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Morbidity and mortality of lobectomy or pneumonectomy after neoadjuvant treatment: an analysis from the ESTS database

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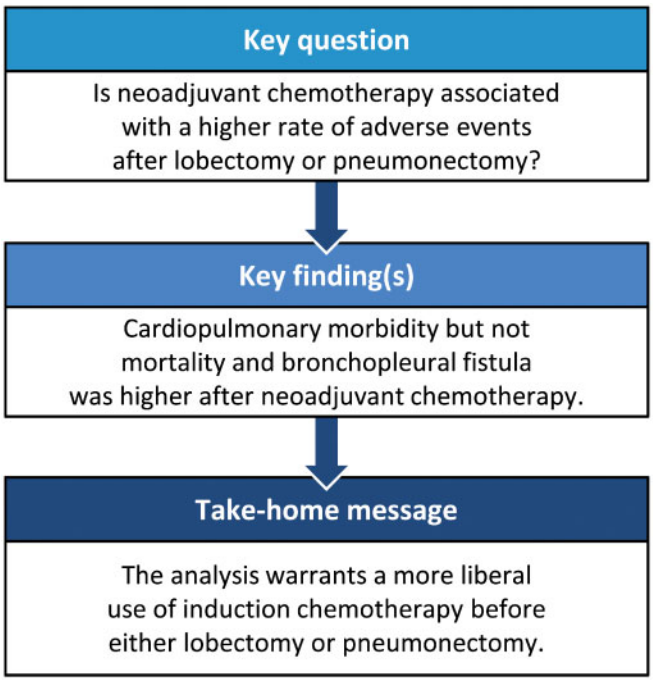

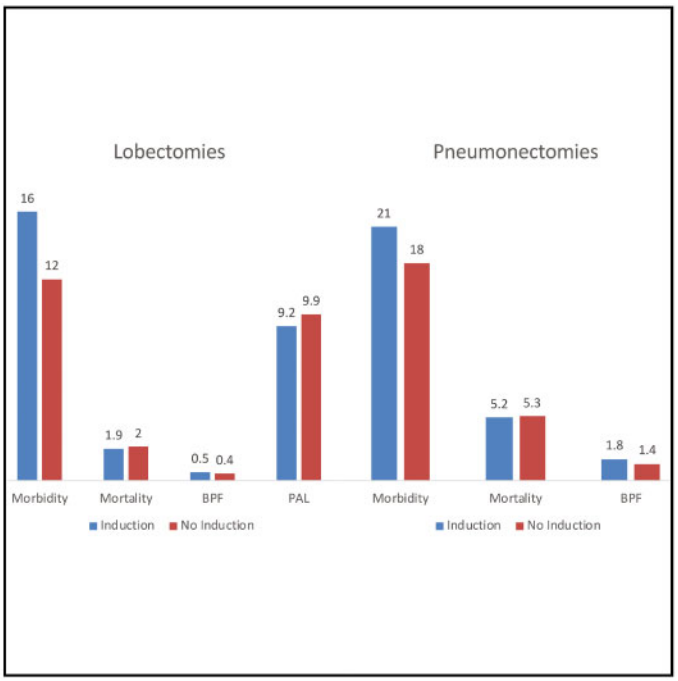

Abstract

OBJECTIVES: To evaluate the postoperative complications and 30-day mortality rates associated with neoadjuvant chemotherapy before major anatomic lung resections registered in the European Society of Thoracic Surgeons (ESTS) database.

METHODS: Retrospective analysis on 52 982 anatomic lung resections registered in the ESTS database (July 2007–31 December 2017) (6587 pneumonectomies and 46 395 lobectomies); 5143 patients received neoadjuvant treatment (9.7%) (3993 chemotherapy alone and 1150 chemoradiotherapy). To adjust for possible confounders, a propensity case-matched analysis was performed. The postoperative outcomes (morbidity and 30-day mortality) of matched patients with and without induction treatment were compared.

