Sublobar Resection in the Treatment of Peripheral Typical Carcinoid Tumors of the Lung

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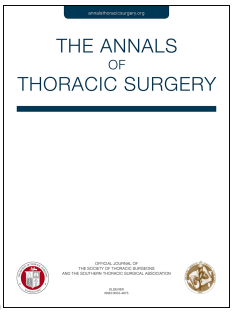

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Sublobar resection in the treatment of peripheral typical carcinoid tumors of the lung

Running Head: Sublobar resection and lung carcinoids

Maria Cattoni[1,2], MD, Eric Vallières[1], MD, Lisa M. Brown[3], MD, MAS, Amir A. Sarkeshik[3], MD, Stefano Margaritora[4], MD, Alessandra Siciliani[4], MD, Pier Luigi Filosso[5], MD, Francesco Guerrera[5], MD, Andrea Imperatori[2], MD, Nicola Rotolo[2], MD, Farhood Farjah[6], MD, Grace Wandell[6], MSc, Kimberly Costas[7], MD, Catherine Mann[1], MD, Michal Hubka[8], MD, Stephen Kaplan[8], MD, Alexander S. Farivar[1], MD, Ralph W. Aye[1], MD, Brian E. Louie[1], MD.

[1]Division of Thoracic Surgery, Swedish Cancer Institute, Seattle, WA, USA; [2]Center for Thoracic Surgery, Department of Medicine and Surgery, University of Insubria, Varese, Italy; [3]Section of General Thoracic Surgery, Department of Surgery, UC Davis Health, Sacramento, CA, USA; [4]Unit of Thoracic Surgery, Catholic University 'Sacred Heart', Rome, Italy; [5]Department of Thoracic Surgery, San Giovanni Battista Hospital, Torino, Italy; [6]Department of Surgery, University of Washington Medical Center, Seattle, WA, USA; [7]Division of Thoracic Surgery, Providence Regional Medical Center, Everett, WA, USA; [8]Division of Thoracic Surgery, Virginia Mason Hospital & Seattle Medical Center, Seattle, WA, USA.

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Corresponding author: Brian E. Louie MD, MHA, MPH, Division of Thoracic Surgery, 900-1101 Madison Street, Seattle, Washington 98104, E-mail: brian.louie@swedish.org

Abstract

Background The role of sublobar resection in the treatment of pulmonary typical carcinoids is controversial. This study aims to compare long-term outcomes between sublobar and lobar resections in patients with peripheral typical carcinoid.

Methods We retrospectively compared consecutive patients who underwent curative sublobar resection to lobectomy for cT1-3N0M0 peripheral pulmonary typical carcinoid in eight centers between 2000-2015. Primary outcomes were rates and patterns of recurrence and overall survival. Cox regression modeling was performed to identify factors influencing overall survival and recurrence. Propensity score analysis was done and overall survival was compared between the two groups.

Results A total of 177 patients were analyzed including 74 sublobar resections and 103 lobectomies with a total of 857 person-years of follow-up. R1 resection rate was 7% and 1% after sublobar resection and lobectomy, respectively (p=0.08). One of 5 patients with sublobar R1 resection developed recurrence. Recurrence rate was 0.02 (95%CI:0.009-0.044) per person year of follow-up after sublobar resection and 0.008 (95%CI:0.003-0.02) after lobectomy (p=0.15). Five-year survival rates were 91.7% (95%CI:78.5-96.9%) and 97.4% (95%CI:90.1-99.4%) after sublobar and lobar resection respectively (p=0.08). Extent of resection was not a predictor of recurrence or survival. Propensity score analysis confirmed a similar survival and freedom from recurrence between the two groups.

Conclusions Sublobar resection of peripheral cT1-3N0M0 pulmonary typical carcinoid was not associated with worse short or long-term outcomes compared to lobectomy. In select patients, sublobar resection may be considered for treatment of peripheral typical carcinoids if an R0 resection is obtained.

Abstract word count: 245 words.

Typical carcinoids (TC) of the lung are low-grade tumors characterized by a neuroendocrine morphology and differentiation [1]. They are rare and indolent with a low rate of lymph node and distant metastases at presentation (5-15% and 3% respectively), limited rate of recurrence after surgical resection (2-9%) and excellent long-term survival (5-year survival rate >90% after surgery) [2-4]. According to the NCCN guidelines, the standard of care for pulmonary TC is anatomic resection but their optimal operative management is still debated [5].

