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Lobectomy vs. segmentectomy. A propensity score matched comparison of outcomes

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ABSTRACT

Background: Segmentectomy has emerged as a lung parenchymal sparring alternative to the gold standard lobectomy in non-small cell lung cancer (NSCLC) patients. We hypothesized that there is parity between functional, local recurrence and survival outcomes.
Patients and methods: Parenchymal sparring procedures including anatomical segmentectomies were propensity score matched 1:1 with lobectomies ($n = 64$). The primary outcomes included survival, functional and oncological outcomes. The oncological outcomes were: post-operative histology, clear margins and local recurrence rates. Kaplan Meier survival curves were used to compare the survival. Oncological and functional variables were assessed by Fischer exact test and *t*-test.
Results: The pre-operative performance status, ASA grade, lung function, risk factors, surgical approach and tumour histology were similar between the groups. The tumour size was significantly higher for lobectomies (32.4 ± 17 vs. 24.6 ± 12 mm, $p = 0.01$). The tumour staging in the segmentectomy group was similar to the lobectomy group (Ia; 50 vs. 34%; Ib: 29 vs. 37%; IIa 11 vs. 9.3%; IIb 5 vs. 14%; IIIa 5 vs. 4.6%, $p = 0.83$). The loco-regional recurrence was lower in the segmentectomy group (1.5 vs. 3.1%, $p = 0.69$). The up-staging and down-staging post-surgery was similar in both groups, while neo-adjuvant therapy was used in 5 lobectomy and 3 segmentectomy cases. The survival was similar at 1 year between the groups (88 vs. 92%, $p = 0.65$). Between 4 and 5 years, the survival reduced in the parenchymal sparing group to 39% vs. 68% in the lobectomy group ($p = 0.04$).
Conclusion: Surgical selection bias could be an important confounder in the selection of patients undergoing segmentectomy. Similar up and down staging were demonstrated in the two groups. This is one of the first studies to investigate the results of segmentectomy versus lobectomy in stage II/IIIa NSCLC tumours. No significant differences were found in functional outcomes, but the survival decreased after 4 years in the segmentectomy group, which could be explained by lower survival in the stage II/IIIa tumours treated with segmentectomy.

Introduction

For several decades, lung cancer has been the most common cancer worldwide with the highest incidence and mortality amongst tumours since 1985 [1]. In 2015, cancer has been a leading cause of mortality, with approximately 8.8 million deaths, amongst which, lung cancer related deaths were at the top of the list with 1.69 million deaths [2].

Lung tumours can be broadly divided into two types: small cell lung cancer, which is highly malignant and accounts for approximately 15% of cases, and non-small cell lung cancer (NSCLC) that constitutes the remaining 85% of cases.

Despite the multi-modality treatments available, the prognosis for lung cancer is poor. The prognosis and 5-year survival rates are highly dependent on the stage of the disease at presentation, ranging from 92% for stage Ia (localised disease) to 1–10% for stage IV in patients diagnosed with NSCLC [3].

Surgical resection has been the mainstay of curative treatment for early stage NSCLC [4]. The type of resection can be divided in

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pneumonectomy, lobar resection and sublobar resection, which includes segmentectomy and wedge resections.

In 1995, the Lung Cancer Study Group (LCSG) showed that limited non-anatomical resection was associated with a three-fold increase in local recurrence and a 50% increase in cancer-related deaths [5]. Hence why, potential disadvantages of sublobar resections include increased local recurrence rate and poorer long-term outcome. These results were re-enforced by the ACCP guidelines and established lobectomy with mediastinal lymph node dissection as the standard of care for stage I NSCLC in patients who are physiologically fit [6].

Recent advances in imaging, clinical staging modalities and the ability to detect smaller tumours by CT [7] have further ignited interest in this sublobar approach for early stage cancers. This has been demonstrated previously by the increased frequency of sublobar resection from 22% in 1993–2005 to 34% in 2006–2011 for asymptomatic patients with clinical stage I disease [8].

In the context of emerging conservative lung parenchymal sparing procedures, segmentectomy has been shown to have similar outcomes when compared to lobectomy in stage Ia NSCLC, but worse outcomes in tumours sized 2–3 cm [9]. Additionally, a large propensity-matched study indicated that anatomic segmentectomy should be considered as an appropriate alternative to lobectomy in selected cases as the peri-operative and oncologic outcomes achieved with the limited pulmonary resection are comparable to those achieved with lobectomy [4].