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RESULTS: 8.2% of all patients undergoing lobectomies and 20% of all patients undergoing pneumonectomies received induction treatment. Lobectomy analysis: propensity score analysis yielded 3824 pairs of patients with and without induction treatment. The incidence of cardiopulmonary complications was higher in the neoadjuvant group (626 patients, 16% vs 446 patients, 12%, $P < 0.001$), but 30-day mortality rates were similar (71 patients, 1.9% vs 75 patients, 2.0%, $P = 0.73$). The incidence of bronchopleural fistula and prolonged air leak >5 days were similar between the 2 groups (neoadjuvant: 0.5% vs 0.4%, $P = 0.87$; 9.2% vs 9.9%, $P = 0.27$). Pneumonectomy analysis: propensity score analysis yielded 1312 pairs of patients with and without induction treatment. The incidence of cardiopulmonary complications was higher in the treated patients compared to those without neoadjuvant treatment (neoadjuvant 275 cases, 21% vs 18%, $P = 0.030$). However, the 30-day mortality was similar between the matched groups (neoadjuvant 68 cases, 5.2% vs 5.3%, $P = 0.86$). Finally, the incidence of bronchopleural fistula was also similar between the 2 groups (neoadjuvant 1.8% vs 1.4%, $P = 0.44$).

CONCLUSIONS: Neoadjuvant chemotherapy is not associated with an increased perioperative risk after either lobectomy or pneumonectomy, warranting a more liberal use of this approach for patients with locally advanced operable lung cancer.

Keywords: Neoadjuvant chemotherapy • Lobectomy • Pneumonectomy • Non-small-cell lung cancer • Outcome • Bronchopleural fistula • Mortality

ABBREVIATIONS

BPF	Bronchopleural fistula
CAD	Coronary artery disease
ESTS	European Society of Thoracic Surgeons

INTRODUCTION

Multimodality treatment is recommended for patients with resectable locally advanced non-small-cell lung cancer. Neoadjuvant chemotherapy alone or in combination with radiotherapy is one of the available options and has been shown to have equivalent effects on long-term survival compared to adjuvant chemotherapy [1, 2]. The growing interest for induction immunotherapy in combination with platinum-based chemotherapy [3–5] will likely increase the utilization of this approach in the near future. However, one of the main concerns for induction treatment is the possible increased risk of postoperative complications. An up-to-date analysis of the association of induction therapy and postoperative outcome performed on a current large multicentre database appears therefore necessary to have solid figures to utilize during the multidisciplinary discussion and to share with patients for appropriate treatment selection. Therefore, the objective of this study was to analyse the incidence of postoperative complications and 30-day mortality associated with neoadjuvant chemotherapy and major anatomic lung resections registered in the European Society of Thoracic Surgeons (ESTS) database.

PATIENTS AND METHODS

This is a retrospective analysis on 52 982 major anatomic lung resections for primary lung cancer registered in the ESTS database from July 2007 to 31 December 2017 (6587 pneumonectomies and 46 395 lobectomies).

The study was reviewed by the Research and Innovation Department of the principle investigator hospital and classified as service evaluation not requiring review by a Research Ethics Committee.

The online ESTS database was open to recruitment in July 2007. It is a free and voluntary platform aimed at collecting data about all general thoracic surgery procedures. Data can be input online through the database website or harvested yearly from existing institutional data sets after an automated variable matching process. Currently, the database includes information submitted by 270 European units from 25 countries. Only a minor portion of data in the ESTS database is audited and precisely for those units which participate in the ESTS Institutional Accreditation program.

The variables and outcomes are defined and standardized according to the joint STS-ESTS definitions [6].

In particular, the variable neoadjuvant therapy is coded as chemotherapy alone, radiotherapy alone and combined chemo and radiotherapy. In addition, the ESTS database contains information about intraoperative mediastinal staging; 85% of lobectomy patients and 81% of pneumonectomy patients in this series received at least a lobe-specific lymphadenectomy.

Statistical analysis

The main outcomes of this analysis were postoperative mortality and cardiopulmonary complications. Morbidity and mortality were considered when occurring within 30 days from the operation or over a longer period of time if the patient remained hospitalized. The following cardiopulmonary complications were included: respiratory failure, need for reintubation, prolonged mechanical ventilation >24 h, pneumonia, atelectasis requiring bronchoscopy, pulmonary oedema, pulmonary embolism, acute respiratory distress syndrome/acute lung injury (ALI), arrhythmia requiring treatment, acute myocardial ischaemia, acute cardiac failure, stroke/transient ischaemic attack (TIA) and acute kidney injury. All complications are defined according to the joint STS-ESTS definitions [6]. In addition, the incidence of prolonged air leak (longer than 5 days-PAL) after pulmonary lobectomy and bronchopleural fistula (BPF) after both lobectomies and pneumonectomies was assessed.

