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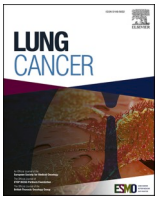

Research Paper

# European experience on oncological outcomes of patients with early-stage non-small cell lung cancer and any prior cancer following lobectomy or segmentectomy

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ABSTRACT

*Objectives:* To assess the impact of lung resection extent on early-stage non-small cell lung cancer with a history of any cancer.

*Methods:* Retrospective multicentric cohort study including patients with ≤2 cm pathologic size lung cancer with a history of any cancer, operated on from 2015 to 2021 across nine European centers (one per country). Overall survival (OS), disease-free survival (DFS) and lung cancer specific death (LCSD) between both groups were assessed before and after propensity score (PS) –matching. Risk factors for oncologic outcomes were analyzed using parsimonious model cox proportional hazard regression. Kaplan Meier and cumulative incidence function assessed the outcomes. Log-rank test and Gray' test compared the groups. Linearized risk was used to assess recurrences.

*Results:* Of the 1910 patients with early-stage lung cancer patients, 540 (28.2%) had a prior cancer. Lobectomy and segmentectomy were performed in 409 (75.7%) and 131 (24.3%) patients respectively. 5-year OS rates:

*Abbreviations:* ALK, Anaplastic Lymphoma Kinase; CI, Confidence Interval; DFS, Disease-free survival; EGFR, Epithelial Growth Factor Receptor; ESTS, European Society of Thoracic Surgeons; Fig, Figure; HR, Hazard ration; IQR, Interquartile range; LCSD, Lung Cancer Specific Death; NSCLC, Non-small cell lung cancer; OS, Overall survival; PET, Positron emission tomography; PS, Performance status; PSM, Propensity score matching; SMD, Standardized mean difference; STAS, Spread through air spaces; SUV max, Maximum standardized uptake value.

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lobectomy 81.5%, segmentectomy 80.8%, p = 0.8; DFS: lobectomy 76.9%, segmentectomy 74.4%, p = 0.6 and LCSD: lobectomy 8.0%, segmentectomy 4.9%, p = 0.2. These finding were similar in the matched cohort.
Locoregional recurrence (linearized risk: lobectomy 0.111, segmentectomy 0.066) and distant recurrence (linearized risk: lobectomy 0.093, segmentectomy 0.055) were not worse in the segmentectomy group.
In multivariable analysis, prior cancer negatively impacted only lung cancer specific death HR:1.27 (95% CI:1.00–1.60).
*Conclusion:* Compared to lobectomy, segmentectomy has not shown a worse oncologic outcome in patients with history of any prior cancer.

## 1. Introduction

Cancer survivorship has markedly increased over the past three decades and now accounts for approximately 1.3% of the global population [1]. Cancer survivors represent nearly 5% of the general population in both the United States [2] and Europe [3]. In Europe, the cancer survivors have increased by an average of 3.5% per year over the last decade, corresponding to a cumulative growth of 41%. Advances in cancer detection and treatment have translated into prolonged survival, with approximately 70% of patients alive at five years and 11% surviving beyond 25 years after their initial diagnosis, in the United States.

This population has 14% more chance of developing another primary malignancy [4] with lung cancer being the most frequently diagnosed [5] and the primary determinant of life expectancy.

Lung cancer screening programs yield a higher incidence of lung cancer in cancer survivors compared to the general population [6,7]. Besides, lung cancer is often early diagnosed in the context of a prior cancer surveillance.

Although many of these patients would be segmentectomy candidates, most of cancer survivors were excluded from studies related to lung resection extent, including 2 recent clinical trials [8,9]. This category of patients is different from the general population by their genetics and/or risk factors that contribute to the oncogenesis processes. Indeed, these inherent and acquired factors, may also influence the response to treatment. For this reason, we performed a European multicentric analysis comparing oncologic outcomes of patients with a history of any prior cancer who underwent either lobectomy or segmentectomy with systematic lymph node dissection for peripheral early-stage lung cancer.

