ORIGINAL ARTICLE

Survival rates after lobectomy versus sublobar resection for early-stage right middle lobe non-small cell lung cancer

Xiayi Lv[1] ⓘ, Jinlin Cao[1], Xiaona Dai[2] & Aizemaiti Rusidanmu[1] ⓘ

1 Department of Thoracic Surgery, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China
2 Quality Management Department, Second Affiliated Hospital of Zhejiang University , School of Medicine, Hangzhou, China

Abstract

Background: Lung cancer in the right middle lobe has a poorer prognosis than tumors located in other lobes. The optimal surgical procedure for early-stage non-small cell lung cancer (NSCLC) in the right middle lobe has not yet been elucidated. The aim of this study was to compare survival rates after lobectomy and sublobar resection for early-stage right middle lobe NSCLC.

Methods: Patients who underwent lobectomy or sublobar resection for stage IA right middle lobe NSCLC tumors ≤ 2 cm between 2004 and 2014 were identified from the Surveillance, Epidemiology and End Results database of 18 registries. Cox regression model analysis was used to evaluate the prognostic factors. The lung cancer-specific survival (LCSS) and overall survival (OS) rates between the two groups were compared.

Results: A total of 861 patients met our criteria, including 662 (76.9%) patients who underwent lobectomy and 199 (23.1%) patients who underwent sublobar resection. No statistical differences in LCSS and OS rates were identified between the groups of patients with stage IA right middle lobe NSCLC ≤ 1 cm. For tumors > 1–2 cm, lobectomy was associated with more favorable LCSS and OS rates compared to sublobar resection.

Conclusion: Lobectomy and sublobar resection deliver a comparable prognosis for patients with stage IA right middle lobe NSCLC ≤ 1 cm. For tumors > 1–2 cm, lobectomy showed better survival rates than sublobar resection.

Introduction

Lung cancer occurring in the right middle lobe is less common than tumors located in other lobes, and accounts for approximately 5% of all primary lung cancers.[1–3] Lung cancer involving the right middle lobe has a poorer prognosis because abundant lymphatic drainage extends to the mediastinal lymph nodes.[3–5] Previous studies have focused mainly on the choice of surgical procedure for all stage resectable tumors, thus the optimal surgical procedure for early-stage right middle lobe lung cancer remains unclear.

With advances in imaging techniques for lung cancer screening, the detection of early-stage non-small cell lung cancer (NSCLC) has increased,[6] and the optimal treatment for these tumors has attracted increasing attention. Lobectomy has always been considered the standard surgical procedure for patients with NSCLC.[7,8] However, several studies have reported that sublobar resection can achieve similar survival rates to lobectomy in patients with early-stage NSCLC, especially those with stage IA tumors ≤ 2 cm.[9–13]

In this study, we obtained cases from the population-based Surveillance, Epidemiology, and End Results (SEER) database of 18 registries to compare prognosis after lobectomy and sublobar resection in patients with stage IA right middle lobe NSCLC stratified on the basis of tumor size (≤ 1 cm, > 1–2 cm). Our analysis may provide the rationale for a clinical treatment recommendation for early-stage right middle lobe NSCLC.

Methods

Patient population

Patients were selected from the updated SEER 18 registries database (1973–2014) released in March 2018, using SEER*

Stat version 8.3.5 software.[14] We extracted the data of eligible patients with microscopically confirmed primary pathologic stage IA right middle lobe NSCLC (≤ 2 cm) who had undergone lobectomy or sublobar resection (segmentectomy or wedge resection) between January 2004 and December 2014. We narrowed our focus to patients who had undergone active follow-up after surgery. Patients were excluded from the study if they had received chemotherapy or radiotherapy before, during, or after surgery or if their radiation status was unknown. The SEER database query selection codes are shown in Supplementary File S1. Age at diagnosis, gender, race, year of procedure, histologic type, tumor size and grade, months of survival, cause-specific death classification, and other cause of death classification were used as variables. Tumor size was stratified into ≤ 1.0 cm and > 1–2 cm according to the proposed eighth edition of the International Association for the Study of Lung Cancer (IASLC) Tumor Node Metastasis (TNM) Classification.[15] The lung cancer-specific survival (LCSS) rate was calculated from the date of surgery to the date of death from lung cancer. The overall survival (OS) rate was calculated from the date of surgery to the date of death from any cause. Follow-up was concluded on 31 December 2014.

