Original Article

Therapeutic options for resectable second lung tumor after previous pneumonectomy: a SEER database analysis

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Background: Therapeutic options for patients with second lung tumor (SLT) after previous pneumonectomy for lung cancer are sparsely reported and controversial. This study aims to compare the short- and long-term outcomes of different treatment patterns in patient with resectable postpneumonectomy SLT.

Methods: Patients received previous pneumonectomy and subsequently occurred resectable SLT were extracted from the Surveillance, Epidemiology, and End Results (SEER) database [1998–2016]. Treatment related mortality was compared using the Pearson chi-square test. Univariate and multivariate Cox regression analyses were performed to identify the independent prognostic factors for cancer-specific survival (CSS) and overall survival (OS).

Results: Ninety-nine patients met the selection criteria with 5-year CSS and OS rates of 60.8% and 53.7%, respectively: 23 patients received no lung resection (nLR) and 76 patients received lung resection (LR). There was no statistically significant difference between nLR group and LR group in both treatment related mortality (0.0% *vs.* 2.6%, P=0.432), CSS (58.3% *vs.* 61.7%, P=0.633) and OS (55.3% *vs.* 53.3%, P=0.635). Patients with subsequent adenocarcinoma (P=0.001) and smaller tumor size of SLT (P<0.001) were more likely to receive LR treatment. In the LR subgroup analysis, patients received sublobar resection (SLR) had better CSS [hazard ratio (HR): 0.381, 95% confidence interval (CI): 0.176–0.827, P=0.030] and OS (HR: 0.562, 95% CI: 0.287–1.100, P=0.051) than those received lobectomy.

Conclusions: SLR or non-surgical resection is reasonable therapeutic option for patients with resectable SLT after previous pneumonectomy to achieve long-term survival, with acceptable treatment related mortality.

Keywords: Lung cancer; pneumonectomy; contralateral lung tumor; survival

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Introduction

On April 1933, Evarts A. Graham performed the first successful one-stage pneumonectomy in a gynecologist with pulmonary squamous cell carcinoma (pathological T2N1M0, stage IIB) who survived for nearly 30 years, as well as the first lung resection (LR) in treatment of lung cancer (1). However, because of a high postoperative complication rate (3.4–54.0%) and mortality (3.0–26.0%), one-sided entire lung removal is recommended only for

patients with centrally-located non-small cell lung cancer (NSCLC), if a margin-negative resection can not be achieved by lung-sparing surgical technique (2-6). Even though, pneumonectomy still accounts for approximately 10% of all lung cancer resections (7).

Patients who have been successfully removed for an initial primary lung cancer remain a continued risk for development of a second primary lung tumor or intrapulmonary metastasis (1.0–2.0% risk per patient per year) (8,9). Repetitive LR with lymph node evaluation for second lung tumor (SLT) can offer a chance of long-term survival (9). Nevertheless, for patients who have underwent one-sided pneumonectomy, respiratory management during contralateral lung surgery is a technical difficulty because of the unfulfillable one-lung ventilation (4,5). Moreover, second LR after previous pneumonectomy will bring non-negligible risk of operative complication rate (0.0–77.7%) and mortality (0.0–33.3%), mainly owing to the respiratory reserve, physical status, and pathophysiological changes (5,10-18). Of note, several retrospective series have suggested that local non-surgical treatments, including stereotactic body radiation therapy (SBRT), conventional radiotherapy (CRT), interventional therapy (IVT) etc., can not only ensure the treatment related safety, but also bring long-term survival in patients with postpneumonectomy SLT (4,19-26). Although the respective advantages and survival outcomes of non-surgical treatment and surgical resection for SLT arising postpneumonectomy have been described detailedly in the published literatures, the comparative analysis between different therapeutic patterns remain unreported (17,27).

In this population-based study, we sought to conduct the comparison of short- and long-term outcomes between different therapeutic options for resectable contralateral lung tumor after prior pneumonectomy. In addition, the potential factors associated with the therapeutic options and the independent prognostic factors for cancer-specific survival (CSS) and overall survival (OS) were identified. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1781).

Methods

Patients selection

Patients who underwent previous pneumonectomy (surgery primary site codes: 40, 50–56, 65–66, 70) for lung cancer [*International Classification of Disease for Oncology*, 3rd edition (ICD-O-3): lung and bronchus] and subsequently occurred a contralateral lung tumor between 1998 and 2016 were extracted from the Surveillance, Epidemiology, and End Results (SEER) database (November 2018 submission) by using SEER*Stat 8.3.6.1. Thereafter, patients with cancer-directed surgery codes for SLT corresponding to "surgery performed", "recommended but not performed", and "recommended" records were identified as resectable cases and included into the study cohort. In addition, patients with incomplete follow-up information and tumor staging were excluded. The selection flow is illustrated in *Figure 1*. This retrospective study based on the National Cancer Institute's SEER database was approved by the institutional review board at Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. NCC201802006) and individual consent for this retrospective analysis was waived. All authors stated that the study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