The postoperative outcomes (morbidity and 30-day mortality) of patients with (NEO) and without (no-NEO) induction treatment were compared. The analyses were performed separately for lobectomies and pneumonectomies. For the purpose of this analysis, patients receiving neoadjuvant chemotherapy alone or in combination with radiotherapy were grouped together due to the small number of patients in the chemoradiotherapy group. However, subgroup analyses were performed before matching. To adjust for possible confounders, a propensity case-matched analysis was performed. Propensity score was calculated using logistic regression analyses without replacement using a caliper including the following variables present in the ESTS database: age, sex, body mass index, predicted postoperative forced

Table 1: Unmatched comparison between patients with and without neoadjuvant treatment undergoing lobectomy

Variables	Without neoadjuvant (42 568 patients)	With neoadjuvant (3827 patients)	Standardized difference (%)
Age (years), mean (SD)	65.0 (9.4)	61.6 (8.9)	37
Female gender, *n* (%)	14 169 (33)	1177 (31)	5
BMI (kg/m^2), mean (SD)	25.5 (4.1)	25.1 (4.0)	10
ppoFEV1%, mean (SD)	73.2 (17.1)	71.2 (16.2)	11
CAD, *n* (%)	3865 (9.1)	299 (7.8)	4
CVD, *n* (%)	1443 (3.4)	95 (2.5)	5
Diabetes, *n* (%)	1565 (3.6)	119 (3.1)	3
PS >1, *n* (%)	3009 (7.1)	313 (8.2)	–4
Minimally invasive access, *n* (%)	10 042 (24)	295 (7.7)	38
pT stage >1, *n* (%)	26 717 (63)	2515 (66)	6
pN stage positive, *n* (%)	14 477 (34)	1789 (47)	27

BMI: body mass index; CAD: coronary artery disease; CVD: cerebrovascular disease; pN: pathological nodal stage; ppoFEV1: predicted postoperative forced expiratory volume in 1 s; PS: performance score; pT: pathological tumour stage; SD: standard deviation.

expiratory volume in 1 s, presence of coronary artery disease (CAD), cerebrovascular disease, diabetes, performance score, surgical access and pathological nodal and tumour stage. A 1:1 nearest neighbour greedy matching without replacement was applied, using a caliper of 0.20 of the pooled standard deviation of the logit estimate [7].

Standardized difference (%) was used to assess adequacy of balance between the groups (>10% and <-10% being inadequately balanced), as this method is regarded more appropriate compared to *P*-values [8]. Postoperative outcomes (mortality and morbidity) between unmatched and matched groups were compared using the χ^2 test and the McNemar test, respectively.

All tests were performed using the Stata 15.0 statistical software (Stata Corp, College Station, TX, USA).

RESULTS

A total of 5143 patients received neoadjuvant treatment (9.7%) corresponding to 8.2% of all lobectomies and 20% of all pneumonectomies.

Analysis of patients undergoing lobectomy

Amongst the 46 395 lobectomies included in the analysis, a total of 3827 (8.2%) patients received induction treatment. The majority received chemotherapy alone (2895 patients), whereas 932 patients had chemoradiotherapy.

Table 1 shows the characteristics of the unmatched patients with and without neoadjuvant treatment before lobectomy. Compared to patients without induction treatment, NEO patients had a lower proportion of patients older than 70 years (17% vs 32%, $P < 0.0001$), a higher proportion of patients with predicted postoperative forced expiratory volume in 1 s lower than 70% (44% vs 39%, $P < 0.0001$), lower rate of patients with CAD (7.8% vs 9.1%, $P = 0.009$) and cerebrovascular disease (2.5% vs 3.4%, $P = 0.003$), lower proportion of females (31% vs 33%, $P = 0.001$), higher proportion of performance score >1 (8.2% vs 7.1%, $P = 0.01$). Only 7.7% of procedures were done by minimally invasive surgery while in the group not receiving induction treatment, this proportion was 24% ($P < 0.0001$). The incidence of cardiopulmonary complications in the induction group was 16% (vs 14%, $P < 0.0001$). The 30-day mortality rate was 1.9% compared to 2.1% in the group without induction ($P = 0.39$).