Statistical analysis

To compare the baseline characteristics of patients between the lobectomy and sublobar resection groups, a Student's t-test was used for continuous variables, and an χ^2 test for categorical variables. Kaplan–Meier curves were calculated to estimate LCSS and OS rates between lobectomy and sublobar resection for patients with tumors ≤ 1.0 cm and > 1–2 cm and statistical differences were obtained using the log-rank test. Survival functions were compared by univariable Cox proportional regression analysis. Predictors ($P < 0.1$) in univariable analysis were entered into multivariable Cox regression analysis, adjusting for the confounders tumor histologic type and grade. A value of $P < 0.05$ was considered statistically significant in all analyses. Hazard ratios (HRs), 95% confidence intervals (CIs), and P values for each variable were calculated using SPSS version 24.0 (IBM Corp., Armonk, NY, USA), and survival curves were drawn using Prism 7.0 (GraphPad Software, San Diego, CA, USA).

Results

Patient characteristics

A total of 861 eligible patients with stage IA right middle lobe NSCLC ≤ 2 cm were identified, including 662 (76.9%) who had undergone lobectomy and 199 (23.1%) sublobar resection. The median follow-up was 39 months (range: 0–131) and the overall five-year survival rate of the entire cohort was 75%. The baseline characteristics of the patients are summarized in

Table 1. Patients who underwent sublobar resection were more likely to have a smaller tumor ($P = 0.001$), to have a better grade ($P = 0.004$), and less likely to have nodes examined ($P < 0.001$) than those who underwent lobectomy.

Surgical procedures for tumors ≤ 1.0 cm

We identified 166 patients with stage IA right middle lobe NSCLC tumors ≤ 1.0 cm: 112 (67.5%) underwent lobectomy, and 54 (32.5%) underwent sublobar resection. Kaplan–Meier survival analysis and log-rank comparison revealed no statistical differences in the LCSS (HR 0.607, 95% CI 0.160–2.304; $P = 0.517$) or OS (HR 0.721, 95% CI 0.259–2.008; $P = 0.559$) rates between the groups (Fig 1). Multivariable Cox regression analysis of survival also showed no statistical differences in the LCSS (HR 0.994, 95% CI 0.187–5.289; $P = 0.994$) or OS (HR 0.923, 95% CI 0.280–3.038; $P = 0.895$) between the groups (Table 2).

Surgical procedures for tumors >1– 2 cm

The analysis included 695 patients with stage IA right middle lobe NSCLC tumors > 1–2 cm: 550 (79.1%) underwent

Table 1 Baseline characteristics of patients with stage IA right middle lobe non-small- cell lung cancer ≤ 2 cm

| Variables	Lobectomy ($n = 662$)	Sublobar resection ($n = 199$)	P
Mean (SD) age (years)	65.9 (10.9)	66.6 (11.3)	0.463
Gender			0.700
Female	436 (65.9)	134 (67.3)	
Male	226 (34.1)	65 (32.7)	
Race			0.944
White	547 (82.6)	164 (82.4)	
Black/other	115 (17.4)	35 (17.6)	
Year of procedure			0.165
2004–2009	276 (41.7)	72 (36.2)	
2010–2014	386 (58.3)	127 (63.8)	
Histology			0.944
Adenocarcinoma	503 (76.0)	529 (76.9)	
Squamous cell carcinoma	87 (13.1)	182 (13.1)	
Other	72 (10.9)	98 (10.1)	
Tumor size (cm)			0.001
0–1.0	112 (16.9)	54 (27.1)	
1.1–2.0	550 (83.1)	145 (72.9)	
Grade			0.004
Grade I	195 (29.5)	81 (40.7)	
Grade II	264 (39.9)	57 (28.6)	
Grade III–IV	115 (17.4)	28 (14.1)	
Not determined	88 (13.3)	33 (16.6)	
Nodes examined			< 0.001
None	43 (6.5)	102 (51.3)	
Yes	566 (85.5)	90 (45.2)	
Unknown	53 (8.0)	7 (3.5)	