For TC that are predominantly endoluminal and confined to the airway there is a general consensus that treatment with a bronchial sleeve resection with negative margins with the aim of sparing lung tissue is an acceptable oncologic operation. However, for peripheral TC, a similar rationale for limited parenchymal sparing resection, in the form of wedge resection or segmentectomy, is not generally applied. Therefore, the role of parenchymal sparing resection for peripheral TC remains controversial [6-9]. Recent evidence is based on studies of limited numbers or administrative data without the necessary granularity to be conclusive. Additionally, there are no randomized controlled trials targeting this topic and the rarity of this disease ($\leq$ 5% of all lung cancers) precludes such a study design [6-8].

This study aims to compare rates and patterns of recurrence and overall survival of patients undergoing sublobar resection versus lobectomy for clinical T1-3N0M0 peripheral TC of the lung. We hypothesize that sublobar resection results in similar survival and recurrence rates compared to lobectomy.

Patients and Methods

We retrospectively reviewed a multi-institutional series of consecutive patients who underwent curative lung resection for pulmonary TC between 2000-2015. Participating institutions included Swedish Cancer Institute (Seattle, WA), UC Davis Health (Sacramento, CA), Catholic University 'Sacred Heart' (Rome, Italy), San Giovanni Battista Hospital (Torino, Italy), University of Insubria-Ospedale di Circolo (Varese, Italy), University of Washington Medical Center (Seattle, WA), Providence Regional Medical Center

(Everett, WA) and Virginia Mason Hospital and Medical Center (Seattle, WA). Patients with clinical T4 and/or N1-2 and/or M1 disease, central tumor location and those with less than 1 month of follow-up were excluded from the study. Central tumors are those that can be visualized via bronchoscopy or associated with atelectasis and/or obstructive pneumonia, whereas peripheral tumors are those not visualized via bronchoscopy [9]. The institutional review board at each center approved this study and de-identified data were transmitted between centers. Individual patient consent was waived due to the retrospective nature of the study.

For each patient, we collected the following data: age, sex, smoking history (current/former/never smoker), Eastern Cooperative Oncology Group (ECOG) performance status, forced expiratory volume in 1 second (FEV_1), previous malignancy, presence of symptoms at diagnosis (patients with respiratory symptoms, thoracic pain and /or carcinoid syndrome were considered symptomatic), preoperative imaging and biopsies, clinical 7^{th} edition TNM stage, surgical reports, postoperative complications, pathological findings, induction/adjuvant therapy and follow-up. Standardized definitions for each data point were decided a priori based on previous literature and distributed to each center for use.

Patients were divided into two groups based on the extent of resection: sublobar and lobar resection. Patients undergoing sublobar resection either underwent wedge resection or segmentectomy. Patients' clinical pathological characteristics, postoperative complications, rate and pattern of recurrence, recurrence-free interval and overall survival were compared between the two groups.

Cox regression modeling was performed to identify factors predicting overall survival and recurrence. Factors analyzed were age, sex, smoking history, ECOG performance status, FEV_1, previous malignancy, presence of symptoms at diagnosis, extent of lung resection, lymphadenectomy, tumor size and clinical tumor stage (cT). Pathologic N and stage were excluded from these analyses because approximately half of patients undergoing sublobar resection were missing data on lymph node sampling/lymphadenectomy.

Because there were factors that may have influenced surgeons' decision on the extent of surgical resection, we performed a propensity matched analysis as a sensitivity analysis using the following parameters for matching: age, gender, smoking history, ECOG performance status, previous malignancy, presence of symptoms at diagnosis, FEV_1 and tumor size. Patients (n=29) without one of these data points were excluded from this analysis. Overall survival and recurrence-free interval were analyzed and compared in the matched cohort.