Patients with neoadjuvant chemotherapy alone had lower cardiopulmonary morbidity rate compared to those with chemotherapy combined with radiotherapy (16% vs 19%, $P = 0.022$). However, the 30-day mortality (1.7% vs 2.5%, $P = 0.11$), BPF (0.4% vs 0.6%, $P = 0.41$) and PAL rates (9.0% vs 9.8%, $P = 0.47$) were similar between these 2 subcategories of treated groups.

Propensity score analysis. Propensity score analysis yielded 3824 pairs of patients with and without induction treatment before lobectomy. The 2 groups were well matched for baseline characteristics, although even after matching the neoadjuvant group showed a lower incidence of operation performed using minimally invasive approach (Table 2).

The incidence of cardiopulmonary complications was higher in the induction group (NEO 626 cases, 16% vs no-NEO 446 cases, 12%, $P < 0.001$), but the 30-day mortality rate was similar (NEO 71, 1.9% vs no-NEO 75 cases, 2.0%, $P = 0.73$). The incidence of BPF and PAL >5 days remained also similar in the 2 matched groups (induction 0.5% vs 0.4%, $P = 0.87$; 9.2% vs 9.9%, $P = 0.27$, respectively).

Table 3 displays the breakdown of the most relevant individual complications occurring in each matched group.

Given the imbalance of minimally invasive surgeries, we further adjusted the analysis using logistic regression analyses performed on all patients and including induction treatment, surgical access and the propensity score as independent variables. We found that neoadjuvant treatment remained significantly associated with cardiopulmonary complications ($P < 0.0001$), but not with mortality ($P = 0.26$). Open surgery (vs video-assisted thoracic surgery) remained significantly associated with both morbidity and mortality events.

Analysis of patients undergoing pneumonectomy

Amongst the 6587 pneumonectomies included in the analysis, a total of 1316 patients received induction treatment (20%). The majority received chemotherapy alone (1098 patients) whilst 218 had chemoradiotherapy.

The induction treatment group had a lower proportion of patients older than 70 years (13% vs 22%, $P < 0.0001$) and a higher proportion of patients with predicted postoperative forced expiratory volume in 1 s lower than 70% (69% vs 63%, $P < 0.0001$).

Table 2: Matched comparison between patients with and without neoadjuvant treatment undergoing lobectomy

Variables	Without neoadjuvant (3824 patients)	With neoadjuvant (3824 patients)	Standardized difference (%)
Age (years), mean (SD)	61.5 (9.2)	61.6 (8.9)	-1
Female gender, *n* (%)	1210 (32)	1175 (31)	2
BMI (kg/m^2), mean (SD)	25.1 (4.1)	25.1 (4.0)	6
ppoFEV1%, mean (SD)	71.1 (16.4)	71.2 (16.2)	-1
CAD, *n* (%)	269 (7.0)	299 (7.8)	3
CVD, *n* (%)	87 (2.3)	95 (2.5)	-1
Diabetes, *n* (%)	109 (2.9)	119 (3.1)	-2
PS >1, *n* (%)	312 (8.2)	311 (8.2)	1
Minimally invasive access, *n* (%)	795 (21)	294 (7.7)	37
pT stage >1, *n* (%)	2504 (65)	2513 (66)	0.5
pN positive, *n* (%)	1765 (46)	1786 (47)	1

BMI: body mass index; CAD: coronary artery disease; CVD: cerebrovascular disease; pN: pathological nodal stage; ppoFEV1: predicted postoperative forced expiratory volume in 1 s; PS: performance score; pT: pathological tumour stage.

Table 3: Incidence of individual complications following lobectomy in the matched groups

Complications	Without neoadjuvant (3824 patients)	With neoadjuvant (3824 patients)	*P*-value
ARDS	26	52	0.003
Pneumonia	248	313	0.004
Atelectasis	225	257	0.13
Respiratory failure	63	76	0.27
Pulmonary embolism	12	16	0.45
Pulmonary oedema	2	4	0.69
Acute myocardial ischaemia	6	7	1.0
AF	165	219	0.005
Cardiac failure	8	20	0.035
Multiorgan failure	4	8	0.39

AF: atrial fibrillation; ARDS: acute respiratory distress syndrome.