The results of these studies demonstrate the need to further clarify the role of lung-sparing procedures in the treatment of early stage NSCLC while taking into consideration factors such as age, comorbidities, tumour characteristics, peri- and post-operative complications as well as survival.

Our objective is to investigate if segmentectomy has similar oncological, functional and survival outcomes when compared to lobectomy in all patients treated with surgery for NSCLC.

Materials and methods

Patient selection

We performed a retrospective analysis of 844 patients who underwent anatomic segmentectomy (n = 64) or lobectomy (n = 780) for clinical all stage NSCLC at a tertiary referral hospital (Nottingham University Hospitals NHS Trust) between 2008 and 2016. All patients were assessed using staging computed tomography with contrast and F-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). Tumor sizes and maximum standardised uptake values (SUVmax) were determined by radiologists at each institution where the scans were performed. Patients were staged according to the seventh edition of the TNM Classification of Malignant Tumours staging system [10]. The decision to perform an anatomic segmentectomy was based on the size of the tumours, histology and location, rather than borderline lung function. The pre-operative size was <3 cm and T1a and T1b according to the Edition VII of the TNM classification. Health Research Authority and Medical Research Council ethical approval was sought and was deemed not necessary. Patient consent was waived. Anonymised data was collected retrospectively from our prospectively collated database.

Statistical analysis

Propensity Score Matching score matching is a method for creating case (segmentectomy) and control (lobectomy) sets that have similar characteristics based on potentially confounding variables [11]. Univariate logistic regression was used to identify these variables. The potential predictors that were not statistically significant (P .05) were removed, and the propensity score was calculated from the logistic regression. Segmentectomy and lobectomy patients were then matched 1:1 using a nearest neighbour matching algorithm. Propensity score matching was used in our study to increase the sensitivity of the comparison between the groups.

The primary outcomes were functional (lung function), oncological and survival outcomes. Functional outcomes included: post-operative predicted lung function and in-hospital length of stay. Oncological outcomes included: post-operative histology, resection margins clearance and loco-regional recurrence rates. Oncological outcomes included post-operative histology, clear margins and local recurrence rates. Oncological and functional parameters were assessed by Fischer exact test to compare the frequencies of categorical measures (e.g. sex, histology, stage) and *t*-test to compare the distributions of continuous data (e.g. age, BMI, lung function, tumor size). Overall survival was defined as the time from surgery to death or last follow-up. The survival data was analysed based on the NSCLC stage. These were estimated using the Kaplan Meier method and compared using the log-rank test. The descriptive statistics and p values were determined using the STATA (StataCorp, TX, USA, 2017) and GraphPad PRISM (version 7, GraphPad Software, La Jolla California, USA) software packages.

Surgical technique and patient follow-up

The video-assisted thoracoscopic surgery or open approach was used in the patients in this study. Anatomic segmentectomy was performed through the isolation and resection of one or more pulmonary parenchymal segments with its corresponding broncho-vascular and lymphatic supply. Lobectomy was performed in a similar manner. Systematic hilar and mediastinal nodal sampling was performed in all patients.

Postoperative follow-up of all patients from the day of surgery included physical examinations and chest X-rays at two weeks, followed by every three months in the first year, every six months in the second and third years, and yearly after up to a total of five years. CT chest was performed where the clinical and X-ray investigations raised suspicion of recurrence. Loco-regional recurrence was defined as evidence of tumor within the same lobe, the hilum, or the mediastinal lymph nodes. Distant recurrences were defined as evidence of tumor in another lobe, the pleural space, or elsewhere outside the hemithorax.

Results

Pre-matched demographics and comorbidities

The average age was 67.7 (n = 780) and 70.1 (n = 64) in the lobectomy and segmentectomy groups respectively. Mean FEV1 was higher in the lobectomy group (2.1L vs. 1.8L). Tumour size was significantly higher in the lobectomy group (35.9 vs. 24.6 mm). The tumour staging was: stage I – 62% vs 75%; stage II – 23% vs. 13% and stage III – 15% vs. 11% in the lobectomy and segmentectomy groups respectively. A history of cancer was present in 19% of the lobectomy and 43% of the segmentectomy patients. There was no difference in the gender, BMI, smoking, asbestos exposure, ASA grade, COPD, asthma, pre-operative histology type, or tumour staging between the two groups.

The pre-operative demographics and comorbidities variables were propensity score matched through univariate analysis between lobectomy and segmentectomy patients. The following variables were significant and included in the propensity score: Age, FEV1, FEV1 %Predicted, FVC, Tumour diameter, COPD history (Hx), Cancer Hx, Pre-operative staging (Supplemental Table 1).