Continuous data were reported as median with interquartile range (IQR) and compared using Mann–Whitney U test. Categorical and count data were presented as frequencies and percentages and compared using Chi-square test or Fisher's exact test if any expected frequency was less than 5. Overall survival was defined as time interval in months from date of surgery until last follow-up or date of death. Recurrence-free interval was defined as time interval in months from date of surgery until date of tumor recurrence. Incidence rates and confidence intervals were estimated using a Poisson model. Overall survival and recurrence-free interval were calculated using Kaplan-Meier estimates. For overall survival, univariate and multivariate analyses were completed using Cox regression modeling stratified by site. For recurrence-free survival, competing risks Cox regression models, stratified by site, were fit where death was considered the competing risk. The complementary models considering death as the event of interest with recurrence as the competing risk were also fit [10]. In multivariate analyses, we included extent of resection and any significant factors from univariate analyses. A *p*-value <0.05 was considered statistically significant. Statistical analyses were undertaken using SAS 9.4 (Cary, NC). Cumulative incidence curves for the competing events analyses were fit using the R function 'cuminc'. Propensity score matching analysis was done using R function 'matchit' and standardized differences between the lobar and sublobar groups were calculated using the R function 'stddiff' (R, Version 3.3.3) [11-13].

Results

Between 2000-2015, 365 patients underwent curative lung surgery for primary lung TC. A total of 188 cases (patients with cT4 and/or cN1-2 and/or M1 disease or central tumor or follow-up <1 month) were excluded from the study. In the remaining 177 patients used for analysis, 26% (46/177) were male and the median age was 62 (IQR:54-70) years. Preoperative stage was assigned based on the available imaging studies in 165 patients (49 computed tomography scan alone, 116 computed tomography and somatostatin receptor scintigraphy and/or fluorodeoxyglucose positron emission tomography), by additional endobronchial ultrasound-guided transbronchial needle aspiration in 2, and by additional mediastinoscopy or other surgical biopsy in 10. 166 patients had clinical stage I disease and 11 stage II. All patients underwent resection with 75% (133/177) of cases undergoing lymph node sampling/lymphadenectomy. Sublobar resection was performed in 74 (20 segmentectomies and 54 wedge resections) (42%) cases and lobectomy in 103 (58%). No significant differences in terms of extent of parenchymal or lymph node resection were observed over the time period (2000-2005 vs 2006-2010 vs 2011-2015) (p=0.69 and p=0.24, respectively). The only significant difference was the higher rate of minimally invasive approaches (video/robotic-assisted thoracic surgery) performed after 2010 (p=0.003).

Patients' demographic and clinical pathological characteristics are listed in Table 1. Patient characteristics were similar between the two groups, except for higher rate of previous malignancy, lower $FEV_{1,}$ higher rate of R1 resection and smaller tumor size in the sublobar versus the lobectomy group (Table 1).

There was no postoperative mortality in either group. Postoperative morbidity was significantly higher in the lobectomy group: 23% (24/103) versus 7% (4/73) respectively (p=0.001). The most frequent complications in the lobectomy group were arrhythmia (6 patients), recurrent pleural effusion (3 patients) and major bleeding requiring reoperation (2 patients). In the sublobar resection group the most frequent complication was pneumothorax post chest tube removal (2 patients). Postoperative length of stay was significantly longer for the lobectomy group compared to the sublobar group: 6 (IQR: 4-9) versus 3 (IQR: 2-5) days (p<0.0001).

Total person-years of follow-up was 857. In the sublobar group, 6 recurrences in 301 person-years of follow-up were observed to yield a recurrence rate of 2.0 (95%CI: 0.9-4.4) per 100 person-years. Recurrence was local in 5/74 (6.8%) patients and systemic in 1/74 (1.4%) (liver). Of the 5 patients with a local recurrence 2 had wedge resection with no lymph node sampling/lymphadenectomy and 3 segmentectomy with lymph node sampling. The treatment of local recurrence in these 5 patients was completion lobectomy in 1, biologic therapy with somatostatin analogues in 2, 1 was not treated due to poor performance status and 1 was not specified. Patient with systemic recurrence received chemotherapy. Clinical and pathological characteristics of these patients are listed in Table 2.

In the lobectomy group, 4 recurrences in 508 person-years of follow-up were observed to yield a recurrence rate of 0.8 (95%CI: 0.3-2.1) per 100 person-years. All recurrences were systemic (1 liver, 1 bone, 1 contralateral lung, 1 ipsilateral pleura). In all cases lymph node sampling was performed. Of the 4 patients with recurrence treatment was chemotherapy (1), radiotherapy (1), one was not treated due to poor performance status and one was not specified. Clinical and pathological characteristics of these patients are listed in Table 2.