## 2. Methodology

### 2.1. Ethics statement

The study was endorsed by the European Society of Thoracic Surgeons on 12.02.2023 and it was approved by the Ethical Committee for Clinical Research of the Institute of Pneumology Marius Nasta (approval number: 13944/16.06.2023). This approval was either automatically accepted by attending centers or required additional local or national ethical approval. Due to the retrospective nature of the study and the deidentified data used for the analyses, patients' consent was waived.

### 2.2. Study cohort

We conducted a retrospective European cohort study across nine European centers, seven of them being contributors to the European Society of Thoracic Surgeons registry (Table 1). The study included demographic, clinical, pathological and follow-up data of patients with a history of any cancer who underwent either lobectomy or segmentectomy and systematic lymph node dissection (according to the ESTS recommendations) [10] for peripheral early-stage lung cancer, between January 2015 and December 2021. Time frame for follow up was until January 2024. Inclusion criteria comprised peripheral (located in the outer 1/3 of the lung), pathological size $\leq$ 2 cm, N0, M0 and R0 resection. Exclusion criteria involved patients with 2/3 inner nodules, and multiples nodules.

Data were collected from each center's prospective database and patients' files. If there were missing data after this first search, the information was searched in pulmonologists, oncologists or family doctors 'records.

Patients with any history of cancer were considered. Prior cancer was the primary one, and the studied lung cancer was the secondary or tertiary, that was either synchronous or metachronous to the prior cancer. 24 months were used as a cut-off as widely accepted in clinical practice. Prior cancers were classified by organ. The maximum standardized uptake value (SUVmax) variable was categorized according to the classification of Sun X-Y et al [11].

Complications grade III or higher according to Clavien-Dindo were considered major. Genetic mutations were not systematically assessed throughout the study period. Segmentectomy was performed based on the discretion of surgeon.

### 2.3. Follow-up

Patients' management was discussed in multidisciplinary team meeting across all centers. Patients were assessed by a surgeon soon after the operation and subsequently followed up by either an oncologist or a pulmonologist. In general, patients were routinely seen every quarter or semester for the first two years, they were then followed by annual visits. Recurrences were categorized as locoregional (occurring in the ipsilateral lung involving resection margins, hilar lymph nodes, mediastinal lymph nodes, or pleural invasion) or distant (in the contralateral lung parenchyma or as extra-thoracic metastases). Second primary cancers were either confirmed or suspected by the multidisciplinary team.

### 2.4. Statistics

Statistical analyses were conducted using R software version 4.2.2. Categorical variables were presented as frequency and percentages, while continuous random variables were described using median and interquartile range (IQR), as well as mean and standard deviation (SD).

Disease-free survival (DFS) was defined as duration from date of surgical intervention to the date of recurrence, death, or last follow-up visit. Overall survival (OS) was defined as time from date of operation to date of death from any cause or last follow-up visit. They were assessed by Kaplan Meier curves, and the groups were compared using the log-rank tests. Lung cancer-specific death (LCSD) was defined as interval from date of operation to date of death due to lung cancer or last

**Table 1**
Attending centres.

| Centre | Country |
|---|---|
| Institute of Pneumology Marius Nasta | Romania |
| St. James's University Hospital | United Kingdom |
| São João University Hospital | Portugal |
| Salamanca University Hospital | Spain |
| Sant'Andrea Hospital | Italy |
| University Medical Centre of Ljubljana | Slovenia |
| St James's Hospital | Ireland |
| Zuyderland Medical Center | Netherlands |
| Copenhagen University Hospital | Denmark |

follow-up visit and was assessed using cumulative incidence function method with mortality from any other cause than lung cancer considered as a competing risk, the Gray' test was used to evaluate the difference between patients who underwent lobectomy or segmentectomy. OS, DFS and LCSD were also truncated at 5-year to extract 5-year OS, DFS and LCSD.

