Survival After Wedge Resection Versus Lobectomy for Stage Ia Second Primary NSCLC with Previous Lung Cancer-Directed Surgery

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Research

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Abstract

Background: The surgical procedure for early-stage second primary non-small cell lung cancer (SP-NSCLC) remains controversial, especially for patients with previous lung cancer-directed surgery. This study aims to compare the survival after wedge resection and lobectomy for these patients.

Methods: Stage IA SP-NSCLC patients with clear information were searched from the Surveillance, Epidemiology, and End Results (SEER) database. Cox proportional hazard model, competing risk model and Kaplan-Meier survival curve were used to describe the survival difference between wedge resection and lobectomy. A 1:1 propensity score matching (PSM) method was also performed to reduce the potential impact of confounding factors between the two groups.

Results: Of the 320 eligible stage IA SP-NSCLC patients included in this study, 238 (74.4%) patients underwent wedge resection and 82 (25.6%) patients received lobectomy. The 5-year overall survival (OS) was 61.3% with wedge resection and was 66.1% with lobectomy. Both before and after PSM, wedge resection showed similar survival rate and lung cancer specific mortality as lobectomy in the entire cohort. Additionally, in all subgroup analyses, wedge resection demonstrated equivalent survival to lobectomy. However, in the female, sub-lobectomy for FPLC and interval ≤ 24 months subgroups, wedge resection had a higher lung cancer specific mortality than lobectomy (fine-gray test, all $p < 0.05$).

Conclusion: In conclusion, wedge resection was comparable to lobectomy in OS with all relevant parameters. In a few cases, lung cancer specific mortality in wedge resection group was higher than that in lobectomy group.

Introduction

With the advancement in early detection technology of lung cancer and the close postoperative follow-up of lung cancer patients, the detection rate of second primary lung cancer (SPLC) has been growing. The efficacy and safety of surgical treatment for second primary non-small cell lung cancer (SP-NSCLC) patients have also been demonstrated in several studies [1–7]. For the patients with resectable early-stage NSCLC, lobectomy remains the accepted standard surgical procedure [8]. However, with the continuous improvement of medical technology and treatment concept, the treatment of lung cancer has become individualized and standardized. Two “maxima”, namely, maximum removal of tumor and maximum preservation of normal lung tissue, have become the development direction of lung tumor surgery. For lung cancer patients with previous lung cancer-directed surgery, in addition to having less lung tissue, they would also have a higher risk of developing another new primary lung cancer than the general population [9]. Clinically, it may be difficult to accurately identify the second tumor as primary, recurrent or metastatic. Since 1975, when Martini and Melamed came up with a diagnostic criteria [10] for multiple primary lung cancer (MPLC), there have been more and more reports on MPLC. In the SEER database, there is also a data set on multiple primary events. The relevant information can be available to us from this website (<https://seer.cancer.gov/tools/mphrules/>). As with the Martini-Melamed criteria [10],

SEER also considers tumor histology, location, and time since initial diagnosis to determine multiple primary events. However, there are still no clear treatment guidelines and plans for MPLC. Surgery, to our knowledge, is still currently the only treatment offering potential cure and long-term survival in patients with SPLC. Despite significant breakthroughs in the diagnosis and treatment of lung cancer, it has not been determined whether lobectomy has a better survival advantage than wedge resection for patients with early-stage SP-NSCLC, especially those with history of radical surgery for the first primary lung cancer (FPLC). A recent SEER-based study [11] has reported that SPLC demonstrated similar survival with lobectomy and wedge resection. However, the study did not delve into the differences in survival between the two procedures in various specific circumstances. Faced with the complexity of patients' clinical situation, further stratified analysis is still necessary. Thus, combining with a variety of methods, this study compared the survival after lobectomy and wedge resection using overall survival (OS) and lung cancer specific mortality as indicators.

Materials And Methods

Data Source and Patient Selection

Using SEER*Stat 8.3.5 software (<http://seer.cancer.gov/seerstat/>), we extracted data from the SEER database, which was open to the public for research purposes. 320 patients with dual primary non-small cell lung cancers were extracted from the SEER database. Patients meeting the following criteria were included in this study: ☐ Year of diagnosis was between 2007 and 2015. ☐ Site and morphology. Site recoded ICD-O-3/WHO 2008: Lung and Bronchus. ☐ Events (1 of 124 Selected for Display): Lung and Bronchus. Furthermore, cases with three or more primary lung cancers and whose first or second primary cancer was small cell lung cancer (SCLC) were excluded from this study. And cases without clear status, survival time, and American Joint Committee on Cancer (AJCC) stage were also removed. The 8th edition of the TNM staging system was applied in the present study. The collected variables included age at diagnosis, sex, "race record", "primary site-labeled", laterality, "ICD-O-3 Hist/behav, malignant", tumor size, "months since index" (the time interval between two primary tumors), AJCC Stage, "COD to site recode", "Rx Sumn-Surg Prim Site (1998+)", "radiation record" and "chemotherapy record".