Although recurrence rate was slightly higher in the sublobar than in the lobectomy group, the difference was not statistically significant (p=0.15). Moreover, recurrence-free interval was also similar when comparing the two groups [5-year: 88.5% (95%CI: 79.6-98.4%) and 98.7% (95%CI: 96.1-100%) for the sublobar and the lobectomy group respectively; p=0.12]. Univariate analyses showed that none of the covariates were independent predictors of recurrence when death was a competing risk whereas age and gender were independent predictors of death when recurrence was a competing risk (Table 3; Figure 1).

During follow-up, 13/177 (7.3%) patients died. The causes of death were disease related in 2 patients and from other causes in 12. No differences in survival were observed when comparing the sublobar to the

lobectomy group [5-year survival rate: 91.7% (95%CI: 78.5-96.9%) and 97.4% (95%CI: 90.1-99.4%) respectively; *p*=0.07; Figure 2]. On univariate analyses, age correlated with overall survival (Table 4). On multivariate analyses, age remained as significant predictor of overall survival after controlling for the extent of resection.

A total of 153 patients were eligible for the propensity score matching analysis. The matched sample included 114 patients: 57 from the sublobar and 57 from the lobectomy group. Demographic and clinical characteristics of the matched cohort are listed in Table 5. The propensity score matched analysis showed no difference in recurrence-free interval and overall survival between patients undergoing sublobar resection and lobectomy. Specifically, 5-year recurrence-free survival was 92.4% (95%CI: 76.2-97.7%) and 100.0% (95%CI: 100.0-100.0%), respectively, for patients undergoing sublobar resection and lobectomy; *p*=0.57. Whereas, 5-year overall survival rate was 92.9% (95%CI: 79.4-97.7%) and 95.1% (95%CI: 81.5-98.8%), respectively, for patients undergoing sublobar resection and lobectomy; *p*=0.26.

Comment

The primary finding of this study is there was no statistically significant difference in recurrence-free and overall survival between patients undergoing sublobar resection and lobectomy for cT1-3N0M0 peripheral TC. We had hoped that by using a large multi-centered, international study methodology, we could overcome the issues of a rare disease with infrequent death rates to provide more granular data to address the question of appropriateness of sublobar resection in select patients with peripheral, TC. Unfortunately, the low rate of death and recurrence-free survival, limited the statistical power to provide a conclusive answer.

Nevertheless, our results are similar to those reported by several prior studies that concluded that sublobar resection in the management of TC did not compromise survival and that lobectomy was not superior. Two studies using the Surveillance Epidemiology and End Results database compared sublobar to lobar

resection over two different time frames and demonstrated 5-year survival rates over 80% in both studies [6-7]. However, these studies included a minority of atypical carcinoid tumors, extended resections and higher clinical stages where sublobar resection may not be utilized. Moreover, neither study was able to focus solely on peripheral lesions, which are most amenable to sublobar resection and this likely resulted in lower survival compared to our cohort. An older multi-institutional study also concluded that sublobar resection was appropriate but only included 22 wedge resections and no segmentectomies and reported a 5-year survival rate of 82% [14]. Lastly, a recent best evidence topic reviewed the literature and showed that sublobar resection resulted in similar survival and concluded that there was little evidence to support the role of lobectomy over sublobar resection for TC [8].

One of our key concerns with sublobar resection was that the observed recurrence rate was higher compared to lobectomy. We assumed that all of our local recurrences occurred along the staple line in patients undergoing either wedge resection or segmentectomy with an R1 resection. However, this was not the case. Obviously, an incompletely resected tumor (R1) creates a risk for local recurrence and a wider resection should be considered in this situation. Our recurrence pattern also suggests that the presence of N1 or N2 positive nodes and the presence of additional tumor nodules are also risk factors for local recurrence. Had these patients undergone completion lobectomy, the overall recurrence rate after sublobar resection drops from 6.8% to 2.7% (1 local and 1 systemic recurrence), which is similar to the recurrence rate (3.9%) of the lobectomy group.

The other consideration in selecting sublobar resection is tumor size. Even though our analysis did not identify tumor size or cT as independent risk factor for survival or recurrence, tumor size and location can influence a surgeon's decision to perform sublobar resection. In our series, patients undergoing sublobar resection had median tumors size of 1.2 cm with an IQR of 1.0-1.6 cm. This suggests that sublobar resection may be selected as an option when the neoplasm is less than 2.0 cm. While, no other data regarding tumor size has been reported in the literature, this size limitation is similar to an ongoing trial in

non-small cell lung cancer comparing sublobar resection vs lobectomy (CALGB 140503) [15]. It might be feasible to consider a slightly larger tumor size of 3 cm or less but this may push the limits of sublobar resection depending on which lobe and the tumor's exact location. It is the combination of a typical or low-grade neuroendocrine histology with a tumor size of less than 3 cm that has been shown to have similar survival in a recent analysis investigating carcinoid staging [4].