Chi-squared test and Fisher's exact test were used for comparing categorical variables between groups; Levene's test and Student's *t*-test assessed equality of variances for normally distributed continuous variables. Mann–Whitney *U* test was performed for comparing continuous

**Table 2**
Patients' characteristics with any history of cancer related to type of operation.

| Before propensity score matching | | | | After propensity score matching | | | |
|---|---|---|---|---|---|---|---|
| Operation | Lobectomy (n = 409) | Segmentectomy (n = 131) | P Value | Lobectomy (n = 131) | Segmentectomy (n = 131) | p value | SMD |
| **Sex** | | | 0.663 | | | 0.537 | 0.08 |
| Female | 194(47.4%) | 65(49.6%) | | 70(53.4%) | 65(49.6%) | | |
| Male | 215(52.6%) | 66(50.4%) | | 61(46.6%) | 66(50.4%) | | |
| **Age** | 70(64–75) | 72(65–75) | 0.096 | 71(64–76) | 72(65–75) | 0.513 | 0.001 |
| **PS** | | | 0.26 | | | 0.373 | 0.17 |
| 0 | 314(77.4%) | 94(72.4%) | | 103(79.8%) | 94(72.4%) | | |
| 1 | 85(20.9%) | 31(23.8%) | | 23(17.8%) | 31(23.8%) | | |
| 2 | 7(1.7%) | 5(3.8%) | | 3(2.4%) | 5(3.8%) | | |
| **Comorbidities** | | | 0.085 | | | 0.782 | 0.12 |
| No | 165(40.3%) | 40(30.5%) | | 46(35.1%) | 40(30.5%) | | |
| Cardiac | 57(13.9%) | 19(14.5%) | | 21(16.1%) | 19(14.5%) | | |
| Respiratory | 34(8.3%) | 7(5.3%) | | 9(6.9%) | 7(5.3%) | | |
| Others | 68(16.6%) | 33(25.3%) | | 26(19.8%) | 33(25.3%) | | |
| More than one | 85(20.9%) | 32(24.4%) | | 29(22.1%) | 32(24.4%) | | |
| **Smoking Status** | | | 0.473 | | | 0.512 | 0.01 |
| Never | 64(15.7%) | 20(15.3%) | | 25(19.1%) | 20(15.3%) | | |
| Ex | 237(57.9%) | 83(63.4%) | | 74(56.5%) | 83(63.4%) | | |
| Current | 108(26.4%) | 28(21.3%) | | 32(24.4%) | 28(21.3%) | | |
| **Pack Year** | | | 0.002 | | | 0.335 | 0.02 |
| <20 | 106(25.9%) | 38(29.0%) | | 44(33.6%) | 38(29.0%) | | |
| ≥20 | 239(58.4%) | 88(67.2%) | | 78(59.5%) | 88(67.2%) | | |
| unknown | 64(15.6%) | 5(3.8%) | | 9(6.9%) | 5(3.8%) | | |
| **Primary Tumor** | | | <0.001 | | | 0.016 | 0.11 |
| Lung | 33(8.2%) | 30(23.4%) | | 12(9.3%) | 30(23.4%) | | |
| Breast | 52(12.9%) | 12(9.4%) | | 18(14.0%) | 12(9.4%) | | |
| Bowel | 73(18.2%) | 16(12.5%) | | 27(20.9%) | 16(12.5%) | | |
| ENT | 40(10.0%) | 9(7.0%) | | 14(10.9%) | 9(7.0%) | | |