The other parameters were similar between the 2 groups (Table 4).

The incidence of cardiopulmonary complications and 30-day mortality rates in the induction group was 21% (vs 20%, $P = 0.22$) and 5.2% (vs 6.8%, $P = 0.027$), respectively.

Total mortality rate was almost double after right pneumonectomy compared to the left one (9.5% vs 4.7%, $P < 0.0001$). More patients received induction treatment before right pneumonectomy compared to the left one (22% vs 19%, $P = 0.02$). Among patients receiving induction treatment, the mortality rate of those after right pneumonectomy was 2-fold higher compared to patients operated on the left side (7.4% vs 3.6%, $P = 0.002$).

Similarly, induction patients had a higher incidence of BPF after right pneumonectomy compared to left one (2.8% vs 1.2%, $P = 0.036$).

Compared to patients with chemotherapy alone, those with chemotherapy combined with radiotherapy had similar cardiopulmonary morbidity (25% vs 20%, $P = 0.14$), but 2-fold higher mortality rates (8.9% vs 4.5%, $P = 0.007$). BPF rates were similar between these 2 subcategories of treated groups (chemoradiotherapy 2.8% vs chemotherapy 1.6%, $P = 0.26$).

Propensity score analysis. Propensity score analysis yielded 1312 pairs of patients with and without induction treatment before pneumonectomy. The 2 groups were well matched for baseline characteristics (Table 5).

The overall incidence of cardiopulmonary complications was higher in the treated patients compared to those without neoadjuvant treatment (NEO 275 cases, 21% vs no-NEO 232, 18%, $P = 0.030$). However, the 30-day mortality was similar between the matched groups (NEO 68 cases, 5.2% vs no-NEO 70, 5.3%, $P = 0.86$). Finally, the incidence of BPF was also similar between the 2 groups (NEO 1.8% vs no-NEO 1.4%, $P = 0.44$).

The incidence of the most relevant individual complications occurring in the matched groups is reported in Table 6.

DISCUSSION

Background and rationale

National Comprehensive Cancer Network guidelines (NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 4.2019. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf), the American Association of Chest Physicians Lung cancer management guidelines [9] and the European Society of Medical Oncology guidelines (https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours) recommend multimodality treatment for patients with locally advanced NSCLC with neoadjuvant chemotherapy alone or in combination with radiotherapy as the preferred modality or at least as one of the possible options as alternative to adjuvant treatment for operable stage IIIA disease. Neoadjuvant treatment provides at least equivalent survival benefits compared to adjuvant treatment [1, 2]. In addition, it allows assessment of treatment response and is more tolerated, ensuring at least that the chemotherapy regimen is administered to most of the patients. One of the theoretical negative effects of induction treatment is the potential increase of postoperative adverse events, especially after pneumonectomy [10–14]. In fact, chemotherapy has been associated with structural changes in the lung leading to decreased diffusion capacity, which in turn may predispose to the development of postoperative respiratory complications [14–17].

Table 4: Unmatched comparison between patients with and without neoadjuvant treatment undergoing pneumonectomy

Variables	Without neoadjuvant (5271 patients)	With neoadjuvant (1316 patients)	Standardized difference (%)
Age (years), mean (SD)	62.7 (9.5)	60.1 (8.5)	27
Female gender, *n* (%)	1226 (23)	295 (22)	2
BMI (kg/m^2), mean (SD)	25.1 (3.9)	25.2 (3.9)	2
ppoFEV1%, mean (SD)	58.7 (19.9)	56.8 (19.6)	9
CAD, *n* (%)	385 (7.3)	80 (6.1)	4
CVD, *n* (%)	131 (2.5)	31 (2.4)	0.7
Diabetes, *n* (%)	159 (3.0)	30 (2.3)	4
PS >1, *n* (%)	487 (9.2)	121 (9.2)	0.1

BMI: body mass index; CAD: coronary artery disease; CVD: cerebrovascular disease; ppoFEV1: predicted postoperative forced expiratory volume in 1 s; PS: performance score.