Covariates and endpoints

The continuous variable of age at SLT diagnosis was divided into two brackets (≤60/>60 years old). According to the modified classification criteria for SLT proposed by the American College of Chest Physicians (ACCP) Guidelines, all histologically different SLTs were defined as metachronous. For histologically same SLTs, the SLTs were also defined as metachronous if the interval between initial pneumonectomy and SLTs has lasted 4 years or longer without systemic metastases (28). In addition, we recategorized the tumor-node-metastasis (TNM) staging documented in the SEER database according to the eighth edition of the TNM classification for lung cancer. No lung resection (nLR) included chemotherapy (CT) alone, radiotherapy (RT) alone, and IVT. Patients received sublobar resection [SLR, including non-anatomical wedge resection (WR) and anatomical segmentectomy (S)] or lobectomy were grouped into LR.

Survival time was calculated from the date of SLT diagnosis to the date of death or the last follow-up. Only deaths caused by lung cancer were recorded as censored cases in the CSS analysis, but the OS analysis included any cause of death. Treatment related mortality was defined as any death within 30 days after the treatment for SLT.

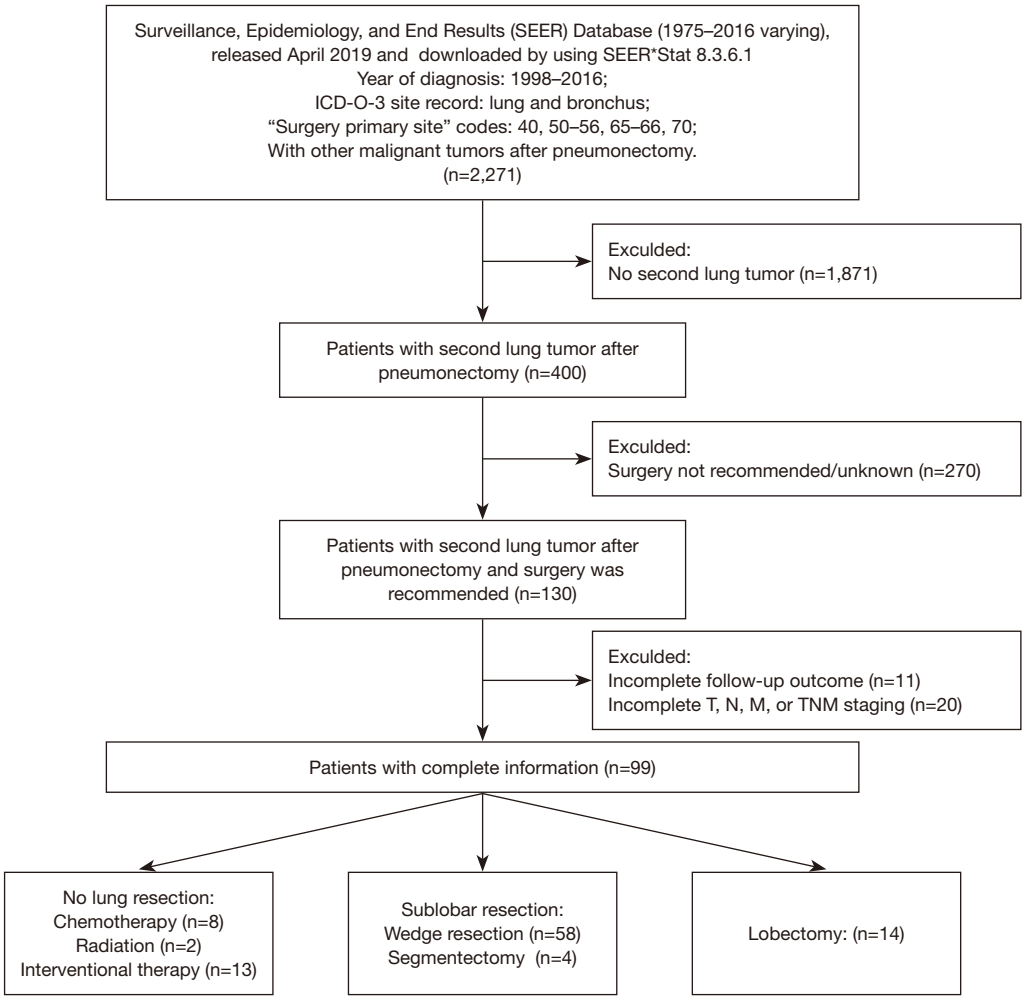

Figure 1 Flowchart of patient selection from the SEER database. SEER, Surveillance, Epidemiology, and End Results; ICD-O-3, *International Classification of Disease for Oncology*, 3rd edition; TNM, tumor-node-metastasis.