Sublobar resection is a reasonable option for select patients with peripheral TC tumors because our data suggest that a sublobar approach is not associated with worse recurrence-free interval or overall survival compared to lobectomy. So, who might be an ideal candidate for sublobar resection? One possible option is to utilize the factors in the ESTS prognostic model for TC to inform such a decision [16]. Older patients with a prior history of malignancy and reduced performance status with a small peripheral lesion may be best suited to undergo sublobar resection as this provides a balance with their other risks. However, the model also suggests that a young healthy female patient with no history of smoking or cancer with a small lesion has an excellent survival regardless of the extent of resection. One challenge in choosing a patient for sublobar resection is the lack of concordance between preoperative biopsy/frozen session and final pathology. In the presence of a peripheral solitary lesion, a reasonable approach is to consider a wedge resection or sublobar resection and await final pathology in order to preserve lung parenchyma [1]. This requires informing the patient about the possibility of returning to the operatory room for a completion lobectomy if the final pathology evaluation reveals atypical carcinoid histology and the patient is fit for a greater resection. In our experience, most patients, when presented with this possibility, will chose the initial limited resection approach, favoring possible lung preservation.

This study has several limitations. First, the numbers of recurrences and of deaths are infrequent and this limits the power to detect a statistically significant difference between the two types of resections. To be adequately powered, the number of observed events would need to increase approximately 10-fold.

Second, this is a retrospective study with all the limitations inherent to this study design, even though, all centers accurately reviewed each record to document the course of every patient in detail and minimize missing data. Moreover, before starting the data collection we built a common database defining each record. Third, a centralized review process for pathology was not available. However, all the results were reviewed in each center, which provides more granular data than an administrative data study. Lastly, a major strength of our study is that we report not only survival but also recurrence, completeness of resection and postoperative complications, leading to a more complete comparison between sublobar resection and lobectomy.

Sublobar resection of peripheral cT1-3N0M0 pulmonary TC results was not associated with worse surgical outcomes, freedom from recurrence or overall survival compared to lobectomy. Patients with positive regional lymph node(s) or additional tumor nodules and/or involvement of the surgical margins should be considered for lobectomy whenever feasible. In select patients, sublobar resection may be a valid treatment for peripheral TC tumors of the lung if an R0 resection is obtained.

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Table 1 Patients' demographic, clinical and pathological characteristics by resection.

	Sublobar group (n=74)	**Lobectomy group (n=103)**	***p*-value**
Median age, year (IQR)	63(54-70)	62(54-71)	0.31
Male, n (%)	16(22)	30(29)	0.26
Current/former smoker, n (%)	33(45)[a]	50(47)	0.66
ECOG performance status, n (%)			0.59
0	58(78)	86(84)	
1	11(15)	13(12)	
≥2	5(7)	4(4)	
Median FEV_1, % (IQR)	89(74-105)[b]	98(83-113)[c]	0.03
Previous malignancy, n (%)	20(27)[a]	14(14)[a]	0.15
Symptoms at diagnosis, n (%)	25(34)	46(45)	0.13
Lymphadenectomy/sampling, n (%)	39(53)	94(94)	<0.001
Median tumor size, cm (IQR)	1.2(1.0-1.6)	2.0(1.5-3.0)	<0.001
cT Status, n (%)	[a]		<0.001
cT1	78(76)	66(89)	
cT2	22(22)	2(3)	
cT3	2(2)	6(8)	
cN Status, n (%)	[a]		
cN0	102(100)	74(100)	
Clinical Stage, n (%)	[a]		0.21
I	98(96)	67(91)	
II	4(4)	7(9)	
pT Status, n (%)		[a]	0.002

pT1	64 (87)	79 (77)	
pT2	3 (4)	20 (20)	
pT3	6 (8)	3 (3)	
pT4	1 (1)	0	
Completeness of resection, n (%)		[a]	0.09
R0	69(93)	101(99)	
R1	5(7)[d]	1(1)	
pN Status, n (%)	[e]	[f]	0.99
pN0	35 (90)	84 (90)	
pN1	3 (8)	6 (6)	
pN2	1 (3)	3 (3)	
Pathological stage, n (%)	[e]	[f]	0.47
I	31(80)	79 (85)	
II	5(13)	11(12)	
III	3(8)	3(3)	