Table 1
Comparison of lung function, operative approach and pre-operative staging between the groups.

Outcomes	Variables	Lobectomy ($n = 64$)	Segmentectomy ($n = 64$)	p-value
Lung function	*FEV1 (L)*	2.1 ± 0.7	1.8 ± 0.6	0.07
	FEV1 (%)	82.8 ± 19.7	76.1 ± 22	0.73
	FVC (L)	3.6 ± 1.8	2.9 ± 1.2	0.18
	FVC (%)	85.7 ± 34.6	87.8 ± 36.4	0.99
Operative details	*VATS*	44 (68%)	40 (62%)	0.57
	Open	20 (31%)	24 (37%)	0.53
Preoperative staging	*Ia*	25 (39%)	32 (50%)	
	Ib	23 (36%)	16 (25%)	
	IIa	7 (11%)	5 (8%)	0.99
	IIb	5 (8%)	4 (6%)	
	IIIa	4 (6%)	7 (11%)	

Following matching (n = 64), the variables were not significantly different between the groups.

Functional outcomes

The lung function was not significantly different between the groups, but it was overall lower in the segmentectomy patients: FEV1 - 1.8L vs. 2.1L ($p = 0.07$); FEV1(%) - 76.1% vs. 82.8% ($p = 0.73$); FVC – 2.9L vs 3.6L ($p = 0.18$) and FVC (%) – 87.8% vs. 85.7% ($p = 0.99$). The operative approach was similar between VATS and Open procedures in the two groups (68%/31% vs. 62%/37%, $p = 0.57$ for VATS and $p = 0.53$ for open). There was no significant difference in the pre-operative stages, with the majority of cases being represented by stage Ia or Ib tumours ($p = 0.99$) (Table 1).

The median length of stay was 6 days in both groups. Lung function tests were performed in 22 lobectomy and 28 segmentectomy patients as part of their follow-up. There were no significant differences between these parameters (Table 2).

Oncological outcomes

The majority of patients had tumours localised in the left upper tri-segments in the segmentectomy group (40.6%) and right upper lobe in the lobectomy group (35.9%) (Supplemental Figure 1). The predominant tumour was Adenocarcinoma in both groups, representing 67% in lobectomy and 56% in segmentectomy groups. The mean size of the tumours was larger in the lobectomy group (32.4 mm vs. 24.6 mm, $p = 0.01$). Of note, stage Ia was the predominant stage in the segmentectomy group, while Ib was predominant in the lobectomy group. Overall stage I was most common in both groups, although stage IIb (5%) and IIIa (5%) were defined in the segmentectomy group as well. The reasons for the advanced stages of NSCLC were: Lobectomy group - 30% T3 satellite nodules and 70% N2 positive lymph nodes; Segmentectomy group - 40% T3 satellite nodules and 60% N2 positive lymph nodes in the segmentectomy group. There was no difference between the overall post-operative stages ($p = 0.83$). A third of the tumours were upstaged following surgery in both groups, while 20.3% were down-staged in the lobectomy and 15.6% in the segmentectomy

Table 2
Postoperative functional outcomes.

Outcomes	Lobectomy ($n = 22$)	Segmentectomy ($n = 28$)	p-value
Post-op FEV1 (L) (Mean ± STD)	1.7 ± 0.6	1.5 ± 0.7	0.19
Post-op FEV1% (% ± STD)	65.8 ± 18	63.6 ± 22.8	0.68
Post-op FVC (L) (Mean ± STD)	2.6 ± 1.7	2.2 ± 1.6	0.3
Post-op FVC% (% ± STD)	115.3 ± 57	105.3 ± 76.7	0.55
LOS (Median)	6	6	0.98

Table 3
Postoperative oncological outcomes.

Outcomes	Variables	Lobectomy ($n = 64$)	Segmentectomy ($n = 64$)	p-value
Histology	*Adenocarcinoma*	43 (67%)	36 (56%)	
	Squamous cell carcinoma	17 (26.5%)	22 (34.3%)	0.99
	Carcinoid	1 (1.5%)	4 (6.2%)	
	Other (Large cell ca)	3 (4.6%)	2 (3.1%)	
Size	*Tumour size (mm)*	32.4 ± 17	24.6 ± 12	0.01
Staging	*Ia*	22 (34%)	*32 (50%)*	
	Ib	24 (37%)	19 (29%)	
	IIa	6 (9.3%)	7 (11%)	
	IIb	9 (14%)	3 (5%)	0.83
	IIIa	3 (4.6%)	3 (5%)	
	Reason for advanced stage	30% T3/Sat nodules, 70% N2	40% Sat nodules, 60% N2	
	Upstaging	21 (32.8%)	21 (32.8%)	0.99
	Down-staging	13 (20.3%)	10 (15.6%)	0.45
	Positive Margins	2 (3.1%)	1 (1.6%)	0.62
	Loco-regional Recurrence	2 (3.1%)	1 (1.5%)	0.49
	Adjuvant therapy	7 (11%)	5 (7.8%)	0.76