Statistical analysis

The optional cutoff values for interval time were determined by using the X-tile software (version 3.6.1, copyright Yale University 2003). Continuous variables were presented as mean ± standard deviation (SD) and compared by the student's *t*-test, and categorical variables were showed as numbers (frequency percentages) and compared using the Pearson chi-square test or Fisher's exact test. Cox regression model was applied to identify the independent prognostic factors associated with CSS and OS in both univariate and multivariate analyses.

All above statistical analyses were performed by the SPSS 25.0 software (IBM SPSS, Armonk, NY, USA) and all P value less than 0.05 at two sides was considered statistically significant difference. Additionally, the Kaplan-Meier survival curves were plotted by using the Graphpad Prism software (version 7.0).

Results

Patient demographics

A total of 400 patients (400 of 10,801, 3.7%) who underwent previous pneumonectomy occurred a contralateral lung tumor, but surgical resection was not recommended for most of the patients (67.5%). Finally, only 99 patients met the selection criteria, including 23 patients received nLR treatment and 76 patients underwent LR treatment (*Table 1* and *Figure 1*). The median interval time between prior

Table 1 Comparison of clinicopathological variables between the nLR group and LR group

Variables	nLR (n=23)	LR (n=76)	P value
Age at pneumonectomy (years), mean ± SD	64.13±9.37	63.57±9.68	0.600
Age at SLT (years), mean ± SD	66.22±12.19	64.13±9.52	0.392
Female sex, n (%)	8 (34.8)	29 (38.2)	0.962
Race, n (%)			0.263
White	20 (87.0)	72 (94.7)	
Black	1 (4.3)	3 (3.9)	
Other	2 (8.7)	1 (1.3)	
Interval time between pneumonectomy and SLT (months), mean ± SD	53.11±37.30	40.69±37.95	0.170
Left-sided pneumonectomy, n (%)	15 (65.2)	48 (63.2)	0.857
Histology of pneumonectomy, n (%)			0.875
Squamous cell carcinoma	15 (65.2)	28 (36.8)	
Adenocarcinoma	8 (34.8)	48 (63.2)	
Grade of pneumonectomy, n (%)			0.790
I, well	1 (4.3)	3 (3.9)	
II, moderately	8 (34.8)	35 (46.1)	
III, poorly	8 (34.8)	25 (32.9)	
IV, undifferentiated	1 (4.3)	4 (5.3)	
Unknown	5 (21.7)	9 (11.8)	
Radiation with pneumonectomy, n (%)	7 (30.4)	21 (28.0)	0.821
CT with pneumonectomy, n (%)	7 (30.4)	20 (26.3)	0.903
TNM staging of pneumonectomy, n (%)			0.305
I	8 (34.8)	16 (21.1)	
II	7 (30.4)	24 (31.6)	
III	8 (34.8)	32 (42.1)	
IV	0 (0.0)	4 (5.3)	
Histology of SLT, n (%)			0.001
Squamous cell carcinoma	11 (47.8)	18 (23.7)	
Adenocarcinoma	3 (13.0)	43 (56.6)	
Neuroendocrine tumor	1 (4.3)	5 (6.6)	
Adenosquamous carcinoma	0 (0.0)	2 (2.6)	
Other/unknown	8 (34.8)	8 (10.5)	
Grade of SLT			
I, well	0 (0.0)	9 (11.8)	0.019
II, moderately	7 (30.4)	24 (31.6)	
III, poorly	6 (26.1)	29 (38.2)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	nLR (n=23)	LR (n=76)	P value
IV, undifferentiated	0 (0.0)	2 (2.6)	
Unknown	10 (43.5)	12 (15.8)	
Tumor size of SLT, mean ± SD	45.72±19.96	27.85±13.77	<0.001
TNM staging of SLT, n (%)			0.160
I	14 (60.9)	55 (72.4)	
II	4 (17.4)	6 (7.9)	
III	5 (21.7)	10 (13.2)	
IV	0 (0.0)	5 (6.6)	
Type of SLT, n (%)			0.212
Metastasis	6 (26.1)	33 (43.4)	
Metachronous	17 (73.9)	43 (56.6)	
Treatment of SLT, n (%)			
CT	8 (34.8)	–	
RT	2 (8.7)	–	
IVT	13 (56.5)	–	
WR	–	58 (76.3)	
S	–	4 (5.3)	
Lobectomy	–	14 (18.4)	

nLR, no lung resection; LR, lung resection; SD, standard deviation; SLT, second lung tumor; CT, chemotherapy; TNM, tumor-node-metastasis; RT, radiotherapy; IVT, interventional therapy; WR, wedge resection; S, segmentectomy.

pneumonectomy and SLT was 35.57 (range, 1.01–183.63) months, and the majority of the SLTs were metachronous (60.6%). In nLR group, most of the patients (13 of 23, 56.5%) received interventional ablation treatment and 34.8% of the patients were given systematic CT alone. Among patients who underwent additional LR, 14 patients received lobectomy and 62 received SLR (including WR =58, S =4).