Description of Surgery Types and Histological Types

In this study, sub-lobectomy includes wedge resection (SEER surgery codes: 21) and segmental resection (SEER surgery codes: 22). Lobectomy means lobectomy with mediastinal lymph node dissection (SEER surgery codes: 33) and pneumonectomy contains complete pneumonectomy, sleeve pneumonectomy, standard pneumonectomy, total pneumonectomy, resection of whole lung (SEER surgery codes: 55) and with mediastinal lymph node dissection (radical pneumonectomy) (SEER surgery codes: 56). Other surgery codes were excluded in our study. The detailed SEER surgery codes can be viewed from the website (https://seer.cancer.gov/manuals/2018/AppendixC/Surgery_Codes_Lung_2018.pdf#search=surgery%20lung).

In addition, by the following International Classification of Diseases for Oncology histology codes, we categorized histology into three groups: □ adenocarcinoma (8140, 8250-8255, 8260, 8310, 8323, 8480-8481, 8550, and 8574); □ squamous cell carcinoma (8070-8074 and 8083); □ other NSCLCs (8012-8013, 8020, 8022, 8033, 8046, 8230 and 8246). The present study did not include the histological type of SCLC (8041 and 8045), either FPLC or SPLC.

Statistical Analysis

In this study, categorical variables were represented by number (percentage), and continuous variables were expressed as mean (standard deviation, SD). The Chi-square test or Fisher's exact test were used to compare differences in baseline characteristics, as appropriate. Cox proportional hazard model, competitive risk model and Kaplan-Meier survival curve were performed to describe the survival difference between wedge resection and lobectomy. Statistical comparisons between survival curves were performed with the log-rank test. Propensity score matching (PSM) was performed using the "nearest" method with a caliper of 0.05 to reduce the potential impact of confounding factors between the two groups. The "MatchIt" package in R was adopted to calculate propensity scores. In addition, subgroup analysis was also performed to better characterize the prognostic differences between the two operations (wedge resection and lobectomy). All analyses were performed in version 3.6.0 of R software. A p value less than 0.05 was accepted for statistical significance.

Results

Patients characteristics

We identified 320 patients with stage IA SP-NSCLC diagnosed from 2007 to 2015. Wedge resection (n = 238, 74.4%) was performed on significantly more patients than lobectomy (n = 82, 25.6%). The detailed clinicopathological features were shown in **Table 1**. Of the 320 patients included, 190 were female and 130 were male. 68.95% (131/190) of the females and 82.31% (107/130) of the males underwent wedge resection for the second NSCLC. The average age of patients with lobectomy and wedge resection was similar, 68.34 ± 8.48 and 68.44 ± 9.05 years, respectively. Adenocarcinoma was predominant in the lobectomy group and wedge resection group (72.0% and 72.7%, respectively). Wedge resection was performed in the overwhelming majority of patients (45/52) when the two lesions were located in the ipsilateral different lobes. There were 259 patients with two lesions in the bilateral, and only 27.03% (70/259) chose lobectomy for the second lesion. Additionally, it could also be observed that regardless of the surgical procedures (sub-lobectomy, lobectomy or pneumonectomy) performed on the first lesion, wedge resection was performed on the second lesion significantly more than lobectomy. In lobectomy group, the patients with tumor diameter less than 10 mm were the least, accounting for 14.6%. In wedge resection group, the patients with tumor diameter ranging from 20 to 30 mm were the least, accounting for 10.9%.

Survival after lobectomy versus wedge resection before and after PSM

To reduce the potential impact of differences in clinical features between the lobectomy group and the wedge resection group on outcomes, we performed PSM. After 1:1 matching, the differences in clinical variables between the two groups were significantly reduced, as shown in **Table 2** and **Figure 1**. To further compare survival after lobectomy and wedge resection, OS and lung cancer specific mortality were used as the main prognostic indicators. We found that OS after wedge resection and lobectomy were comparable both before (log-rank test, $p = 0.724$; **Figure 2A**) and after (log-rank test, $p = 0.308$; **Figure 2B**) PSM. In the entire cohort ($n = 320$), the 5-year OS was 61.3% with wedge resection and was 66.1% with lobectomy. The two were also comparable in lung cancer specific mortality (fine-gray test, all $p > 0.05$), as shown in **Figure 3**.