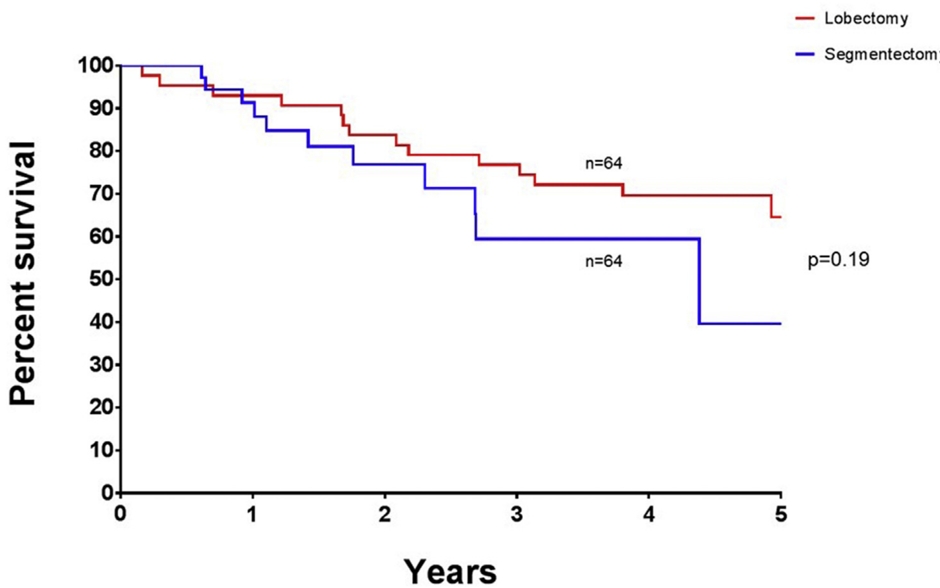

Fig. 1. Survival comparison between all stages of NSCLC in the two groups.

groups. There was 1 loco-regional recurrence detected in the segmentectomy group, with 2 cases diagnosed in the lobectomy group. The rates of adjuvant therapy were similar between the groups: 11% vs 7.8% in the lobectomy and segmentectomy groups respectively. One case with positive margins was diagnosed in the segmentectomy group, while two were diagnosed in the lobectomy group (Table 3).

Survival outcomes

The survival was compared between the lobectomy and segmentectomy groups through Kaplan-Meier curves and based on the stages of the tumours. Although the curves were becoming divergent after 3 years, the overall survival at 5 years was not statistically significant between groups when including all stages of NSCLC in the two groups ($p = 0.19$, $n = 64$ vs. $n = 64$) (Fig. 1).

When comparing stage I tumours there was no difference in survival at 5 years ($n = 46$ vs $n = 51$, $p = 0.53$). Although not different statistically, the survival was lower for stage II/III NSCLCs treated by segmentectomy, with 20% vs. 68% survival at 3 years ($n = 18$ vs. $n = 13$, $p = 0.07$). The survival curves were worse when compared to stage I NSCLC survivals (Fig. 2 and Fig. 3).

In the multivariate analysis, COPD significantly affected survival ($p = 0.009$). None of the other variables had an association with survival or loco-regional recurrence (Supplemental Figure 2). Segmentectomy was not a predictor of survival.

Conclusion

Since the introduction of lobectomy in the late 50s for treatment of lung cancer, it has become the golden standard surgical procedure for patients with resectable and operable NSCLC [5].

