgery. The excess cancer-related mortality in non-surgical patients suggested that aiming for lung resection should be considered to improve survival in this population.

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## Authors contribution

Arianne Tardif, Claudia LeBlanc, Pascal Roy, Marie Parizeault, Catherine Labbé, Frédéric Nicodème, Emma Roy, Gabriel Chouinard, Éliane Pelletier, Marie-Christine Blais, Sabrina Biardel, Serge Simard, Yves Lacasse, François Maltais all contributed to this work and reached the criteria for authorship.



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**Table 1. Characteristics of the study population**

	Overall (n= 1307)	Surgically- treated group (n = 918)	Non-surgically treated group (n = 389)	p-value
Age, years	68.9 ± 7.9	66.9 ± 7.3	73.5 ± 7.4	<0.0001
Sex, (F), n (%)	613 (46.9)	457 (49.8)	156 (40.1)	0.0016
Body mass index, kg/m <sup>2</sup>	26.3 ± 5.3	26.2 ± 5.0	26.4 ± 5.9	0.5582
Smoking history, n (%)				
Active smokers	377 (29.1)	237(25.8)	140 (36.9)	<0.0001
Ex-smokers	907 (69.9)	675(73.5)	232 (61.2)	
Never smokers	13 (1.0)	6 (0.7)	7 (1.8)	
Smoking exposure (pack-years)†	46 (32, 57)	45 (30, 56)	50 (35, 60)	0.0135
Comorbid conditions, n (%)				
Coronary artery disease	333 (25.5)	190 (20.7)	143 (36.8)	<0.0001
Diabetes	206 (15.8)	124 (13.5)	82 (21.1)	0.0009
Renal insufficiency	1270 (3.2)	8 (0.9)	382 (8.6)	<0.0001
Peripheral artery disease	223 (17.1)	131 (14.3)	92 (23.7)	0.0001
Hypertension	756 (57.8)	504 (54.9)	252 (64.8)	0.0009
Dyslipidemia	740 (56.6)	497 (54.1)	243 (62.5)	0.0060
Two and + comorbid conditions	675 (51.6)	426 (46.4)	249 (64.0)	<0.0001
Medication, n (%)				
Statins	542 (54.6)	354 (51.4)	188 (61.8)	0.0024
β-blockers	272 (27.4)	157 (22.8)	115 (37.8)	<0.0001
Oral hypoglycemic	162 (16.3)	92 (13.4)	70 (23.0)	0.0003
Inhaled therapy	574 (58.8)	335 (48.6)	239 (78.6)	<0.0001
Antihypertensive	367 (37.0)	236 (34.3)	131 (43.1)	0.0084
Pulmonary function tests				
FEV <sub>1</sub> , L	1.8 ± 0.6	2.0 ± 0.6	1.5 ± 0.5	<0.0001
FEV <sub>1</sub> , % predicted	72.7 ± 19.9	77.0 ± 17.9	62.6 ± 20.7	<0.0001
FVC, L	3.1 ± 0.9	3.2 ± 0.8	2.7 ± 0.8	<0.0001
FVC, % predicted	94.4 ± 19.6	97.9 ± 18.2	86.3 ± 20.5	<0.0001
FEV <sub>1</sub> /FVC	0.59 ± 0.09	0.61 ± 0.08	0.54 ± 0.10	<0.0001
GOLD Status, n (%)				
1	488 (37.3)	412 (44.9)	76 (19.5)	<0.0001
2	641 (49.0)	443 (48.3)	198 (50.9)	
3	162 (12.4)	62 (6.8)	100 (25.7)	
4	16 (1.2)	1 (0.1)	15 (3.9)	
Histologic diagnosis, n (%)				
Adenocarcinoma	816 (62.4)	667 (72.7)	149 (38.3)	<0.0001
Squamous cell carcinoma	361 (27.6)	221 (24.1)	140 (36.0)	
Others	62 (4.7)	30 (3.2)	32 (8.2)	
No histological diagnosis	68 (5.2)	0 (0)	68 (17.5)	
Lung cancer staging*				
IA	702 (53.7)	480 (52.2)	222 (57.1)	<0.0001
IB	303 (23.2)	235 (25.6)	68 (17.5)	
IIA	100 (7.7)	86 (9.4)	14 (3.6)	
IIB	202 (15.5)	117 (12.8)	85 (21.9)	
Tumor size (mm)	22 [15, 33]	22 [14, 33]	23 [16, 35]	0.0030
Lymph node staging, n (%)				
N0	1164 (89.1)	817 (89.0)	347 (89.2)	0.9232