| Others | 172(42.7%) | 45(35.2%) | | 47(36.4%) | 45(35.2%) | | |
| More than one | 32(8.0%) | 16(12.5%) | | 11(8.5%) | 16(12.5%) | | |
| **Intertumoral Interval** | | | 0.355 | | | 0.227 | 0.19 |
| Synchronous | 106(27.4%) | 29(23.2%) | | 38(29.9%) | 29(23.2%) | | |
| Metachronous | 281(72.6%) | 96(76.8%) | | 89(70.1%) | 96(76.8%) | | |
| **Diagnosis under follow-up circumstance** | 232(57.9%) | | 0.03 | | | 0.180 | 0.19 |
| | | 82(68.9%) | | | | | |
| | | | | 79(60.8%) | 82(68.9%) | | |
| **Postoperative** | | | 0.109 | | | 0.790 | 0.06 |
| **Complications** | 273(66.7%) | 100(76.3%) | | 98(74.8%) | 100(76.3%) | | |
| No | 91(22.3%) | 22(16.8%) | | 21(16.0%) | 22(16.8%) | | |
| Minor | 45(11.0%) | 9(6.9%) | | 12(9.2%) | 9(6.9%) | | |
| Major | | | | | | | |
| **Histological type** | | | 0.303 | | | 0.651 | 0.07 |
| **Adenocarcinoma** | 307(75.1%) | 98(74.8%) | | 100(76.3%) | 98(74.8%) | | |
| **Squamous** | 91(22.2%) | 26(19.8%) | | 27(20.6%) | 26(19.8%) | | |
| **Others** | 11(2.7%) | 7(5.4%) | | 4(3.1%) | 7(5.4%) | | |
| **Surg. approach** | | | <0.001 | | | 0.844 | 0.01 |
| Open | 82(20.0%) | 51(38.9%) | | 51(38.9%) | 51(38.9%) | | |
| VATS | 319(78.0%) | 78(59.6%) | | 79(60.3%) | 78(59.6%) | | |
| RATS | 8(2.0%) | 2(1.5%) | | 1(0.8%) | 2(1.5%) | | |
| **Molecular Mutations** | | | 0.744 | 124(94.6%) | | 0.367 | 0.12 |
| Not tested | 263(91.4%) | 86(91.5%) | | 5(3.8%) | 86(91.5%) | | |
| EGFR | 13(4.5%) | 3(3.2%) | | 1(0.8%) | 3(3.2%) | | |
| KRAS | 7(2.4%) | 2(2.1%) | | 1(0.8%) | 2(2.1%) | | |
| ALK | 1(0.3%) | 0(0.0%) | | 0(0.0%) | 0(0.0%) | | |
| ROS 1, BRAF and Others | 4(1.4%) | 3(3.2%) | | | 3(3.2%) | | |
| **Tumor Size** | | | 0.122 | | | 0.894 | 0.04 |
| ≤1 | 103(25.2%) | 42(32.1%) | | 41(31.3%) | 42(32.1%) | | |
| 1 < x ≤ 2 | 306(74.8%) | 89(67.9%) | | 90(68.7%) | 89(67.9%) | | |
| **SUV max** | | | 0.378 | | | 0.292 | 0.19 |
| Not done | 29(7.1%) | 16(12.2%) | | 12(9.2%) | 16(12.2%) | | |
| <2.01 | 86(21.0%) | 27(20.7%) | | 27(20.6%) | 27(20.7%) | | |
| 2.01 ≤ x < 7.41 | 165(40.3%) | 51(38.9%) | | 44(33.6%) | 51(38.9%) | | |
| ≥7.41 | 92(22.6%) | 29(22.1%) | | 30(22.9%) | 29(22.1%) | | |
| unknown | 37(37.0%) | 8(6.1%) | | 18(13.7%) | 8(6.1%) | | |
| **Adjuvant Treatment** | 38(9.3%) | 25(19.1%) | 0.002 | 22(16.8%) | 25(19.1%) | 0.629 | 0.05 |

