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Predictors of respiratory failure after thoracic surgery: a retrospective cohort study with comparison between lobar and sub-lobar resection

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Abstract

Objective: Only approximately 15% of patients with lung cancer are suitable for surgery and clinical postoperative outcomes vary. The aim of this study was to investigate variables associated with post-surgery respiratory failure in this patient cohort.

Methods: Patients who underwent surgery for lung cancer were retrospectively studied for respiratory function. All patients had undergone lung resection by a mini-thoracotomy approach. The study population was divided into two subgroups for comparison: lobectomy group, who underwent lobar resection; and sub-lobar resection group.

Results: A total of 85 patients were included, with a prevalence of lung cancer stage IA and adenocarcinoma histotype. Lobectomy (versus sub-lobar resection), the presence of chronic obstructive pulmonary disease (COPD), and a COPD assessment test (CAT) score >10, were all associated with an increased risk of respiratory failure. The partial pressure of arterial oxygen

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decreased more in the lobectomy group than in the sub-lobar resection group following surgery, with a significant postoperative between-group difference in values. Postoperative CAT scores were also better in the sub-lobar resection group.

Conclusions: Post-surgical variations in functional parameters were greater in the group treated by lobectomy. COPD, high CAT score and surgery type were associated with postoperative development of respiratory failure.

Keywords

Lung cancer, respiratory function variability, type of lung resection, respiratory failure, COPD, lung surgery

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Introduction

Lung cancer is the leading cause of cancer death worldwide. Classified based on histology, lung cancer includes squamous, adenocarcinoma, large cell and small cell types, and is often associated with chronic obstructive pulmonary disease (COPD).[1,2]

Chronic obstructive pulmonary disease is defined as a chronic inflammatory bronchial condition, characterized by airflow limitation that is not fully reversible. COPD is usually caused by exposure to noxious particles or gases, predominantly cigarette tobacco smoke, though other exposures, such as biomass fuels, are important causes of this disease. Cigarette tobacco smoke is the major cause of morbidity and mortality worldwide, causing both inflammation to the airways and carcinogenesis.[1] Tobacco smoke contains more than 5 000 identified chemicals, including tobacco-specific carcinogens, such as nitrosamines, nitric oxide, and benzopyrene. Accordingly, smoking cessation is recognized to be the main therapeutic intervention capable of changing the course of COPD.[3]

Lung cancer and COPD are closely related and share the same initial pathogenesis.[2] Respiratory failure is a possible complication of both diseases, and often occurs after thoracic surgery, as a portion of the parenchyma is removed.[4] Lung cancer survival depends on the initial stage of the disease, with surgery being the first therapeutic option in an early disease stage. However, respiratory complications may occur following surgery.

The aim of the present study was to investigate respiratory function changes according to surgery type, and to highlight variables that may be associated with respiratory failure following lung surgery in patients with lung cancer.

Patients and methods

Study population

Patients who underwent thoracic surgery for stage I–III lung cancer at Sant'Andrea Hospital, Sapienza University, Rome, between September 2019 and April 2020, were sequentially enrolled into this retrospective cohort study. Patients with severe and acute comorbidities, and/or previous history of thoracic surgery, were excluded from the study. Patients had undergone different degrees of lung resection via a mini-thoracotomy approach that comprised a 3–4-inch incision between the ribs, and were categorized into two subgroups: one treated by sub-lobar resection and the other treated by lobectomy. Data were extracted from medical records, including: patient demographics; lung function; tumour size, stage and histotype; duration of hospitalization; duration of surgery; and volume of blood loss during surgery.

The study was approved by the Sant'Andrea Hospital of Sapienza University Ethics Committee and written informed consent was provided by each patient included in the study. The reporting of this cohort study conforms to STROBE guidelines.[5]

Study parameters

All patients underwent spirometry prior to surgery and at 3 months after surgery, with detection of post-bronchodilator values. Arterial blood gases were analysed using an IL GEM Premier 3000 device (Werfen, Bedford, MA, USA). A COPD assessment test (CAT) was also administered, with a score >10 considered to be positive for exacerbation risk, according to Global Initiative for Obstructive Lung Disease (GOLD) guidelines.[6]

Spirometry was performed by body plethysmography (MasterScreen Body Plethysmograph; Erich Jaeger GmbH, Hochberg, Germany) as follows: briefly, flow and dynamic volumes were measured by the pneumotachograph method and volumes and resistances by the plethysmography method. Data comprising post-bronchodilator forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), recorded as litres and % of predicted value, and total lung capacity (TLC), were collected. Post-bronchodilation measurements were obtained at 25 min following administration of 400 µg salbutamol by inhalation. Procedures followed the American Thoracic Society and European Respiratory Society task force guidelines.[7]

