

1 **Article type: Original article**

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3 **Lobectomy vs. Segmentectomy.**
4 **A propensity score matched comparison of outcomes.**
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18 **Disclosure**

19 The authors have no conflicts of interest to disclose.
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29 **Words count:** 2692
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33 **Key words:** Segmentectomy, Lobectomy, Non-small cell lung cancer, Oncological
34 outcomes.

35 **Abstract**

36 **Background**

37 Segmentectomy has emerged as a lung parenchymal sparing alternative to the gold
38 standard lobectomy in non-small cell lung cancer (NSCLC) patients. We hypothesized
39 that there is parity between functional, local recurrence and survival outcomes.

40 **Patients and Methods**

41 Parenchymal sparing procedures including anatomical segmentectomies were
42 propensity score matched 1:1 with lobectomies (n=64). The primary outcomes included
43 survival, functional and oncological outcomes. The oncological outcomes were: post-
44 operative histology, clear margins and local recurrence rates. Kaplan Meier survival
45 curves were used to compare the survival. Oncological and functional variables were
46 assessed by Fischer exact test and t-test.

47 **Results**

48 The pre-operative performance status, ASA grade, lung function, risk factors, surgical
49 approach and tumour histology were similar between the groups. The tumour size was
50 significantly higher for lobectomies (32.4 ± 17 vs. 24.6 ± 12 mm, $p=0.01$). The tumour
51 staging in the segmentectomy group was similar to the lobectomy group (Ia; 50 vs. 34
52 %; Ib: 29 vs. 37%; IIa 11 vs. 9.3%; IIb 5 vs. 14%; IIIa 5 vs. 4.6%, $p=0.83$). The loco-
53 regional recurrence was lower in the segmentectomy group (1.5 vs. 3.1%, $p=0.69$).
54 The up-staging and down-staging post-surgery was similar in both groups, while neo-
55 adjuvant therapy was used in 5 lobectomy and 3 segmentectomy cases. The survival
56 was similar at 1 year between the groups (88 vs. 92%, $p=0.65$). Between 4 and 5 years,
57 the survival reduced in the parenchymal sparing group to 39% vs. 68% in the
58 lobectomy group ($p=0.04$).

59 **Conclusion**

60 Surgical selection bias could be an important confounder in the selection of patients
61 undergoing segmentectomy. Similar up and down staging were demonstrated in the
62 two groups. This is one of the first studies to investigate the results of segmentectomy
63 versus lobectomy in stage II/IIIa NSCLC tumours. No significant differences were
64 found in functional outcomes, but the survival decreased after 4 years in the
65 segmentectomy group, which could be explained by lower survival in the stage II/IIIa
66 tumours treated with segmentectomy.

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69 Introduction

70 For several decades, lung cancer has been the most common cancer worldwide with
71 the highest incidence and mortality amongst tumours since 1985.⁽¹⁾ In 2015, cancer
72 has been a leading cause of mortality, with approximately 8.8 million deaths, amongst
73 which, lung cancer related deaths were at the top of the list with 1.69 million deaths.⁽²⁾
74 Lung tumours can be broadly divided into two types: small cell lung cancer, which is
75 highly malignant and accounts for approximately 15% of cases, and non-small cell lung
76 cancer (NSCLC) that constitutes the remaining 85% of cases.

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

81 Surgical resection has been the mainstay of curative treatment for early stage
82 NSCLC.⁽⁴⁾ The type of resection can be divided in pneumonectomy, lobar resection
83 and sublobar resection, which includes segmentectomy and wedge resections.

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

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

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

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

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

110 **Materials and Methods**

111 **Patient selection**

112 We performed a retrospective analysis of 844 patients who underwent anatomic
113 segmentectomy (n=64) or lobectomy (n=780) for clinical all stage NSCLC at a tertiary
114 referral hospital (Nottingham University Hospitals NHS Trust) between 2008 and 2016.
115 All patients were assessed using staging computed tomography with contrast and F-
116 18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-
117 PET/CT). Tumor sizes and maximum standardised uptake values (SUVmax) were
118 determined by radiologists at each institution where the scans were performed.
119 Patients were staged according to the seventh edition of the TNM Classification of
120 Malignant Tumours staging system.⁽¹⁰⁾ The decision to perform an anatomic
121 segmentectomy was based on the size of the tumours, histology and location, rather
122 than borderline lung function. The pre-operative size was <3 cm and T1a and T1b
123 according to the Edition VII of the TNM classification. Health Research Authority and
124 Medical Research Council ethical approval was sought and was deemed not
125 necessary. Patient consent was waived. Anonymised data was collected
126 retrospectively from our prospectively collated database.