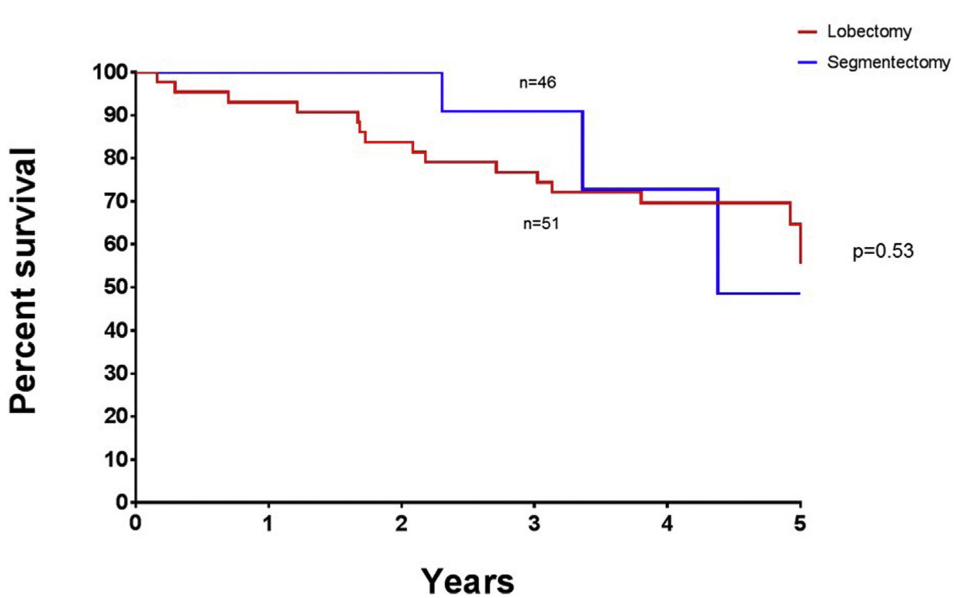

Fig. 2. Survival comparison between Stage I of NSCLC in the two groups.

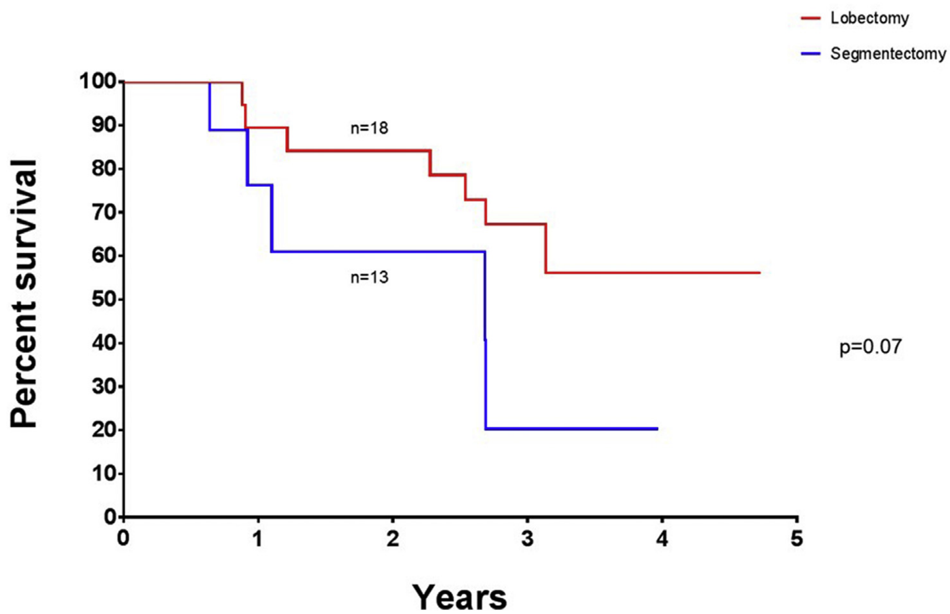

Fig. 3. Survival comparison between Stages II/III of NSCLC in the two groups.

Contributing factors to the improvement of surgical outcomes are: the progression of surgical technique, surveillance and detection protocols, introduction of high resolution imaging and early detection of smaller tumours [12].

More recently, the emergence and development of SABR and more targeted oncological treatments are claiming to achieve comparable outcomes to surgery in early stage NSCLC [13]. This has been proposed as possible first-line treatment for recurrent lung cancers [14]. However, the wide adoption of the technique is yet modest, is to be proven by high quality studies, while long term results are still awaited [15].

The results of large-population CT screening programs for early lung cancer detection [16] have led to an increased number of clinically suspicious lung nodules suggestive of early-stage NSCLC and subsequently to cases being offered segmentectomy as curative surgical intent procedures [17]. There is ongoing debate about the treatment [18] and size of the resection in stage I NSCLCs and segmentectomy emerged as an alternative surgical option for patients with limited lung function [19].