Respiratory failure type I was defined as a partial pressure of arterial oxygen (PaO_2) level <60 mmHg and partial pressure of carbon dioxide ($PaCO_2$) level ≤45 mmHg. The ratio of PaO_2 to fractional inspired oxygen (PaO_2/FiO_2) was assessed during oxygen therapy by Venturi mask. Only one case required high flow nasal cannula (HFNC). The ROX index (ratio of peripheral blood oxygen saturation [SpO_2]/FiO_2 to respiratory rate) was calculated for each case. The diffusing capacity of the lungs for carbon monoxide (DLCO) was determined by the single breath DLCO manoeuvre and calculated as % of predicted value. COPD was diagnosed based on an FEV_1/FVC ratio < 70%.

Statistical analyses

Data distribution was assessed by Kolmogorov–Smirnov test to evaluate the need to perform parametric or non-parametric statistical tests. Data are presented as mean ± SD or median (interquartile range), as appropriate.

Mann–Whitney *U*-test or a contingency table test were applied for continuous or categorical data, respectively, to assess between-group differences. Within-group differences were analysed using Wilcoxon signed-rank test. A logistic regression analysis was performed to determine the variables associated with respiratory failure. One-way analysis of variance was applied to calculate and compare post-surgery changes in FEV_1 and PaO_2 between the two groups.

All statistical analyses were performed using SPSS software, version 24.0 (IBM, Armonk, NY, USA), and a P value <0.05 was considered statistically significant.

Results

A total of 85 patients were included: 45 patients treated by sub-lobar resection and

40 patients treated by lobectomy. Overall mean age was 71.5 ± 7 years and the male/female rate was 45/40. COPD was the main comorbidity, occurring in 59 patients (69%). The most prevalent lung cancer stage was IA2 and the prevalent histotype was adenocarcinoma (in 38 and 46 patients, respectively). Demographic and clinical data at baseline (pre-surgical), including lung function parameters, are summarised in Table 1.

A comparison between the two surgical groups revealed no statistically significant differences in volume of blood loss during surgery or surgery duration (both $P > 0.05$; Table 2). Fifteen patients (33%) in the sub-lobar resection group and 22 patients (55%) in the lobectomy group developed respiratory failure. The groups were comparable regarding age, smoking pack-years and prevalence of COPD (all $P > 0.05$), however, duration of hospitalization was longer in patients treated by lobectomy ($P < 0.03$ versus sub-lobar resection group). Baseline PaO_2 levels were similar between the two groups but 3-month post-surgery PaO_2 levels were significantly higher in patients treated by sub-lobar resection ($P < 0.03$; Table 2). PaO_2 deficiency was treated with oxygen therapy by Venturi mask to reach a $PaO_2/FiO_2 > 200$, and only one case required HFNC to reach an oxygen saturation >92% and a ROX index value of 4.

Table 1. Baseline demographic and clinical data from 85 patients who underwent thoracic surgery for lung cancer.

Characteristic	Study population
Age, years	71.5 ± 7
Male/female	45/40
Duration of hospitalization, days	7.8 ± 2.5
Smoking history, pack-years	34.0 ± 11.3
BMI, kg/m^2	25.4 ± 3.3
CAT score,	16.5 ± 7.1
FVC, l	2.5 ± 0.9
FEV1, l	1.7 ± 0.77
FEV1, % predicted	73.6 ± 27.5
Tumour size, cm	3.5 ± 0.5

Data presented as mean ± SD or *n* prevalence.
BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

Baseline FEV_1 values, DLCO %, and CAT scores were similar between the two groups, but there were statistically significant between-group differences in these parameters at 3-months post-surgery ($P < 0.01$, $P < 0.01$ and $P < 0.05$, respectively; Table 2). Statistically significant within-group changes in FEV_1, FVC and DLCO between baseline and 3-month postsurgical values were observed within the lobectomy group ($P < 0.01$).

Of note, the median decline of FEV_1 was 30 ml in the sub-lobar resection group versus 200 ml in the lobectomy group, with a statistically significant post-surgery reduction in the lobectomy group only ($P < 0.01$ versus baseline; Table 2). There was also a statistically significant reduction in DLCO % at 3 months post-surgery in the lobectomy group ($P < 0.01$ versus baseline) but not in the sub-lobar resection group.