127 **Statistical analysis**

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

136 The primary outcomes were functional (lung function), oncological and survival
137 outcomes. Functional outcomes included: post-operative predicted lung function and

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

150 **Surgical technique and patient follow-up**

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

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

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Results

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Pre-matched demographics and comorbidities

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

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Functional outcomes

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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.**)

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Oncological outcomes

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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 Table 2.**) The predominant tumour was Adenocarcinoma in both

200 groups, representing 67% in lobectomy and 56% in segmentectomy groups. The mean
201 size of the tumours was larger in the lobectomy group (32.4mm vs. 24.6mm, $p=0.01$).
202 Of note, stage Ia was the predominant stage in the segmentectomy group, while Ib
203 was predominant in the lobectomy group. Overall stage I was most common in both
204 groups, although stage IIb (5%) and IIIa (5%) were defined in the segmentectomy
205 group as well. The reasons for the advanced stages of NSCLC were: Lobectomy group
206 - 30% T3 satellite nodules and 70% N2 positive lymph nodes; Segmentectomy group
207 - 40% T3 satellite nodules and 60% N2 positive lymph nodes in the segmentectomy
208 group. There was no difference between the overall post-operative stages ($p=0.83$). A
209 third of the tumours were upstaged following surgery in both groups, while 20.3% were
210 down-staged in the lobectomy and 15.6% in the segmentectomy groups. There was 1
211 loco-regional recurrence detected in the segmentectomy group, with 2 cases
212 diagnosed in the lobectomy group. The rates of adjuvant therapy were similar between
213 the groups: 11% vs 7.8% in the lobectomy and segmentectomy groups respectively.
214 One case with positive margins was diagnosed in the segmentectomy group, while two
215 were diagnosed in the lobectomy group. **(Table 3.)**

216 **Survival outcomes**

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

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

227 In the multivariate analysis, COPD significantly affected survival ($p=0.009$). None of
228 the other variables had an association with survival or loco-regional recurrence.
229 **(Supplemental Table 3.)** 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⁾ 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 $\leq 1\text{cm}$ in size⁽²¹⁾ and $\leq 2\text{cm}$ 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 2.1-3cm 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 $\leq 3\text{ cm}$ 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 $\leq 2\text{cm}$, 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

265 volume of blood loss compared to the lobectomy group. These were attributed to post-
266 operative air leak associated with dissection of the intersegmental plane.⁽²⁷⁾

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

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

288 Our results confirmed similar survival results for stage I NSCLC, but worse survival for
289 stage II/III NSCLC when performing segmentectomy. This reflects the role of surgery
290 in the definitive and accurate staging of NSCLC. In our cohort, adjuvant treatment was
291 given to 5 of the segmentectomy patients, while 13 patient had stage II/III tumours.
292 Similar results have been previously shown by several authors for stage I tumours ⁽⁸⁾,
293 including Landreneau et al in a propensity matched cohort.⁽⁴⁾ Additionally, this latter
294 study showed similar recurring tumour locations: left upper lobe for patients undergoing
295 segmentectomy and right upper lobe for patients undergoing lobectomy.⁽⁴⁾ To our best
296 knowledge, this is the first study to compare segmentectomy and lobectomy for clinical
297 integrated stage II/III NSCLCs.

298 Despite strategies used in multivariate and propensity-matching analysis, this study
299 has possible inherent limitations. This was a retrospective cohort analysis, where the
300 full integrity of the data is difficult to confirm, hence why the propensity score matching

301 was performed. A potential selection bias of patients undergoing segmentectomy could
302 be an important confounding factor.

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

309 **Key Message**

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

318 **Legend of Figures and Tables**

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

321 **Table 2.** Postoperative functional outcomes.

322 **Table 3.** Postoperative oncological outcomes.

323 **Figure 1.** Survival comparison between all stages of NSCLC in the two groups.

324 **Figure 2.** Survival comparison between Stage I of NSCLC in the two groups.

325 **Figure 3.** Survival comparison between Stages II/III of NSCLC in the two groups.

326 **Appendix**

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