Survival comparison based on subgroup analysis

To further clarify the survival after lobectomy and wedge resection in different clinical subgroups, we conducted subgroup analysis based on age, sex, histology, grade, tumor size, tumor distribution, time interval between two primary cancers, and type of first operation. We found that in all clinical subgroups, wedge resection demonstrated equivalent OS to lobectomy (all $p > 0.05$; **Figure 4**). Similarly, wedge resection and lobectomy had similar lung cancer specific mortality in most clinical subgroups (**Figure 5**). However, in the female, sub-lobectomy for FPLC and interval ≤ 24 months subgroups, wedge resection had a higher lung cancer specific mortality than lobectomy (fine-gray test, all $p < 0.05$; **Figure 5D, 5L, 5N**).

Discussion

At present, there is no uniform standard for the surgical method of MPLC. Some scholars [12-14] have reported that lobectomy should be the first choice for the second primary tumor, followed by segment or wedge resection. However, sublobectomy, including segmentectomy and wedge resection, has also been studied as the main surgical method [3, 15]. At the cost of damaging more pulmonary functional reserve compared with segmentectomy or wedge resection, lobectomy can remove more intrapulmonary lymph nodes and significantly reduce the recurrence rate of tumor [8], which can undoubtedly affect the postoperative quality of life of patients, especially those with history of lung cancer-directed surgery. For stage IA SP-NSCLC patients with previous lung cancer-directed surgery, to date, it has not been fully understood whether lobectomy is more conducive to survival than wedge resection. Although several retrospective studies [16-18] and a recent SEER-based study [11] have found that lobectomy did not show a significant survival advantage over sublobectomy for SPLC patients, these researches still lacked an in-depth study on SPLC patients who have undergone radical surgery for primary lung cancer. To better solve this problem and provide references for further clinical research and practice, we carried out this study.

In the present study, wedge resection demonstrated equivalent OS to lobectomy, both before and after PSM. Similar results were observed in all clinical subgroups. Unlike the previous studies [4, 15, 19, 20], participants in this study were patients with stage IA SP-NSCLC with previous NSCLC resection. Besides, the sublobectomy mentioned in their studies not only included wedge resection, but also other

surgical methods such as segmental resection. To our knowledge, although wedge resection and segmentectomy were classified as sublobectomy, there were significant differences between them. Wedge resection was defined as non-anatomical resection of the lung parenchyma, and was not necessary to determine the histological structure of bronchus and pulmonary vessels. While segmentectomy was the anatomical resection of the lung parenchyma, and required the disconnection of segmental bronchus, segmental vessels and segmental parenchyma. In view of the different anatomical pathways of wedge resection and segmentectomy, it was necessary to discuss the two surgical methods separately. Different from the general sublobectomy in previous studies, the sublobectomy in this study was limited to wedge resection. This study further confirmed that stage IA SP-NSCLC patients with previous lung cancer-directed surgery demonstrated similar OS with lobectomy and wedge resection.

In clinical practice, the relative location of two primary tumors had an extremely important influence on the final selection of surgical procedure. Generally speaking, when two tumor lesions were in the ipsilateral different lobes, lobectomy for the second lesion tended to lead to pneumonectomy, which was a risk factor affecting the prognosis of patients [4, 14, 18]. This study found that when the two lesions were in the ipsilateral different lobes, wedge resection demonstrated equivalent OS to lobectomy. Thus, we believe that in this case, lobectomy for the second lesion may not result in a greater survival benefit than wedge resection. In agreement with our research, Ishigaki T and his colleagues [4] suggested that if FPLC and SPLC were on the same side of the lung and FPLC received lobectomy, sublobectomy should be a priority for the SPLC. Additionally, surgical choice regarding the optimal extent of resection for a second primary tumor on the contralateral side, is also controversial. Yang et al. [16] reported that a limited resection (sublobectomy) for the contralateral second tumor did not have a negative effect on OS in these patients with stage I bilateral MPLC. This was also confirmed by the findings of this study. Similarly, other previous studies [1, 14, 17, 18] did not demonstrate a significant difference in prognosis with respect to lobectomy versus sublobectomy for the second tumor. The choice of surgery for the second primary tumor is challenging for thoracic surgeons, especially for patients with history of lobectomy or pneumonectomy. In addition to the maximum preservation of pulmonary functional reserve, maximum tumor resection is also an oncological principle to be followed. An adequate margin (>2 cm or the tumor diameter) is a prerequisite for sublobectomy. In a number of studies [17, 21], sublobectomy has been proved to have similar therapeutic effect to lobectomy for patients with early single primary lung cancer. Therefore, we believe that under strict patient screening criteria, sublobectomy including wedge resection is worthy of choice for thoracic surgeons.