N1	143 (11.0)	101 (11.0)	42 (10.8)	
VATS		752 (81.9)	----	
Type of resection, n (%)				
Pneumonectomy	---	32 (3.5)	---	
Bilobectomy	---	51 (5.6)	---	
Lobectomy	---	678 (73.9)	---	
Sublobar resection	---	154 (16.8)	---	
Other	---	3 (0.3)		
Radiation treatment				
SBRT, n (%)	---	---	147 (37.8)	
Conventional, n (%)	---	---	86 (22.1)	
No active therapy, n (%)		---	156 (40.1)	
30-day mortality, %		0.4	0	

Data are mean (SD) except for tumor size where median [IQR] is presented.

\*Pathological staging for the surgical group, clinical staging for the non-surgical group; † median [IQR].

Definition of abbreviations: FEV<sub>1</sub> = forced expiratory volume in 1 s; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; VATS = video-assisted thoracoscopic surgery; SBRT: stereotactic body radiation therapy.

Other histologic diagnosis includes not otherwise specified non-small cell carcinoma, large cell carcinoma, adenosquamous carcinoma and sarcomatoid carcinoma.

Note: BMI was available for 388/394 patients in the non-surgically treated group; smoking history for 379/389 patients in the non-surgically treated group; pack-years for 868/918 in the surgically-treated group and 288/389 patients in the non-surgically treated group; renal failure for 888/918 of the surgically-treated group and 382/389 patients in the non-surgically treated group; medication 689/918 of the surgically-treated group and 304/389 patients in the non-surgically treated group; tumor size available 368/389 patients in the non-surgically treated group.



**Table 2. Univariable and multivariable predictors of surgical resection.**

	Univariable analysis		Multivariable analysis		Rank*
	OR (95% CI)	p-value	OR (95% CI)	p-value	
Age < 75, years	0.92 (0.89, 0.94)	<0.0001	0.91 (0.88, 0.94)	<0.0001	1
Age ≥ 75 years	0.78 (0.73, 0.83)	<0.0001	0.69 (0.63, 0.75)	<0.0001	
Sex, (F)	1.48 (1.16, 1.88)	0.0018	0.68 (0.48, 0.96)	0.0309	10
Body mass index, kg/m <sup>2</sup>	1.02 (0.99, 1.05)	0.1900	1.03 (0.99, 1.07)	0.1233	7
Body mass index ≥ 35 kg/m <sup>2</sup>	0.85 (0.77, 0.94)	0.0024	0.80 (0.71, 0.91)	0.0002	
Active smokers	0.60 (0.46, 0.77)	<0.0001	0.37 (0.25, 0.53)	<0.0001	4
Comorbid conditions, n (%)					
Coronary artery disease	0.45 (.035, 0.58)	<0.0001	0.54 (0.38, 0.78)	0.0010	6
Diabetes	0.59 (0.43, 0.80)	0.0006	-		
Renal insufficiency	0.10 (0.05, 0.22)	<0.0001	0.18 (0.07, 0.47)	0.0006	9
Peripheral artery disease	0.54 (0.40, 0.72)	<0.0001	0.56 (0.37, 0.83)	0.0045	8
Hypertension	0.66 (0.52, 0.85)	0.0010	-		
Dyslipidemia	0.71 (0.56, 0.90)	0.0056	-		
Pulmonary function tests					
FEV <sub>1</sub> , < 40% predicted	1.25 (1.11, 1.41)	0.0003	1.27 (1.12, 1.44)	0.0002	2
40 ≤ FEV <sub>1</sub> , % predicted	1.04 (1.03, 1.04)	<0.0001	1.05 (1.04, 1.06)	<0.0001	
GOLD Status					
1	Ref				
2	0.41 (0.30, 0.56)	<0.0001			
3	0.14 (0.08, 0.17)	<0.0001			
4	0.01 (0.002, 0.09)	<0.0001			
Histologic diagnosis, n (%)					
Squamous cell carcinoma	Ref		Ref		3
Adenocarcinoma	2.84 (2.15, 3.74)	<0.0001	1.81 (1.27, 2.57)	0.0009	
Others	0.19 (0.12, 0.30)	<0.0001	0.20 (0.11, 0.35)	<0.0001	
Lung cancer staging*, n (%)					
IA	Ref		Ref		5
IB	1.60 (1.17, 2.19)	0.0040	2.05 (1.36, 3.09)	0.0006	
IIA	2.84 (1.58, 5.11)	0.0004	4.41 (2.12, 9.18)	<0.0001	
IIB	0.64 (0.46, 0.88)	0.0042	-		