SD, standard deviation.
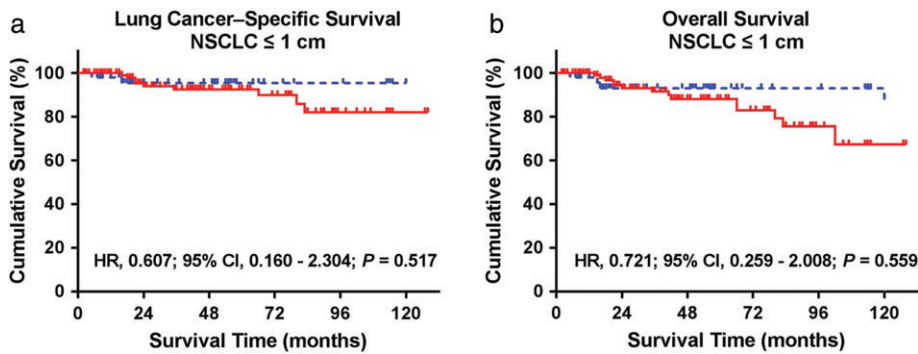
Figure 1 Kaplan–Meier curves of survival estimates for patients with stage IA right middle lobe non-small cell lung cancer (NSCLC) (≤ 1 cm) who underwent lobectomy versus sublobar resection: (**a**) lung cancer-specific survival; (**b**) overall survival. (———) Lobectomy and (·-·-·-·) Sublobar resection.

Table 2 Univariable and multivariable Cox regression analysis of patients with stage IA right middle lobe non-small cell lung cancer ≤ 1 cm

	Lung cancer-specific survival				Overall survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.031 (0.969–1.098)	**0.335**			1.039 (0.989–1.091)	**0.133**		
Gender		**0.100**				**0.044**		**0.209**
Female	Reference				Reference		Reference	
Male	2.713 (0.825–8.926)				2.610 (1.026–6.637)		1.914 (0.696–5.265)	
Race		**0.621**				**0.875**		
White	Reference				Reference			
Black/other	1.477 (0.315–6.914)				0.888 (0.202–3.905)			
Year of procedure		**0.069**		**0.120**		**0.470**		
2004–2009	Reference		Reference		Reference			
2010–2014	0.142 (0.017–1.161)		0.185 (0.022–1.554)		0.657 (0.210–2.051)			
Histology		**0.206**		**0.407**		**0.044**		**0.288**
Adenocarcinoma	Reference		Reference		Reference		Reference	
Squamous cell carcinoma	3.276 (0.839–12.792)	0.088	1.906 (0.461–7.877)	0.373	3.566 (1.284–9.905)	0.015	2.103 (0.701–6.309)	0.185
Other	0.864 (0.105–7.104)	0.892	0.428 (0.050–3.647)	0.437	1.074 (0.234–4.927)	0.926	0.696 (0.145–3.346)	0.651
Grade		**0.116**		**0.321**		**0.054**		**0.261**
Grade I	Reference		Reference		Reference		Reference	
Grade II	3.452 (0.357–33.397)	0.285	2.663 (0.267–26.514)	0.404	3.487 (0.708–17.170)	0.125	3.142 (0.629–15.699)	0.163
Grade III–IV	9.900 (1.143–85.751)	0.037	7.184 (0.717–72.009)	0.094	7.172 (1.477–34.815)	0.015	5.383 (0.995–29.116)	0.051
Not determined	2.786 (0.252–30.794)	0.403	2.770 (0.249–30.789)	0.407	1.932 (0.320–11.657)	0.473	2.320 (0.377–14.288)	0.364
Surgical procedure		**0.522**		**0.994**		**0.467**		**0.895**
Lobectomy	Reference		Reference		Reference		Reference	
Sublobar resection	0.606 (0.131–2.810)		0.994 (0.1873–5.289)		0.663 (0.219–2.006)		0.923 (0.280–3.038)	

Bold value indicates *P* < 0.05 was considered statistically significant. CI, confidence interval; HR, hazard ratio.

lobectomy and 145 (20.9%) underwent sublobar resection. Kaplan–Meier survival analysis and log-rank comparison revealed that compared to sublobar resection, lobectomy was significantly associated with better LCSS (HR 2.179, 95% CI 1.174–4.044; *P* = 0.002) and OS (HR 1.611, 95% CI 1.030–2.519; *P* = 0.015) rates in patients with stage IA right middle lobe NSCLC tumors > 1–2 cm (Fig 2). Multivariable Cox regression analysis also revealed independent associations of sublobar resection with a poorer LCSS (HR 2.070, 95% CI 1.245–3.443; *P* = 0.005) and OS (HR 1.498, 95% CI 1.019–2.200; *P* = 0.040) compared to lobectomy (Table 3).