Overall, this study provided evidence that wedge resection produced similar survival rate to lobectomy in stage IA SP-NSCLC patients with previous lung cancer-directed surgery, and wedge resection and lobectomy had similar lung cancer specific mortality in most cases. A correct understanding of the difference in OS and lung cancer specific mortality between the two surgical approaches might help clinicians make more reasonable choices.

This study still has the following limitations. First, much of the detailed information (such as imaging findings, pulmonary function index, related basic diseases, etc.), which may be an important reference for

clinicians to make treatment decisions, is not available in the SEER database. Second, the number of patients with stage IA SP-NSCLC included in this study was still relatively small, and the postoperative follow-up time was also short. Third, the nature of a retrospective study, and the strict screening criteria in this study inevitably resulted in selection bias. Considering the deficiency of retrospective analysis, further prospective analysis is recommended.

In conclusion, wedge resection demonstrated equivalent survival to lobectomy in Stage IA second primary NSCLC patients with lung cancer-directed surgery. Considering the limitations of the present study, relevant prospective studies are still necessary.

Abbreviations

FPLC

first primary lung cancer; SPLC:second primary lung cancer; SP-NSCLC:second primary non-small cell lung cancer; MPLC:multiple primary lung cancer; OS:overall survival; RMST:restricted mean survival time; SCLC:small cell lung cancer; AJCC:American Joint Committee on Cancer; ICD-O:International Classification of Diseases for Oncology; SEER:Surveillance, Epidemiology, and End Results.

Declarations

Author contribution

CS and WH: designed the study. CS, SL and WH: reviewed relevant literature and drafted the manuscript. CS, QW and YW conducted all statistical analyses. All authors read and approved the final manuscript.

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This study used the Surveillance, Epidemiology, and End Results (SEER) database. We acknowledge the efforts of the National Cancer Institute in the creation of the database.

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Availability of data and materials

The datasets supporting the conclusion of this article are included within the article. We have been authorized by the SEER database.

Ethics approval and consent to participate

The SEER database is an open-access cancer database that only contains de-identified patient data. Therefore, this study was exempted from the approval of the institutional review board of Zhongnan

Hospital of Wuhan University.

Consent for publication

Not applicable.

Competing on interests

The authors declare no conflicts of interest.

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Tables

Table 1
Characteristics of patients in wedge resection group and lobectomy group before PSM.

Characteristics	Subgroups	Lobectomy (No., %)	Wedge resection (No., %)	P value
Total	—	82 (100%)	238 (100%)	
Age (years)	Continuous (mean, SD)	68.34 (8.48)	68.44 (9.05)	0.930
Sex	Female	59 (72.0)	131 (55.5)	0.011
	Male	23 (28.0)	107 (45.0)	
Race	White	72 (87.8)	201 (84.5)	0.724
	Black	6 (7.3)	20 (8.4)	
	Others	4 (4.9)	17 (7.1)	
Histology of SPLC	Adenocarcinoma	59 (72.0)	173 (72.7)	0.317
	Squamous CC	21 (25.6)	50 (21.0)	
	Other NSCLCs	2 (2.4)	15 (6.3)	
Tumor distribution	Same lobe	5 (6.1)	4 (1.7)	0.014
	Ipsilateral different lobes	7 (8.5)	45 (18.9)	
	Bilateral	70 (85.4)	189 (79.4)	
Grade of SPLC	I / well	25 (30.5)	55 (23.1)	0.232
	II / moderate	28 (34.1)	109 (45.8)	
	III/IV poor/undifferentiated	23 (28.0)	53 (22.3)	
	Unknown	6 (7.3)	21 (8.8)	
Interval (months)	Continuous (mean, SD)	36.15 (21.96)	32.86 (21.38)	0.234
Surgery types of FPLC	Sublobectomy	13 (15.9)	35 (14.7)	0.581
	Lobectomy	69 (84.1)	200 (84.0)	
	Pneumonectomy	0 (0.0)	3 (1.3)	
AJCC stage of FPLC	Stage I	68 (82.9)	173 (72.7)	0.274
	Stage II	6 (7.3)	23 (9.7)	
	Stage III	7 (8.5)	33 (13.9)	
	Stage IV	1 (1.2)	9 (3.8)	