Factors associated with therapeutic options

Therapeutic options for resectable SLTs after previous pneumonectomy were not interfered with the initial clinicopathological characteristics. Patients in LR group were more likely to be subsequent adenocarcinoma (P=0.001), to have a smaller tumor size of SLT (P<0.001; *Table 2*). In addition, compared with patients received lobectomy for SLT, those received SLR were more likely to be white race (P=0.027), to have longer interval time (P=0.043) and early stage (stage I/II, P= 0.037; Table S1).

Survival outcomes

Overall, only 2 patients (2.0%) died with 30 days after the treatment for SLT. There was no difference in treatment related mortality between nLR group and LR group (0.0% *vs.* 2.6%, P=0.432). The median follow-up time for the whole patients was 60 (range, 1–219) months with 5-year CSS and OS rates of 60.8% and 53.7%, respectively.

Separately, there was no statistically significant difference between nLR and LR in both CSS (P=0.633) and OS (P=0.635; *Table 2*). In univariate analyses, sex, interval time between pneumonectomy and SLT, TNM staging of SLT, and type of SLT showed significant associations both with CSS and OS (all P<0.05; *Table 2*). After adjusting these potential predictors in multivariate Cox regression models, female (P=0.006 and 0.001, respectively; *Figure 2A,B*), interval time greater than 53 months (P=0019 and 0.003, respectively; *Figure 2C,D*), and early stage of SLT (I–II; P<0.001 and <0.001, respectively; *Figure 2E,F*) were

Table 2 Univariate Cox regression analysis of the whole patients with resectable SLT after previous pneumonectomy

Variables	N	CSS		OS	
		5-year rate (%)	P value	5-year rate (%)	P value
Age at SLT			0.346		0.219
≤60 years old	35	63.5		57.0	
>60 years old	64	59.3		51.8	
Sex			0.019		<0.001
Female	37	74.9		69.7	
Male	62	49.8		44.2	
Race			0.774		0.929
White	92	61.0		53.4	
Black	4	50.0		50.0	
Other	3	66.7		66.7	
Year of first lung tumor diagnosis			0.978		0.995
1998–2003	53	58.6		52.6	
2004–2009	39	63.4		55.5	
2010–2014	7	71.4		57.1	
Year of SLT diagnosis			0.078		0.091
1998–2003	19	41.4		36.1	
2004–2009	51	60.0		51.0	
2010–2014	29	71.4		61.7	
Interval time between pneumonectomy and SLT			<0.001		<0.001
≤53 months	68	47.9		40.3	
>53 months	31	87.0		83.6	
Histology of pneumonectomy			0.513		0.035
Squamous cell carcinoma	63	63.2		59.8	
Adenocarcinoma	36	56.4		43.0	
Grade of pneumonectomy			0.080		0.045
I–II	38	48.6		41.1	
III–IV	47	63.1		54.5	
Unknown	14	85.7		85.7	
Radiation with pneumonectomy			0.754		0.772
Yes	20	60.4		57.9	
No	79	62.7		52.7	
CT with pneumonectomy			0.763		0.670
Yes	27	59.4		52.9	
No/unknown	72	61.5		54.0	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	N	CSS		OS	
		5-year rate (%)	P value	5-year rate (%)	P value
TNM staging of pneumonectomy			0.133		0.691
I–II	55	67.3		57.4	
III–IV	44	52.7		49.0	
Laterality of SLT			0.513		0.035
Right	63	63.2		59.8	
Left	36	56.4		43.0	
Tumor size of SLT			0.883		0.251
≤30 mm	65	61.4		51.6	
>30 mm	34	59.9		57.8	
Histology of SLT			0.370		0.713
Squamous cell carcinoma	46	53.8		47.0	
Adenocarcinoma	29	60.0		51.0	
Neuroendocrine tumor	2	33.3		33.3	
Adenosquamous carcinoma	6	100.0		50.0	
Other/unknown	16	80.4		75.0	
Grade of SLT			0.411		0.610
I–II	40	57.0		46.6	
III–IV	37	69.9		61.4	
Unknown	22	54.5		54.5	
TNM staging of SLT			<0.001		<0.001
I–II	79	67.2		61.0	
III–IV	20	34.6		25.0	
Type of SLT			0.007		0.009
Metastasis	39	45.7		39.3	
Metachronous	60	70.1		62.9	
Treatment of SLT			0.633		0.635
nLR	23	58.3		55.3	
LR	76	61.7		53.3	

SLT, second lung tumor; CSS, cancer-specific survival; OS, overall survival; CT, chemotherapy; TNM, tumor-node-metastasis; nLR, no lung resection; LR, lung resection.

identified as strong predictors for better CSS and OS in SLT after previous pneumonectomy (*Table 3*).