Table 5: Matched comparison between patients with and without neoadjuvant treatment undergoing pneumonectomy

Variables	Without neoadjuvant (1312 patients)	With neoadjuvant (1312 patients)	Standardized difference (%)
Age (years), mean (SD)	60.4 (8.7)	60.2 (8.4)	2
Female gender, *n* (%)	263 (20)	295 (23)	-6
BMI (kg/m^2), mean (SD)	25.5 (4.1)	25.2 (3.9)	6
ppoFEV1%, mean (SD)	57.0 (19.4)	56.9 (19.6)	1
CAD, *n* (%)	78 (5.9)	80 (6.1)	-1
CVD, *n* (%)	33 (2.5)	31 (2.4)	1
Diabetes, *n* (%)	27 (2.1)	30 (2.3)	-1
PS >1, *n* (%)	117 (8.9)	120 (9.1)	-1
pT stage >1, *n* (%)	1095 (83)	1094 (83)	1
pN positive, *n* (%)	857 (65)	895 (68)	-6

BMI: body mass index; CAD: coronary artery disease; CVD: cerebrovascular disease; pN: pathological nodal stage; ppoFEV1: predicted postoperative forced expiratory volume in 1 s; PS: performance score; pT: pathological tumour stage.

Table 6: Incidence of individual complications following pneumonectomy in the matched groups

Complications	Without neoadjuvant (1312 patients)	With neoadjuvant (1312 patients)	*P*-value
ARDS	27	36	0.25
Pneumonia	79	74	0.68
Atelectasis	21	26	0.46
Respiratory failure	33	40	0.41
Pulmonary embolism	4	9	0.27
Pulmonary oedema	6	0	0.03
Acute myocardial ischaemia	10	10	1
AF	131	151	0.21
Cardiac failure	20	18	0.74
Multiorgan failure	9	11	0.82

AF: atrial fibrillation; ARDS: acute respiratory distress syndrome.

To corroborate this concern, a recent big data analysis from the National Cancer Database analysing more than 130 000 patients undergoing lung resection for lung cancer from 2004 to 2014 found an increased incidence of 30- and 90-day mortality after neoadjuvant treatment [18]. The promising preliminary findings of immunotherapy and chemotherapy delivered in the neoadjuvant setting [3, 4] and the probable increased utilization of this approach in the near future warrant a timely analysis of postoperative outcome associated with induction therapy. Therefore, it seemed appropriate to assess the relationship between induction therapy and postoperative adverse events on a modern and representative population of lung cancer patients such as the one included in the ESTS database.

Main findings

Patients operated on after induction treatment had 3–5% higher incidence of cardiopulmonary complications, but similar 30-day mortality rates compared to patients without induction treatment. This finding applied for both lobectomies and pneumonectomies.

This result is in keeping with previous investigations, which did not find differences of perioperative mortality between patients undergoing neoadjuvant chemotherapy and those who were submitted to upfront surgery [2, 19–21].

On the other hand, we confirmed the increased risk of right pneumonectomy after neoadjuvant treatment [11]. In our analysis, the 30-day mortality rate was twice as high on the right compared to left side in patients who received induction treatment. However, in our modern and representative population, the mortality rate was considerably lower than the one reported at 30 days in a recent systematic review [11] of studies with enrolment periods spanning back more than 25 years. In that

systematic review, the pooled mortality rate at 30 days was 11% and 5% after postinduction right and left pneumonectomies, while in our study, the figures were 7.4% and 3.6%, respectively. Certainly, our rates are much smaller than those found in the randomized trial from Albain *et al.* [10] who reported a 30-day mortality rate of nearly 20% after postinduction pneumonectomy.

Our findings differ from those reported in a recent retrospective analysis from the NCD which showed an increased 30-day mortality rate after induction treatment [18]. However, that study including almost 10 000 patients undergoing induction treatment had a much higher proportion of patients receiving preoperative chemoradiation (62% vs only 22% in our study). This difference may reflect a different trend of preoperative treatment before Europe and North America [22], with the former favouring chemotherapy alone, particularly before pneumonectomy in which only 17% of the induction patients also received radiation therapy. Considering the increased complications and mortality rates observed in the chemoradiation group in both Yendamuri *et al.* [18] and our analyses, the smaller number of patients receiving chemoradiation treatment likely explained the fact that we did not observe an increased rate of mortality in the postinduction patients. Our findings are more aligned with a more recent analysis reported from the NCD on ~1500 patients undergoing pneumonectomy after induction chemotherapy and showing 30-day mortality rates similar to ours (with the right side shown to be a significant predictor of mortality) [23].