random variables.

Follow-up was assessed by number of outcomes/100 patients-year.

Parsimonious Cox proportional hazards regression was performed, including all variables (listed in table 2) to analyze overall survival, disease-free survival and lung cancer specific death. Interaction of variable that violated proportional hazard assumption with time was considered for the model. The final model was obtained by stepwise method.

Propensity score matching (PSM) was performed 1:1 using the nearest neighbour method, including the following variables sex, age, pack-year, primary tumor, surgical approach, and adjuvant treatment. SMD (Standardized mean difference) assessed imbalance of covariates. To compare matched groups, paired tests were performed, however stratified tests were used to compare survivals outcomes between these matched groups.

As, the curves crossed, Schoenfeld residuals test assessed the proportional hazards assumptions.

Recurrences were assessed by linearized risks, the number of events per 100 patients per year.

Primary endpoints:

DFS, OS and LCSD of early-stage NSCLC patients with a history of any cancer who underwent lobectomy vs segmentectomy with systematic lymph node dissection.

Secondary endpoints:

- We assessed if segmentectomy was an independent risk factor for DFS, OS, LCSD in patients with early-stage NSCLC with a history of any cancer.
- We compared locoregional and distant recurrence between NSCLC patients who underwent lobectomy and those operated on by segmentectomy
- We explored if the timing of the prior cancer, i.e., synchronous or metachronous, was an independent risk factors for DFS, OS and LCSD.

## 3. Results

From a total of 1910 patients with early-stage lung cancer, 1476 (77.3%) underwent lobectomy and 434 (22.7%) segmentectomy with systematic lymph node dissection (Supplementary Table 1). 540 (28.2%) of them had a history of any cancer. Among patients with history of prior cancer, those with colorectal cancer 89 patients (16.5%), lung cancer 65 patients (12%) and breast cancer 65 patients (12%) were the most prevalent.

314 patients of 540 were diagnosed in a context of another prior tumor follow-up both synchronous and metachronous (Table 2).

Number of outcomes/100 patients-year were: 6.71 for OS, 2.82 DFS and LCSD 2.29. (Supplementary Table 2).

There was no significant difference in 5-year OS rates, 5-year DFS rates, and 5-year LCSD rates, before PSM. (Fig. 1.) After PSM, the corresponding rates were: 5-year OS: lobectomy 84.9% (95%CI 78.4–91.9) vs segmentectomy 80.8% (95%CI 72.4–90.2) ($p = 0.4$); 5-year DFS: lobectomy 76.9% (95%CI 69.3–85.3) for segmentectomy 74.4% (95%CI 65.5–84.5) ($p = 0.5$); and 5-year LCSD: lobectomy 6.5% vs segmentectomy 4.5% ($p = 0.2$) (Fig. 2).

In the matched cohort, locoregional recurrence (linearized risk: lobectomy 0.111 vs. segmentectomy 0.066) and distant recurrences (linearized risk: lobectomy 0.093 vs segmentectomy 0.055) were not worse in patients who underwent segmentectomy. (Table 3).

In the multivariable analysis, sex HR:1.58 (95%CI: 1.02–2.47) $p = 0.04$, comorbidities HR:1.21 (95%CI: 1.06–1.38) $p = 0.003$, postoperative complications HR:1.49 (95%CI: 1.13–1.97) $p = 0.005$, and lung cancer histology HR:1.45 (95%CI: 1.01–2.07) $p = 0.042$ impacted overall survival. However, previous cancer HR:1.27 (95%CI: 1.00–1.60) $p = 0.04$, lung cancer histology HR:2.39 (95%CI: 1.43–4.015) $p < 0.001$, and adjuvant treatment HR:2.71 (95%CI: 1.24–5.93) $p = 0.01$ influenced lung cancer specific death. No variables impacted DFS.

Proportional hazard assumption was not violated for survival ($p = 0.13$), recurrence ($p = 0.19$) or lung cancer specific death ($p = 0.13$).