In the LR subgroup analysis, the SLR group had better CSS in statistics (P=0.030, *Figure 3A*), and better OS in trend (P=0.051, *Figure 3B*) than the lobectomy group. Additionally, in the univariate analyses of OS, sex, interval time, TNM staging of SLT, radiation with SLT, CT with SLT, type of SLT were also identified as independent predictors (Table S2). Similar results (except for the sex variable) were obtained from the univariate analyses of CSS

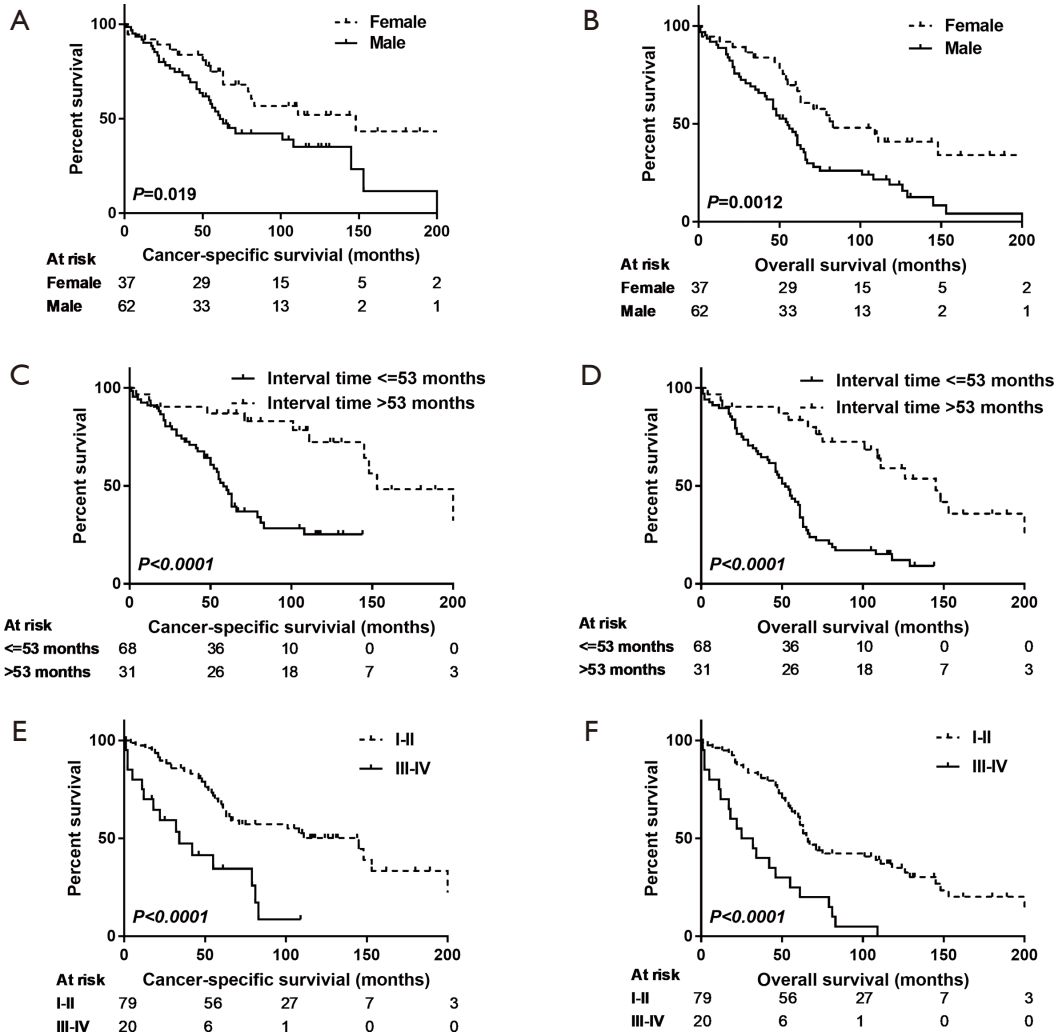

Figure 2 CSS (A,C,E) and OS (B,D,F) of the whole patients based on sex, interval time between pneumonectomy and SLT, and TNM staging of SLT. CSS, cancer-specific survival; OS, overall survival; SLT, second lung tumor; TNM, tumor-node-metastasis.

(Table S2). The above variables were further examined in the multivariate Cox regression models (Table S3). Interval time greater than 53 months (P=0.003 for CSS; P=0.001 for OS), early stage of SLT (I–II; P=0.026 for CSS; P=0.011 for OS), CT with SLT (P=0.008 for CSS, *Figure 3C*; P=0.001 for OS, *Figure 3D*), and SLR for SLT (P=0.015 for CSS; and P=0.093 for OS) were significantly associated with longer survival, whereas the female was a significant predictor only for better OS (P=0.003).