Similarly, neoadjuvant treatment was not associated with increased risk of BPF after either lobectomies or pneumonectomies.

The overall incidence of BPF in our population was relatively small, 0.4% after lobectomy and 1.9% after pneumonectomy.

These figures are somewhat smaller than those recently reported from another big data analysis performed using a French database. In that study including almost 5000 pneumonectomies, the BPF incidence after pneumonectomy was 3% [24] and the authors were not able to find an association between neoadjuvant chemotherapy and incidence of BPF confirming our results.

Despite the low incidence, we found that the risk of BPF was increased in the postinduction right pneumonectomies compared to left side. This finding confirms previous reports analysing the relationship between side and incidence of BPF, but adds information about the association between this complication and preoperative chemotherapy [25, 26]. Although not negligible, the incidence of BPF found in the current analysis after chemoradiation and after postinduction right pneumonectomy remains acceptable (both at 2.8%).

Limitations

The study may have some limitations

- The ESTS database is a voluntary database. Only a minority of data are audited, namely a sample of those units applying for European Institutional Accreditation. The voluntary nature of the database questions the representativeness of the data and whether they reflect the real European thoracic surgical practice. Although it represents the most current and comprehensive registry of lung cancer operation in Europe, it does not capture the entirety of lung surgeries performed in the Continent. In addition, given the lack of a unified mandatory European registry, it is impossible to determine the exact percentage of all lung cancer operations performed in the Continent contained in the database.
- The analysis of mortality is limited to in-hospital or 30-day mortality. The ESTS database has only recently started to collect 90-day mortality and this outcome is largely incomplete and as such, cannot be analysed. Nevertheless, 90-day mortality is an important end point and may more reliably reflect the real association between induction treatment and adverse postoperative events as shown in recent reports in which 90-day mortality is more than doubled compared to that assessed at 30 days [18]. In addition, the difference of mortality between induction and non-induction treatment has been shown to be even larger at 90 days.
- Due to the structure and nature of the database, the exact cause of death cannot be determined.
- An important limitation is the lack of detailed information about the indications for chemotherapy and radiotherapy and the regimens/drugs used. In this context, an important limitation is the lack of details about the clinical stage of disease. This variable has been introduced only recently in the database and not available as such for the analysis. The retrospective multi-institutional nature of the data prevents us from retrieving this information.

Similarly, we do not have access to information about the compliance to chemotherapy, how many patients completed all prescribed cycles and how many patients started chemotherapy and eventually did not proceed to surgery due to complications or cancer progression. Ideally, this information would be important to have a more precise account of the treatment-related adverse events associated with chemotherapy.

- The ESTS database does not contain survival data preventing us from performing a proper comparative longer-term survival analysis between treated and untreated patients. In addition, structural information that may have been associated with outcome, such as individual or unit surgical volume, qualification of the centre is also not present in the ESTS database.
- Finally, as in all retrospective analyses, the study may have had selection biases. There are important disease-related, patient-related and physician-related factors that may have contributed to selecting a patient for preoperative chemotherapy. Although propensity score was used to mitigate these biases, it cannot adjust for variables not present in the database or for unknown factors potentially associated with outcome.

CONCLUSION

Although induction treatment was associated with an increased morbidity rate, we were not able to find an association between neoadjuvant chemotherapy and increased rate of postoperative mortality after both lobectomy and pneumonectomy. This finding warrants a more liberal use of this approach for patients with locally advanced operable lung cancer. Nevertheless, combined

chemotherapy and radiotherapy should be use with caution before pneumonectomy.

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Conflict of interest: none declared.

Author contributions

Alessandro Brunelli: Conceptualization; Data curation; Formal analysis; Methodology; Writing—Original Draft; Writing—Review & Editing. **Gaetano Rocco:** Methodology; Writing—Review & Editing. **Zalan Szanto:** Methodology; Writing—Review & Editing. **Pascal Thomas:** Methodology; Writing—Review & Editing. **Pierre Emmanuel Falcoz:** Conceptualization; Methodology; Writing—Review & Editing.

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