Although postsurgical CAT scores were significantly different between the two surgical groups (stated above), the postsurgical increase in CAT score observed in the lobectomy group was not statistically significant versus baseline scores (Table 2).

Logistic regression analyses of factors associated with respiratory failure revealed that resection type (lobectomy), co-existent COPD and CAT score >10 were significantly associated with development of lung failure (odds ratios of 2.8 [$P < 0.04$], 2.1 [$P < 0.03$], and 1.3 [$P < 0.01$] for lobectomy, COPD and CAT score >10, respectively; Table 3).

A statistically significant difference in variation of functional parameters before

Table 2. Differences in demographic and clinical characteristics between patients with lung cancer treated by sub-lobar resection or lobectomy.

Characteristic	Sub-lobar resection group $n = 45$	Lobectomy group $n = 40$	Statistical significance[a]
Age, years	73 (68–75)	74 (67–76)	NS
Hospitalization, days	6 (4.5–8)	9 (7–12)	$P < 0.03$
Smoking history, pack-years	35.0 (30–40)	40 (35–40)	NS
Baseline FEV_1, l	1.75 (1.62–1.85)	1.8 (1.60–1.81)[b]	NS
3-month postsurgical FEV_1, l	1.72 (1.51–1.85)	1.6 (1.50–1.75)	$P < 0.01$
Baseline PaO_2, mmHg	65.5 (61–70.5)	62.5 (58.1–61.2)[b]	NS
3-month postsurgical PaO_2, mmHg	60.6 (58.1–62.3)	48.6 (51.5–59.5)	$P < 0.03$
Baseline DLCO, %	65 (60–75)	68 (60–75)[b]	NS
3-month postsurgical DLCO, %	64 (58–70)	52 (48–60)	$P < 0.01$
Surgery duration, min	75 (65–85)	80 (75–100)	NS
Blood loss during surgery, ml	100 (80–120)	110 (75–130)	NS
Baseline CAT score	15.5 (12–17)	17.0 (13–19)	NS
3-month postsurgical CAT score	16 (14–18)	21 (16–23)	$P < 0.05$
Baseline FVC, l	2.5 (2.3–2.9)	2.6 (2.4–3.0)[b]	NS
3-month postsurgical FVC, l	2.4 (2.1–2.8)	2.3 (2.1–2.9)	$P < 0.03$

Data presented as median (interquartile range).
CAT, chronic obstructive pulmonary disease assessment test; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PaO_2, partial pressure of arterial oxygen; DLCO, diffusing capacity of the lungs for carbon monoxide.
[a]Between-group differences (Mann–Whitney *U*-test).
[b]Statistically significant within-group difference between pre- and postsurgical values ($P < 0.01$; Wilcoxon signed-rank test).
NS, no statistically significant between-group difference ($P > 0.05$).

Table 3. Logistic multi-regression analyses of parameters associated with respiratory failure in patients with lung cancer treated by sub-lobar resection or lobectomy.

Parameter	Odds ratio (95% CI)	Statistical significance
Age	0.9 (0.83, 1.1)	NS
FEV1	1.0 (0.9, 1.0)	NS
CAT score >10	1.3 (1.2, 1.4)	$P < 0.01$
FVC	1.1 (0.9, 1.08)	NS
Lobectomy/sub-lobar resection	2.8 (2.2, 3.2)	$P < 0.04$
TLC	1.0 (0.9, 1.0)	NS
Smoking history	0.7 (0.1, 4.9)	NS
COPD	2.1 (1.6, 2.9)	$P < 0.03$

COPD, chronic obstructive pulmonary disease; CAT, COPD assessment test; CI, confidence interval; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; TLC, total lung capacity.
NS, no statistically significant association ($P > 0.05$).

and after surgery was shown between the two groups, with a greater decrease in post-surgery FEV_1 and PaO_2 shown in the group treated by lobectomy ($P < 0.001$; Table 4).

Discussion

Patients are often concerned about the prospect of oxygen therapy postoperatively, and this factor may affect their choice of lung cancer treatment.[8]

Table 4. Comparison of changes in FEV_1 and PaO_2 before and after surgery between patients with lung cancer treated by sub-lobar resection or lobectomy.

Parameter	Sub-lobar resection group Mean variation	Lobectomy group Mean variation	F	Statistical significance
FEV_1, l	0.03	0.22	252.3	$P < 0.001$
PaO_2, l	4.55	13.20	225.19	$P < 0.001$

Mean square and one-way analysis of variance.
FEV_1, forced expiratory volume in one second; PaO_2, partial pressure of arterial oxygen.