Discussion

In this population-based analysis, patients with one-sided entire lung removal for initial lung cancer showed a 3.7% risk of having a SLT, with median interval time to development longer than 3 years. Compared with those received non-surgical treatment, patients received secondary LR had similar treatment-related mortality and long-term survival. Additionally, patients in SLR subgroup showed longer CSS in statistics and better OS in trend than those in lobectomy subgroup.

According to the latest National Cancer Comprehensive Network and ACCP Guidelines for NSCLC, if patients who are able to withstand definitive local therapy, lung-sparing resection is recommended as a primary therapeutic option for SLT to obtain long-term survival (2,28). Even though, the proportion of patients received additional LR for SLT following a surgical resection

Table 3 Multivariate Cox regression analysis of the whole patients with resectable SLT after previous pneumonectomy

Variables	CSS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex				
Male	Reference		Reference	
Female	0.415 (0.223–0.773)	0.006	0.394 (0.226–0.689)	0.001
Interval time between pneumonectomy and SLT				
>53 months	Reference		Reference	
≤53 months	3.070 (1.201–7.851)	0.019	3.105 (1.417–6.550)	0.003
Histology of pneumonectomy				
Squamous cell carcinoma			Reference	
Adenocarcinoma			0.669 (0.203–2.202)	0.508
Grade of pneumonectomy				
Unknown			Reference	
I–II			1.023 (0.824–1.221)	0.134
III–IV			1.488 (0.872–2.538)	0.145
Laterality of SLT				
Right			Reference	
Left			2.118 (0.678–6.618)	0.197
TNM staging of SLT				
III–IV	Reference		Reference	
I–II	0.282 (0.142–0.557)	<0.001	0.252 (0.139–0.462)	<0.001
Type of SLT				
Metachronous	Reference		Reference	
Metastasis	1.339 (0.700–2.560)	0.377	1.109 (0.626–1.965)	0.722

SLT, second lung tumor; CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; TNM, tumor-node-metastasis.

of the initial lung cancer remains low, because the therapeutic options of these patients are affected by the patients' respiratory reserve, physical status, clinical stage, and pathophysiological changes etc. Zhang *et al.* stated that about 17.3% (1,171 of 6,751) of the patients who underwent previous lobectomy or bilobectomy were given the surgical treatment for SLT (9). However, up to date, only approximately 169 cases received subsequent LR on a single remaining lung were reported in the literatures (*Table 4*). Grodzki *et al.* reported that the percentage of patients had the chance of secondary LR for postpneumonectomy SLT was 18.0% (18 of 100) in their single center (12). Another study based on the SEER database revealed that about 13.7% of patients (63/459) who underwent previous pneumonectomy for initial lung cancer went on to secondary LR during a 25-year period, which was the largest series in the published literatures (5). Similar proportion (76 of 400, 19.0%) was observed in present study as well. Although secondary resection for SLT arising postpneumonectomy can bring acceptable long-term survival (5-year OS rate: 25.0–66.6%), the high perioperative morbidity (0.0–77.7%) and mortality (0.0–33.3%) are not negligible (*Table 4*) (5,10-18). Before 2009, surgical resection was performed in all reported patients with postpneumonectomy SLT, including 80 WRs (77.7%), 16 Ss (15.5%), and 7 lobectomies (6.8%). However, in the recent