135 patients (7%) had an adjuvant systemic treatment in the entire

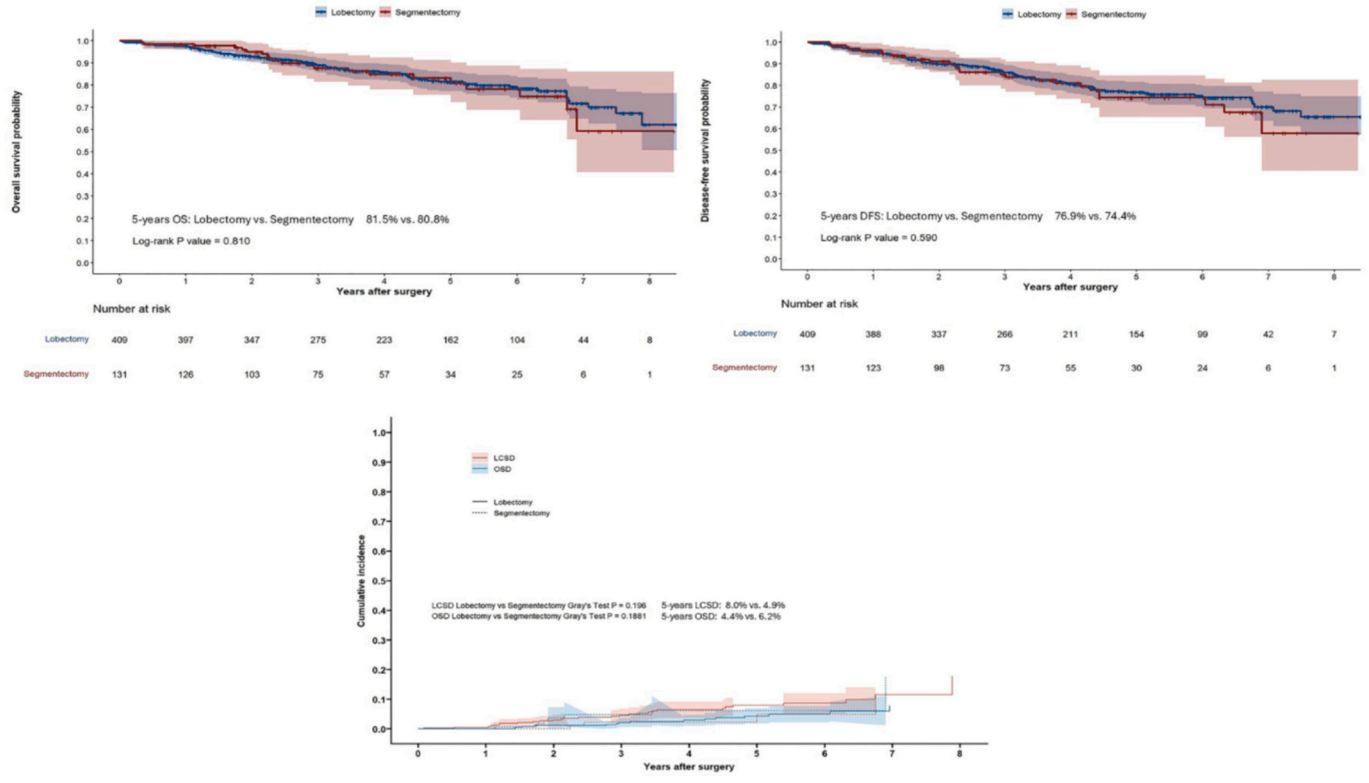


**Fig. 1.** Overall survival, Disease-free survival and lung cancer specific death in the unmatched cohort.

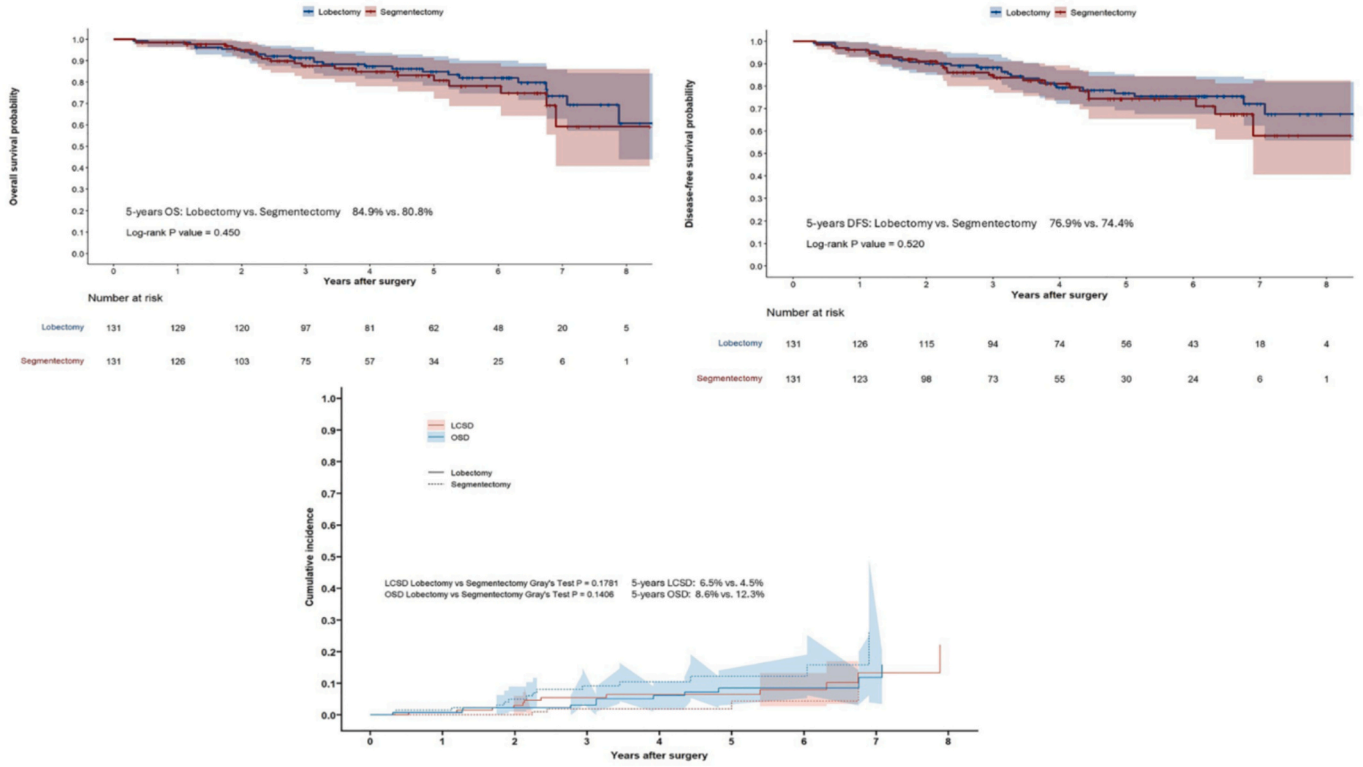


**Fig. 2.** Overall survival, Disease-free survival and lung cancer specific death in the matched cohort.

**Table 3**
Linearized risk for locoregional and distant recurrence according to type of operation.

| | Unmatched cohort | | Matched cohort | |
|---|---|---|---|---|
| | Lobectomy (n = 409) | Segmentectomy (n = 131) | Lobectomy (n = 131) | Segmentectomy (n = 131) |
| Loco-regional | 0.049 | 0.066 | 0.111 | 0.066 |
| Distant | 0.071 | 0.055 | 0.093 | 0.055 |

dataset; this happened in cases of synchronous (the adjuvant treatment may be prescribed for the other cancer) (Supplementary Materiel Table 1). In addition, in some centers, patients with poor pathological features such visceral pleural invasion, STAS, lymphovascular invasion, necrosis), particularly in the segmentectomy group had an adjuvant treatment.

## 4. Discussion

We demonstrated that patients with early-stage lung primary lung cancer and a history of any cancer had a similar OS, DFS and LCSD when they were operated on by segmentectomy compared to lobectomy.

Locoregional and distant recurrence were not superior in the segmentectomy group.

Adjuvant treatment and nature of the prior cancer only impacted LCSD.

The majority (58.1%) of patients with early-stage lung cancer were diagnosed in the context of the prior cancer follow-up.

Cancer survivorship remains an understudied population, despite its growing size. One of the most clinically relevant risks in this group is the occurrence of a second primary malignancy. About 7–15% of lung cancers have been reported in cancer survivorship [12–16]. In our series, the incidence was substantially higher. This difference may partly reflect the continuous increase in cancer survivorship [12,15,17]. Importantly, unlike many prior studies, we did not exclude patients with a history of malignancies known to confer a particularly high susceptibility to subsequent lung cancer, such as prior lung, laryngopharyngeal, or head and neck cancers. In addition, our analysis was restricted to early-stage lung cancer, thereby reducing the denominator. Cancer survivors are more likely to have subsequent lung cancers detected at an early stage rather than at an advanced stage, owing to closer oncologic surveillance during follow-up.