The present study showed important findings concerning the need for oxygen therapy after thoracic surgery and the different variations in respiratory function between surgery types. In addition, parameters that may affect the development of respiratory failure are highlighted. Of note, lobar resection was associated with a significantly increased risk of lung failure compared with sub-lobar resection

In the present study, several variables were analysed, including smoke exposure history (in pack-years), which, along with inflammation, is linked with both COPD and lung cancer.[2]

Surgery is the best option in patients with early-stage lung cancer with or without associated chemotherapy.[9] Depending on the extent, pulmonary resections lead to different levels of loss in pulmonary function. Thoracic surgery along with COPD determine a greater decline of lung function, so that a pre-operative clinical evaluation is required to select the correct surgical technique, with FEV_1 being a predictor of post-operative complications.[4]

In the current study, a longer duration of hospitalization was recorded in patients who underwent lobectomy compared with sub-lobar resection, with no significant differences in surgical bleeding and surgery duration between the surgery types. A pre-operative functional assessment is needed in patients undergoing thoracic surgery, and the main lung function parameters were assessed before and 3 months after surgery in the present cohort. A minimum value of FEV_1 is generally agreed to be required pre-operatively (2 l before pneumonectomy and 1.5 l in cases of lobectomy).[4,9] Variable cut-off values of FEV_1 (ranging between 35% and 80%) have been arbitrarily chosen to assess the severity of COPD and to predict the risk for pulmonary complications. The best cut-off value of FEV_1 percentage of predicted is described to be about 60% in the scientific literature.[10]

To the best of our knowledge, there are no previously published studies that compare sub-lobar and lobar resection in terms of functional changes and risk of respiratory failure. In the present study, the mean FEV_1 value was 1.7 l at baseline, and was a parameter that guided choice of surgery type. Notably, the coexistence of COPD, irrespective of baseline FEV_1 value, influenced the post-operative outcome favouring lung failure, which was particularly observed to develop in patients with a high CAT score.

An obstructive syndrome with uncontrolled symptoms may contribute to post-surgery complications.[11,12] The grade of airflow limitation and the presence of cardiovascular comorbidities are associated with an increased probability of complications.[13,14] In addition, patient age, type of resection and FEV_1 are all variables that may affect post-surgery outcome and functional decline.[15,16]

In the present study, only a small percentage of patients treated by sub-lobar resection showed a clear picture of respiratory failure, with little decrease in PaO_2 level at 3 months following surgery. The patients did not require mechanical ventilation because PaO_2 values were corrected with oxygen supplied via an oxygen-mask that exploited the Venturi effect. Respiratory failure type I occurred in some patients, which is characterized by a PaO_2 level below 60 mm Hg, with a normal $PaCO_2$ level. Positive end-expiratory pressure applied during thoracic surgery is known to provide a potential benefit in terms of PaO_2/FiO_2 ratio.[17] It was not considered in the present cohort due to the presence of emphysema in some of the patients, that may predispose to pneumothorax. HFNC therapy was not administered, except in one patient who did not respond to oxygen therapy by Venturi oxygen mask, because the PaO_2/FiO_2 was <200.[18] The ROX index was calculated to be 4 in this patient following HFNC, indicating a good response.[19]

The prediction of functional decline with lung failure after surgery is an important aspect in the clinical evaluation of patients with lung cancer.[20] The present data show that COPD is a frequent comorbidity in patients with lung cancer, which should be treated with bronchodilators along with smoking cessation.[21] There is a need for interdisciplinary cooperation between the pulmonologist and thoracic surgeon in managing patients with lung cancer, as it plays an essential role in the correct approach to treating the disease.[22]

The results of the present study may be limited by several factors, including the retrospective study design and the relatively small study population. In addition, the study was designed for short-term evaluation. A further investigation of 12-month follow-up data is planned for the same patients.

Conclusions

In patients with early-stage lung cancer, the type of surgery and coexistence of COPD, particularly with high exacerbation risk, are associated with the development of respiratory failure and post-surgery functional decline. A more conservative approach, along with treatment of COPD and smoking cessation, may allow the clinician to obtain a more successful post-surgery outcome.

Data accessibility

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Author contributions

All authors contributed to the conception and drafting of the manuscript. Aldo Pezzuto, Massimo Ciccozzi and Beatrice Trabalza Marinucci analysed the data.

Declaration of conflicting interest

The Authors declare that there is no conflict of interest

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