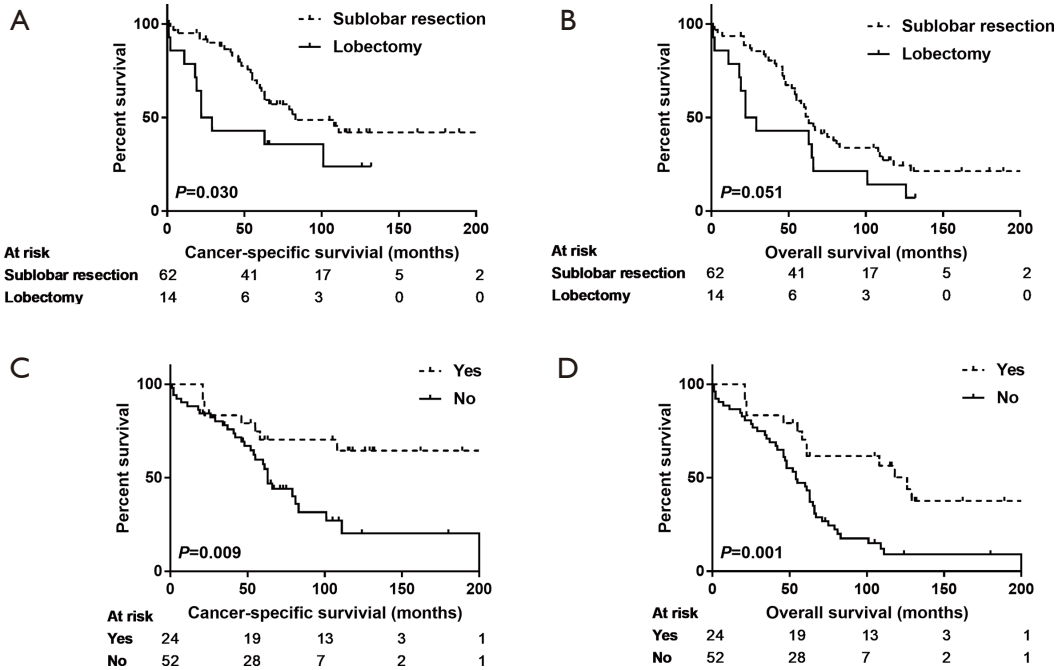

Figure 3 CSS (A,C) and OS (B,D) of the patients who underwent LR treatment based on CT with SLT and surgical procedure of SLT. CSS, cancer-specific survival; OS, overall survival; LR, lung resection; CT, chemotherapy; SLT, second lung tumor.

10 years, most of the patients (296/365, 81.1%) received non-surgical therapy, i.e., CT, RT, and IVT (*Table 4*).

In recent years, evidence from several larger study series indicated that, because of a good local control and low toxicity, SBRT can be a reasonable option for medically inoperable patients with early-stage lung cancer (2,28). The early literature on SBRT for postpneumonectomy SLT was reported by Haasbeek *et al.* in the year of 2019 (*Table 4*) (26). Although half of the 15 cases from two centers accompanied with severe chronic obstructive pulmonary disorder (COPD), only two patients occurred grade ≥3 toxicity and the actuarial 2-year rates of local control and OS were 91% and 100%, respectively (26). Subsequently, his colleagues, Senthi *et al.*, updated the late toxicity after long-term follow-up, and supplemented the additional outcomes of modern RT technique, including conventional RT (n=1), hypofractionated RT (n=6), and SBRT (n=20) (23). Similarly, only three patients experienced grade 3 or higher radiation pneumonitis and the actuarial 3-year rates of local control and OS were 92% and 63.0%, respectively (23). What's more, no RT related death was observed in the above two retrospective studies (23,26). Recently, the largest cohort of 122 patients who underwent RT for inoperable postpneumonectomy SLT retired from the SEER database was published by Ayub *et al.*, and the mortality within 90-day after RT was 4.9% and a median OS for patients receiving RT was 25.0 months (3-year OS rate, 34%) (4).

Another therapeutic modality, IVT (including thermal ablation and cryotherapy) is also recommended for patients with medically inoperable early-stage and multiple lung cancer to achieve definitive local therapy (2,28). Nevertheless, up to now, only 27 patients with postpneumonectomy SLT received thermal ablation treatment in the published literatures (24,25). Taken together, the treatment related complications included mild parenchymal hemorrhages during ablation (n=5), pneumothoraces (n=10), pulmonary infection (n=1), and limited hemoptysis (n=2); and two procedural deaths (2/27, 7.4%) occurred (24,25). In addition, the 2- and 3-year OS rate after ablation for postpneumonectomy SLT, reported in the above two pilot studies, were 71.4% and 30.0%, respectively, which was consistent with the present study based on SEER database (2-year OS rate, 69.2%; and 3-year OS rate, 44.0%). Of note, according to the horizontal comparison of these contemporaneous literatures, local recurrence of patients with interventional ablation treatment (2-year local recurrence rate, 5.0–80.4%) was higher than that of those with RT (2-year local recurrence

Table 4 Published data of therapeutic options for SLT after previous pneumonectomy