IQR=interquartile range; ECOG=Eastern Cooperative Oncology Group; FEV_1=forced expiratory volume in 1 second; [a]=data not available in 1 patient; [b]=data not available in 15 patients; [c]= data not available in 11 patients; [d]=4 wedge resection, 1 segmentectomy; [e]=data not available in 35 patients who did not have lymph node sampling/lymphadenectomy; [f]=data not available in 9 patients who did not have lymph node sampling/lymphadenectomy and in 1 who did not have this data reported.

Table 2 Clinical and pathological characteristics of patients with recurrent disease.

	Patients	Recurrence	FEV_1,%	R	Tumor size, cm	pT	pN
Sublobar	1	Local[a]	76	R1	0.9	pT1a	pNX
resection	2	Local[b]	n.a.	R0	1.6	pT1a	pN0
group	3	Local[b]	104	R0	1.8	pT1a	pN2
	4	Local[b]	n.a.	R0	1.0	pT1a	pN1
	5	Local[b]	59	R0	1.1	pT3[c]	pNX
	6	Systemic	n.a.	R0	1.4	pT1a	pNX
Lobectomy	1	Systemic	72	R0	2.4	pT1b	pN0
group	2	Systemic	n.a.	R0	6.0	pT2b	pN0
	3	Systemic	n.a.	R0	3.4	pT2a	pN0
	4	Systemic	143	R0	0.5	pT1a	pN1

FEV_1=forced expiratory volume in 1 second; R=completeness of resection; n.a.=data not available; [a]=the tumor recurred along surgical margins; [b]=the tumor recurred in the same lobe; [c]=2nd separate tumor nodule in the same lobe.

Table 3 Factors influencing recurrence and death: univariate Cox regression models stratified by site with death as a competing risk and recurrence as a competing risk, respectively.

	Recurrence (death as competing risk)		**Death** (recurrence as competing risk)	
	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age (continuous)	1.02 (0.96-1.08)	0.56	1.10 (1.05-1.15)	<.0001
Gender (Reference=Female)	0.30 (0.04-1.99)	0.21	3.02 (1.03-8.79)	0.04
Smoking history (Reference=Non-Smoker)	0.55 (0.13-2.40)	0.43	1.51 (0.46-4.93)	0.49
ECOG performance status ≥1 (reference 0)	1.74 (0.32-9.41)	0.52	3.94 (0.96-16.12)	0.06
FEV_1 (continuous)	0.98(0.95-1.02)	0.27	0.99 (0.95-1.03)	0.71
Previous malignancy (Reference=No)	2.26 (0.59-8.60)	0.23	1.11 (0.23-5.28)	0.9
Symptoms (Reference=No)	0.66 (0.19-2.33)	0.51	1.27 (0.40-4.06)	0.68
Extent of resection (Reference=Lobar)	1.82 (0.54-6.13)	0.33	2.10 (0.71-6.23)	0.18
Lymphadenectomy/Sampling (no vs yes)	0.34 (0.04-2.65)	0.30	0.41 (0.11-1.50)	0.18
Tumor size (continuous)	1.01(0.69-1.46)	0.97	0.99 (0.62-1.60)	0.98
cT2-3(reference=cT1)	1.14 (0.32-3.97)	0.84	1.90 (0.53-6.86)	0.32

HR=hazard ratio; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; FEV_1=forced expiratory volume in 1 second.

Table 4 Factors influencing overall survival: univariate Cox regression models stratified by site.

Factors	Univariate analysis	
	HR (95%CI)	***p*-value**
Age (continuous)	1.12 (1.05-1.20)	<0.001
Gender (Reference=Female)	2.34 (0.72-7.61)	0.16
Smoking history (Reference=Non-Smoker)	1.50 (0.50-4.51)	0.47
ECOG Performance Status ≥1 (reference 0)	3.31 (0.80-13.71)	0.10
FEV_1 (continuous)	0.99 (0.96-1.02)	0.44
Previous malignancy (Reference=No)	1.44 (0.38-5.40)	0.59
Symptoms (Reference=No)	0.97 (0.31-3.00)	0.96
Extent of resection (Reference=Lobar)	2.77 (0.87-8.76)	0.08
Lymphadenectomy/Sampling (Reference=No)	0.30 (0.07-1.29)	0.10
Tumor size (continuous)	0.78 (0.43-1.42)	0.41
cT2-3(reference=cT1)	1.61 (0.42-6.18)	0.84

HR=hazard ratio; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; FEV_1=forced expiratory volume in 1 second.