\*The order of multivariable model building based on Akaike information criterion (AIC).

Definition of abbreviations: OR: odds ratio; CI: confidence interval; FEV<sub>1</sub> = forced expiratory volume in 1 s; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

**Table 3. Survival status and mortality causes for the entire cohort**

	<b>Deceased</b>				<b>Alive</b>	<b>Total</b>	<b>P</b>
	Causes of mortality						
	Lung cancer	Cardio-vascular diseases	Chronic respiratory diseases	Other			
Surgically treated	128 13.9%	14 1.5%	15 1.6%	35 3.8%	726 79.1%	918	<0.0001
Non surgically treated	169 43.4%	16 4.1%	20 5.1%	24 6.2%	160 41.1%	389	
Conventional radiotherapy	50 58.1%	3 3.5%	7 8.1%	4 4.7%	22 25.6%	86	<0.0001
SBRT	17 11.6%	8 5.4%	3 2.0%	5 3.4%	114 77.6%	147	
No active therapy	102 65.4%	5 3.2%	10 6.4%	15 9.6%	24 15.4%	156	

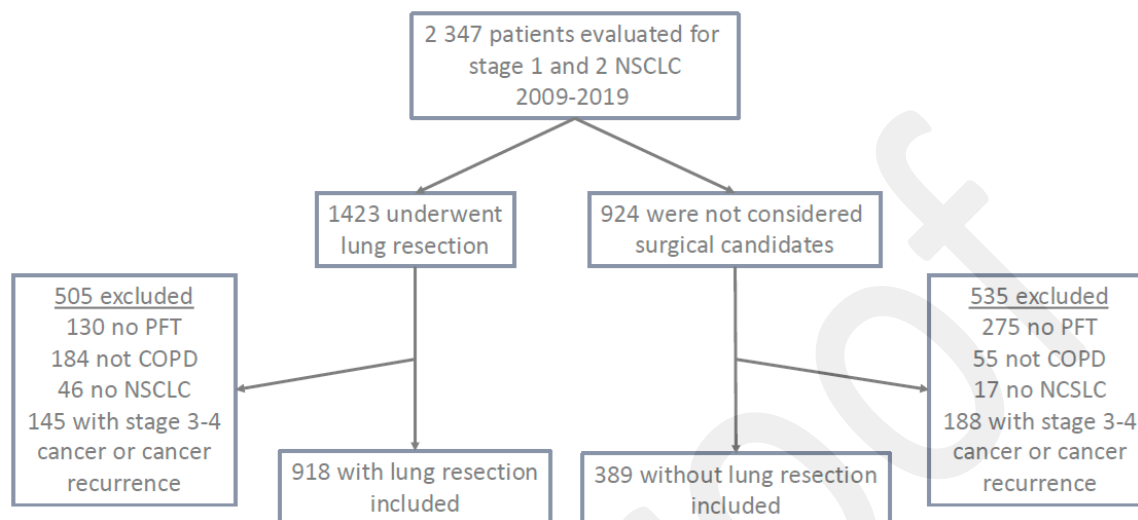
Definition of abbreviation: SBRT stereotactic body radiation therapy.

## Legends for figures

**Figure 1.** Flow of patients. PFT = pulmonary function tests, COPD = chronic obstructive pulmonary disease, NSCLC = non-small cell lung carcinoma.

**Figure 2.** Unadjusted (top panel, A) and propensity score-adjusted (lower panel, B) Cox regression statistical models for long-term survival in patients with COPD and resectable lung cancer treated with surgical resection (black line), stereotactic body radiotherapy (SBRT) (yellow line), conventional radiotherapy (purple) or observational therapy (red line).

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