Unlike previous reports [3,6,7,15,16,18,19] where breast cancer was the prevalent prior cancer in cancer survivors, in our series, colorectal cancer was the most prevalent. Although there is no obvious reason, this may be related to a higher likelihood of colorectal cancer survivors to have follow-up CT-scan (compared to breast cancer ones). We also noticed a major proportion of previous lung cancer.

The effect of a prior malignancy on primary lung cancer outcome has been studied but the results are inconsistent. Some studies showed no influence of the prior cancer [12,16,19,20], while others, noticed a negative influence in overall survival [13,15,17,18]. It is worth mentioning that in series with negative impact, patients with prior cancers were older and that prior malignancies had no impact on DFS. It is evident that a prior cancer can influence the prognosis of a new primary lung cancer depending on many factors like the previous tumor organ, histologic type, stage, interval between cancers, and importantly the treatment received for the prior cancer. The main idea is that a previous malignancy in a patient with a primary lung cancer is not a contraindication for lung cancer surgical resection. Additionally, patients with early-stage lung cancer and a history of previous extrapulmonary cancer have been reported to have a better prognosis when they undergo a lung resection (compared to other treatment alternatives) [14].

Patients with previous lung cancer history who underwent a lung resection for an early-stage second primary lung cancer were reported to have an acceptable OS rate [21] even when the new primary lung cancer was on the same lung side [22,23].

Primary lung cancer in cancers survivors is predominantly early

diagnosed [12,15,17–20,24]. In this circumstance sublobar resection appears to be an appropriate choice both in patients with pulmonary prior cancers [21,24] and in those with extra-pulmonary prior malignancies [16,17,20]. Sublobar resection [24–27] especially segmentectomy [21] have been proven to be non-inferior to lobectomy in patients with second primary cancer. However, Brown et al. reported a higher recurrence rate in patients with a second primary lung cancer when they underwent segmentectomy. In this study, patients with prior lung cancer group had a higher proportion of smaller resection margin and a large frequency of patients who ended up having a pathological stage beyond stage IA2. Despite this, DFS remained similar between patients who underwent segmentectomy and those operated on by lobectomy [28].

We proved that segmentectomy can be safely performed in patients with any prior cancer and has no inferior oncological outcome compared to lobectomy. OS, DFS and LCSD are similar in both groups, and locoregional recurrences were not higher in the segmentectomy group. So, the managing physician should not hesitate to indicate segmentectomy for cancer survivors with early-stage lung cancer.

Segmentectomy has been reported to be related to a better immune-nutritional status compared to lobectomy [29] making patients who underwent segmentectomy more able to face further diseases, including malignancies leading to better overall survival [8]. Additionally, patients with high comorbidities have been reported to have poorer outcomes after lobectomy compared to segmentectomy [30]. This may be applied to patients with prior of cancer, which can be considered as a double comorbidity due to, on one hand its organic aspect of a previous disease and its potential treatment and on the other hand its attending oncological component. Our study reinforces the idea that segmentectomy is not only an option but a preference for cancer survivors with primary early-stage lung cancer. These patients are at a higher risk of developing a new lung cancer, and a parenchyma-sparing resection may be useful to indicate a new resection in case of a new lung cancer.

The retrospective nature of this study is its main limitation, however its multicenter design strengthens the robustness of the findings. Our results spread light on an emerging clinical question about the extent of resection for primary early-stage lung cancer in cancer survivors in a European context of a clinical practice outside of clinical trials. We did not use more prior cancer parameters (for instance the prior cancer stage or treatment) that might influence prognosis. Further research is needed to assess features that may influence survival of patients with early-stage NSCLC and history of cancer.

## 5. Conclusion

Segmentectomy is a valid option for patients with peripheral early-stage NSCLC and a history of any cancer.

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## CRediT authorship contribution statement

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

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