Characteristics	Subgroups	Lobectomy (No., %)	Wedge resection (No., %)	P value
Tumor size of SPLC	< 10 mm	12 (14.6)	86 (36.1)	< 0.001
	≥ 10 mm, < 20 mm	50 (61.0)	126 (52.9)	
	≥ 20 mm, ≤ 30 mm	20 (24.4)	26 (10.9)	
Radiation for SPLC	Unknown/No	81 (98.8)	225 (94.5)	0.191
	Yes	1 (1.2)	13 (5.5)	
Chemotherapy for SPLC	Unknown/No	80 (97.6)	228 (95.8)	0.698
	Yes	2 (2.4)	10 (4.2)	

Table 2
Characteristics of patients in wedge resection group and lobectomy group after PSM.

Characteristics	Subgroups	Lobectomy (No., %)	Wedge resection (No., %)	P value
Total	—	70 (100%)	70 (100%)	
Age (years)	Continuous (mean, SD)	68.59 (8.18)	69.30 (9.01)	0.624
Sex	Female	49 (70.0)	52 (74.3)	0.706
	Male	21 (30.0)	18 (25.7)	
Race	White	60 (85.7)	61 (87.1)	0.771
	Black	6 (8.6)	4 (5.7)	
	Others	4 (5.7)	5 (7.1)	
Histology of SPLC	Adenocarcinoma	50 (71.4)	52 (74.3)	0.925
	Squamous CC	18 (25.7)	16 (22.9)	
	Other NSCLCs	2 (2.9)	2 (2.9)	
Tumor distribution	Same lobe	1 (1.4)	4 (5.7)	0.366
	Ipsilateral different lobes	6 (8.6)	7 (10.0)	
	Bilateral	63 (90.0)	59 (84.3)	
Grade of SPLC	I / well	18 (25.7)	21 (30.0)	0.494
	II / moderate	25 (35.7)	29 (41.4)	
	III/IV poor/undifferentiated	22 (31.4)	14 (20.0)	
	Unknown	5 (7.1)	6 (8.6)	
Interval (months)	Continuous (mean, SD)	35.10 (21.24)	36.67 (21.90)	0.667
Surgery types of FPLC	Sublobectomy	12 (15.7)	16 (22.9)	0.392
	Lobectomy	59 (84.3)	54 (77.1)	
	Pneumonectomy	0 (0.0)	0 (0.0)	
AJCC stage of FPLC	Stage I	57 (81.4)	57 (81.4)	0.847
	Stage II	6 (8.6)	4 (5.7)	
	Stage III	6 (8.6)	7 (10.0)	
	Stage IV	1 (1.4)	2 (2.9)	

Characteristics	Subgroups	Lobectomy (No., %)	Wedge resection (No., %)	P value
Tumor size of SPLC	< 10 mm	10 (14.3)	11 (15.7)	0.960
	≥ 10 mm, < 20 mm	45 (64.3)	45 (64.3)	
	≥ 20 mm, ≤ 30 mm	15 (21.4)	14 (20.0)	
Radiation for SPLC	Unknown/No	69 (98.6)	70 (100.0)	1.000
	Yes	1 (1.4)	0 (0.0)	
Chemotherapy for SPLC	Unknown/No	68 (97.1)	70 (100.0)	0.476
	Yes	2 (2.9)	0 (0.0)	

Figures

A Before PSM Wedge resection group VS. lobectomy group

B After PSM

Figure 1

Density distribution of propensity score before (A) and after (B) PSM in patients with wedge resection and lobectomy. Before PSM, there was a significant asymmetry in the density distribution of propensity scores between the two groups, while propensity score distributions were similar between the two groups after PSM.

Figure 2

Overall survival after wedge resection versus lobectomy before (A) and after (B) PSM.

Figure 3

Lung cancer specific mortality after wedge resection versus lobectomy before (A) and after (B) PSM.

Figure 4

The survival differences between the two operations based on subgroup analyses of factors with prognostic significance.

Figure 5

The differences in lung cancer specific mortality between the two operations based on subgroup analyses of factors with prognostic significance.