Discussion

Despite high-quality evidence from multi-institutional randomized controlled trials evaluating the efficacy of lobectomy versus sublobar resection in NSCLC (Cancer and Leukemia Group B 140503 trial, Japan Clinical Oncology Group 0802, and West Japan Oncology Group 4607L trial),[16,17] an increasing number of retrospective reviews have demonstrated that sublobar resection is an acceptable alternative to lobectomy in patients with early-stage NSCLC.[9–13] Several recent studies have identified that sublobar resection is an effective equivalent to lobectomy for

Figure 2 Kaplan–Meier curves of survival estimates for patients with stage IA right middle lobe non-small cell lung cancer (NSCLC) (> 1–2 cm) who underwent lobectomy versus sublobar resection: (**a**) lung cancer-specific survival; (**b**) overall survival. (——) Lobectomy and (······) Sublobar resection.
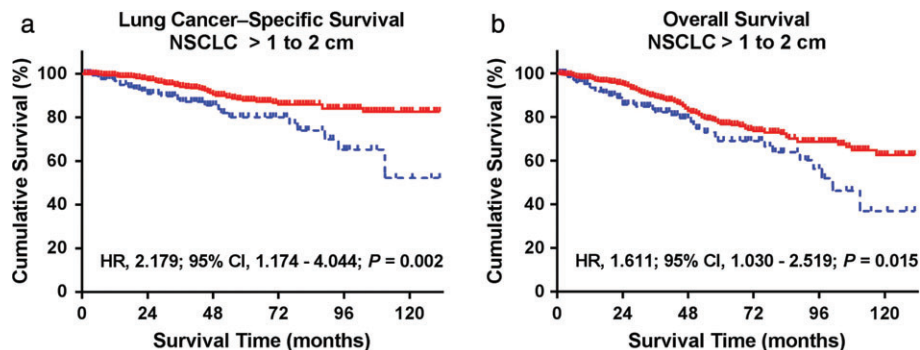

Table 3 Univariable and multivariable Cox regression analysis of patients with stage IA right middle lobe non-small cell lung cancer > 1–2 cm

	Lung cancer-specific survival				Overall survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.063 (1.035–1.092)	**< 0.001**	1.059 (1.030–1.088)	**< 0.001**	1.063 (1.043–1.083)	**< 0.001**	1.060 (1.040–1.082)	**< 0.001**
Gender		**0.002**		**0.010**		**< 0.001**		**< 0.001**
Female	Reference		Reference		Reference		Reference	
Male	2.091 (1.304–3.353)		1.900 (1.166–3.096)		2.151 (1.537–3.012)		1.965 (1.386–2.785)	
Race		0.855				0.665		
White	Reference				Reference			
Black/other	0.944 (0.506–1.760)				1.098 (0.720–1.674)			
Year of procedure		0.123				0.137		
2004–2009	Reference				Reference			
2010–2014	0.625 (0.344–1.136)				0.725 (0.475–1.107)			
Histology		0.083		0.980		**< 0.001**		0.118
Adenocarcinoma	Reference		Reference		Reference		Reference	
Squamous cell carcinoma	1.818 (1.009–3.276)	0.046	1.046 (0.569–1.922)	0.885	2.383 (1.597–3.554)	< 0.001	1.477 (0.972–2.244)	0.068
Other	1.626 (0.838–3.154)	0.151	1.061 (0.528–2.130)	0.868	1.868 (1.173–2.975)	0.009	1.419 (0.867–2.321)	0.164
Grade		**< 0.001**		**< 0.001**		**< 0.001**		**< 0.001**
Grade I	Reference		Reference		Reference		Reference	
Grade II	2.920 (1.212–7.036)	0.017	2.469 (1.003–6.078)	0.049	2.026 (1.196–3.432)	0.009	1.536 (0.888–2.657)	0.125
Grade III–IV	7.168 (2.959–17.363)	< 0.001	5.988 (2.406–14.904)	< 0.001	4.237 (2.461–7.296)	< 0.001	3.095 (1.750–5.472)	< 0.001
Not determined	3.125 (1.050–9.301)	0.041	3.358 (1.117–10.097)	0.031	1.649 (0.779–3.492)	0.191	1.688 (0.789–3.613)	0.177
Surgical procedure		**0.001**		**0.005**		**0.006**		**0.040**
Lobectomy	Reference		Reference		Reference		Reference	
Sublobar resection	2.275 (1.378–3.755)		2.070 (1.2453–3.443)		1.707 (1.170–2.492)		1.498 (1.019–2.200)	