Table 5 Demographic, clinical and pathological characteristics of the matched cohort with standardized difference between sublobar and lobar groups for the matched and entire cohort.

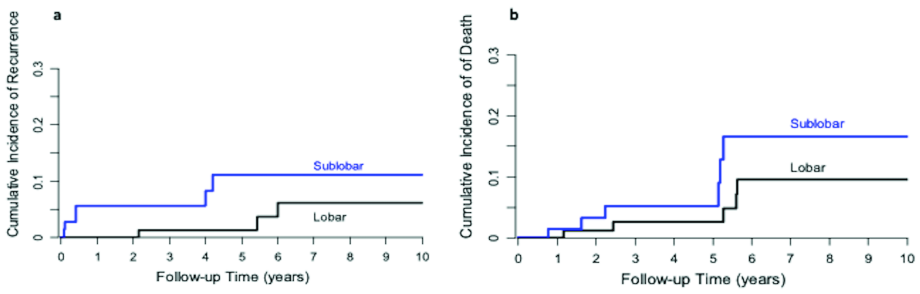
Patients' data	**Sublobar group (n=57)**	**Lobectomy group (n=57)**	**Standardized Difference[a] Matched Cohort**	**Standardized Difference[a] Entire Cohort**
Mean age, year (SD)	58.9 (18.3)	61 (10.6)	0.14	0.05
Male, n (%)	15 (26)	20 (35)	0.19	0.17
Current/former smoker, n (%)	25 (44)	28 (49)	0.11	0.07
ECOG performance status, n (%)			0.10	0.15
0	44 (77)	46 (81)		
1	10 (18)	8(14)		
$\geq$2	3 (5)	3 (5)		
Mean FEV_1, % (SD)	89.5 (25)	94.3 (23.2)	0.20	0.37
Previous malignancy, n (%)	15 (26)	11 (19)	0.17	0.34
Symptoms at diagnosis, n (%)	35 (28)	51 (39)	0.23	0.22
Mean tumor size, cm (SD)	1.3 (0.6)	1.6 (0.5)	0.47	0.95

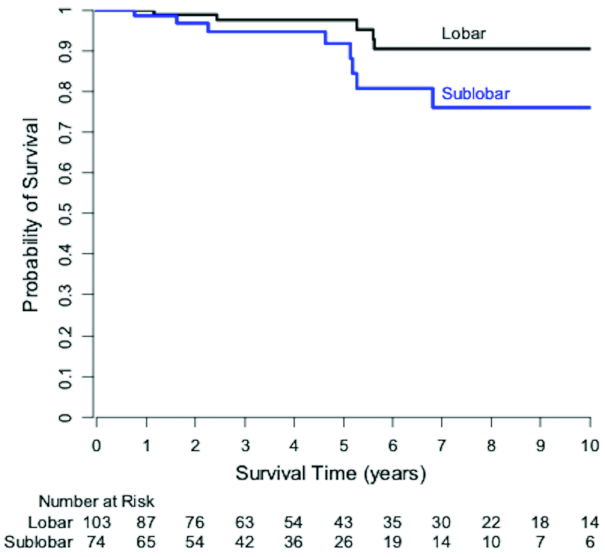
[a]Standardized difference = $(X_2\ X_1)/((S_2^{\ 2} + S_1^{\ 2})/2)^{1/2}$, X_1 and X_2 are samples means in the sublobar and lobar groups respectively, and $S_2^{\ 2}$ and $S_1^{\ 2}$ are the sample standard deviations.

Figure Legends

Figure 1 Cumulative incidence estimates for competing risks of recurrence (a) and death (b).

Figure 2 Kaplan-Meier estimates for overall survival.





Number at Risk											
Lobar	103	87	76	63	54	43	35	30	22	18	14
Sublobar	74	65	54	42	36	26	19	14	10	7	6