Furthermore, it was shown that a sublobar approach is appropriate for lesions that appear as pure ground-glass opacities, a characteristic feature of the slowly growing broncho-alveolar adenocarcinomas [20], but also for tumours $\leq$ 1 cm in size [21] and $\leq$ 2 cm in size [22]. Similarly, a study by Nomori et al. found that prognosis and 5-year overall survival after segmentectomy were not different to the values previously reported for lobectomy. The authors suggest that segmentectomy may be adequate even for tumours 2.1–3 cm in size as long as there is extended lymph node dissection and adequate surgical margin resection [23]. These findings have been subsequently confirmed through equivalent lung-cancer specific survival between segmentectomy and lobectomy patients with stage IA lung cancer manifesting as a solid nodule [24]. Furthermore, segmentectomy has been demonstrated to be more beneficial than lobectomy for stage IA tumours $\leq$ 3 cm without nodal involvement found during surgery [25].

Contradicting studies found that sublobar resection was associated with a shorter disease-free interval and poorer survival than lobectomy, even for tumours $\leq$ 2 cm, but these included wedge resections, while the segmentectomy was not clearly defined [26]. Similarly, Ohtsuka et al. found that segmentectomy was associated with higher morbidity, postoperative complications, longer operating times and a larger estimated volume of blood loss compared to the lobectomy group. These were attributed to post-operative air leak associated with dissection of the intersegmental plane [27].

Despite a parenchymal conservative approach with intuitively preserved lung function when performing a segmentectomy [28], this has been shown more recently to have a limited impact on long term lung function preservation when compared with lobectomy [29]. Now the boundaries of indications for segmentectomy are extended by enthusiasts, including resection of one or multiple segments, through multiple or single VATS port approaches. While segmentectomies are being performed in majority for stage I NSCLC tumours [9], the post-operative diagnosis may upstage the tumours to clinical stage II or III based on satellite lung nodules or positive N2 lymph nodes. In our segmentectomy cohort, a combination of extended segmentectomies (e.g. left upper tri-segment, basal, S5/6) were performed when tumours exceeded 2 cm or the location was precluding a single segment resection. Of note, 25% of the segmentectomy group had a pre-operative clinical staging of IIa,IIb or IIIa. These stages were clinical and based on positive lymph nodes on PET-CT, but not proven histologically, while 15% of these tumours were down-staged following surgery.

In this analysis, there was no difference in functional or oncological outcomes between cohorts. We have shown that segmentectomy can clearly achieve the same rate of negative margins for tumour presence and without significant difference in loco-regional recurrence rates. It is important to note the significant integrated operative up and down staging achieved in our cohort, achieved through full resection and clearance of the lymph nodes, which is higher when compared to non-surgical methods reported previously [30].

Our results confirmed similar survival results for stage I NSCLC, but worse survival for stage II/III NSCLC when performing segmentectomy. This reflects the role of surgery in the definitive and accurate staging of NSCLC. In our cohort, adjuvant treatment was given to 5 of the segmentectomy patients, while 13 patient had stage II/III tumours. Similar results have been previously shown by several authors for stage I tumours [8], including Landreneau et al.

in a propensity matched cohort [4]. Additionally, this latter study showed similar recurring tumour locations: left upper lobe for patients undergoing segmentectomy and right upper lobe for patients undergoing lobectomy [4]. To our best knowledge, this is the first study to compare segmentectomy and lobectomy for clinical integrated stage II/III NSCLCs.

Despite strategies used in multivariate and propensity-matching analysis, this study has possible inherent limitations. This was a retrospective cohort analysis, where the full integrity of the data is difficult to confirm, hence why the propensity score matching was performed. A potential selection bias of patients undergoing segmentectomy could be an important confounding factor.

In conclusion, we have shown that segmentectomy and lobectomy have comparable functional and oncological outcomes irrespective of the stage, but the survival is reduced when segmentectomy was performed in stage II/III NSCLC. An argument could be made for an aggressive adjuvant approach in these cases, which was not present in our cohort. Randomised control trials are much needed to confirm our results and support guidelines and recommendations of treatment.

Key message

This is one of the first studies to investigate the results of segmentectomy versus lobectomy in stage II/IIIa NSCLC tumours. Similar up and down staging were demonstrated in the two groups. Segmentectomy and lobectomy have comparable functional and oncological outcomes irrespective of the stage, but the survival is reduced when segmentectomy was performed in stage II/III NSCLC. Randomised control trials are much needed to confirm our results and support guidelines and recommendations of treatment.

Disclosure

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi:10.1016/j.ejso.2018.10.534.

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