Bold value indicates *P* < 0.05 was considered statistically significant. CI, confidence interval; HR, hazard ratio.

selected patients with stage IA NSCLC.[11,18,19] Moreover, a recent study using SEER data demonstrated that sublobar resection is not inferior to lobectomy, even in patients aged ≤ 35 years with stage IA NSCLC.[20] However, in clinical practice, sublobar resection is more acceptable for patients with tumors ≤ 2 cm.[9,10,12] Sublobar resection has the advantages of preserving better lung function, with fewer postoperative complications and a lower mortality rate.[21,22] However, few reports have focused on the therapeutic efficacy for early-stage NSCLC arising from the right middle lobe.

The right middle lobe is the smallest lobe of the lung, surrounded by two large lobes with abundant lymphatic drainage extending to the mediastinal lymph nodes. Lymphatic drainage from the middle lobe of the lung involves right paratracheal, right peribronchial, pretracheal, subcarinal, perioesophageal, and left peribronchial lymph nodes.[23] Several studies have demonstrated the differences in lymph node metastasis rates and prognosis depending on tumor location.[24–26] Right middle lobe NSCLC is more likely to involve lymph node metastasis and has a significantly poorer prognosis than lung cancer in other lobes.[3–5] Mazza

et al. advised that prospective studies of right middle lobe resection associated with either extended lymph node dissection or wider resection margins are needed to evaluate efficacy in these patients.[2]

In this study we compared survival rates after lobectomy and sublobar resection for stage IA right middle lobe NSCLC ≤ 2 cm. Tumor size was stratified based on the IASLC proposal to alter the existing T stage in the eighth TNM classification into: T1a (≤ 1 cm) and T1b (> 1–2 cm).[15] We found that lobectomy and sublobar resection yield equivalent survival rates for tumors ≤ 1 cm. However, for tumors > 1–2 cm lobectomy achieved better survival rates than sublobar resection. We also found that patients who underwent sublobar resection were more likely to have a smaller tumor and a better grade than those who underwent lobectomy. Based on these results, the choice of surgical procedure for stage IA right middle lobe NSCLC needs to be conservative compared to the other lobes. Sublobar resection for selected patients with stage IA right middle lobe NSCLC tumors ≤ 1 cm and lobectomy or more extensive resection for tumors > 1 cm is recommended.

There are several inherent limitations in the SEER database. First, the database is retrospective, thus selection bias is inevitable. Although we used rigorous selection procedures and multivariate analyses to balance the apparent biases among the arms, potential biases such as information regarding patients' performance status, visceral pleural invasion, and lymphovascular invasion remain unknown. Second, the SEER database does not provide specific information about ground glass opacity (GGO) components in pulmonary nodules. GGOs are frequently encountered in lung adenocarcinoma, and their presence has significant prognostic and predictive value in patients with early-stage NSCLC.[27–29] According to the eighth edition TNM classification, the invasive component of GGO dominant, rather than the whole tumor size, is thought to be a better measure for T staging and prognostic prediction.[29,30] Third, although our study focused on patients who were pathologically diagnosed with stage IA right middle lobe NSCLC ≤ 2 cm, the number of negative lymph nodes removed between the two groups may have influenced the outcomes.[31,32] Most patients treated via lobectomy may undergo systematic lymph node dissection, whereas patients undergoing sublobar resection may not undergo lymph node dissection or only receive lymph node sampling as a result of their earlier tumor staging or poorer physical status. However, a randomized study demonstrated that mediastinal lymph node dissection does not improve survival in early-stage NSCLC patients.[33] Finally, recurrence-free survival rates and indications for sublobar resection in the SEER database are unclear; patients who undergo sublobar resection tend to have poorer general status or radiologically noninvasive cancer, thus our results may be conservative. Additional high-level continuous large-scale registry analyses or randomized controlled trials are needed to verify our results and may help to determine clinical treatment recommendations for early-stage right middle lobe NSCLC.

Acknowledgments

Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

File S1. Program selection codes for SEER database queries.