Year	Authors	N	Median age [range], years	Stage	Therapeutic option	Treatment related complication rate (%)	Treatment related mortality rate (%)	OS rate (%)
2020	Present study	23	66.0 [49–79]	I–III	CT =8, RT =2, IVT =13	NR	0.0	55.3 (5-year)
2020	Present study	76	63.0 [41–83]	I–IV	WR =58, S =4, L =14	NR	2.6	53.3 (5-year)
2019	Goto *et al.* (11)	3	66.0 [43–69]	I	S =3	0.0	0.0	66.6 (5-year)
2018	Ayub *et al.* (4)	191	68.4 [58–78]	I–IV	RT =122, no RT =69	NR	14.7	27.0 (3-year)
2017	Ayub *et al.* (5)	63	67.5 [NR]	I–IV	SLR =56, L =7	NR	11.1	52.0 (3-year)
2015	Giaj Levra *et al.* (20)	9	74.0 [63–82]	I	SBRT =9	77.7	0.0	NR
2015	Testolin *et al.* (19)	12	NR	I–IIIA	SBRT =12	33.3	0.0	80.0 (2-year)
2014	Simpson *et al.* (22)	2	69.0 [68–70]	II	SBRT =2	0.0	0.0	NR
2014	Thompson *et al.* (21)	13	NR	II–IIIB	SBRT =13	15.4	7.7	61.0 (2-year)
2013	Senthi *et al.* (23)	27	74.0 [59–91]	I–II	SBRT =20, CRT =7	11.1	0.0	63.0 (3-year)
2011	Hess *et al.* (25)	15	64.0 [42–82]	II–IV	IVT =15	31.0	0.0	71.4 (2-year)
2011	Sofocleous *et al.* (24)	12	63.0 [44–81]	NR	IVT =12	33.3	19.0	30.0 (3-year)
2009	Haasbeek *et al.* (26)	15	NR	I	SBRT =15	26.7	0.0	91.0 (2-year)
2008	Grodzki *et al.* (12)	18	57.0 [44–69]	IIB–III	WR =18	38.9	0.0	44.0 (5-year)
2004	Terzi *et al.* (13)	14	64.0 [51–74]	I–IV	WR =12, S =2	21.0	0.0	30.0 (5-year)
2002	Donington *et al.* (10)	24	64.0 [43–84]	I–IV	WR =20, S =3, L =1	44.0	8.3	40.0 (5-year)
1996	Spaggiari *et al.* (14)	13	64.0 [40–79]	I–III	WR =9, S =3, L =1	30.8	0.0	46.0 (3-year)
1995	Massard *et al.* (18)	4	57.0 [51–61]	I–II	WR =1, S =1, L =2	50.0	0.0	25.0 (5-year)
1993	Westermann *et al.* (15)	8	NR	NR	WR =7, L =1	25.0	12.5	63.0 (3-year)
1992	Levasseur *et al.* (16)	7	59.0 [51–63]	I–III	WR =5, S=1, L =1	NR	33.3	NR
1985	Kittle *et al.* (17)	15	53.0 [32–73]	III	WR =8, S =6, L =1	NR	6.7	35.0 (3-year)

SLT, second lung tumor; OS, overall survival; NR, no reported; CT, chemotherapy; RT, radiotherapy; IVT, interventional therapy; WR, wedge resection; S, segmentectomy; L, lobectomy; SLR, sublobar resection; SBRT, stereotactic body radiation therapy; CRT, conventional radiotherapy.

rate, 0.0–35.5%). To sum up, RT or interventional ablation treatment may be attractive and safe therapeutic option for patients with postpneumonectomy SLTs, especially for those with medically inoperable SLT.

Much of the nonrandomized clinical data on patients with resectable SLT after previous lobectomy or bilolobectomy demonstrated that surgical resection plus lymph nodes dissection, no matter SLR or lobectomy, was associated with significantly longer survival compared with non-surgery (2,9,28). Similarly, through reviewing the two largest series on postpneumonectomy SLT extracted from the SEER database and all reported by Ayub *et al.* (*Table 4*), we found that patients with resectable SLT receiving surgical resection had higher treatment related mortality (12.7% *vs.* 4.9%) and 3-year OS rate (54.0% *vs.* 34.0%) than those with unresectable SLT who receiving RT (4,5). However, to our knowledge, there is no special focus on the comparison between non-surgery and surgery for patients with resectable SLT after previous pneumonectomy. In the present study on patients with resectable postpneumonectomy SLT, compared with those received non-surgical treatment, patients received secondary LR had

similar treatment-related mortality and long-term survival. We speculate that patients recommended for surgery for SLT in the SEER database may have satisfactory pulmonary function reserve, good performance status, and early-stage SLT; therefore, they could well tolerate the treatment related complications to obtain long-term survival. However, surgical specimens could help oncologists to more accurately evaluate the genetic mutations and tumor microenvironment to guide the subsequent targeted therapy and immunotherapy (2,28). For the extent of resection, almost all literatures on patients received surgery for postpneumonectomy SLT demonstrated that patients in SLR group had a higher OS than those in lobectomy group in trend (*Table 4*). Similar result was verified in this population-based study, and the significant difference was firstly found.

Undeniably, our study has several limitations. First, this retrospective, small sample cohort study is abstracted from a national database and the year of diagnosis spans nearly 20 years, which inevitably cause selection bias. Second, the main factors, such as pulmonary function reserve, performance status, postpneumonectomy complications, location of SLT (central or peripheral) *et al.*, that may effect the surgeon's intention to select therapeutic options are not available within the SEER database. Third, individual RT techniques, doses and fractions, CT regimens, and interventional ablation techniques, which may affect the therapeutic efficacy, are not documented in the SEER database as well. Fourth, limited by the number of patients who underwent CT alone, or RT alone for postpneumonectomy SLT, the outcomes of the different therapeutic options are not further compared.

Conclusions

Aggressive treatment, no matter surgical resection or not, should be considered for patients with resectable SLT after previous pneumonectomy. Moreover, more accurate diagnosis of pathology, advanced molecular and genomic detections, and long-term survival can be obtained with limited resection, especially in patients with early-stage disease (I–II) and interval time to development of SLT longer than 4 years.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective study based on the SEER database was approved by the Surveillance Research Program in National Cancer Institute's Division of Cancer Control and Population Sciences (DCCPS) (reference number: 12101-Nov2018). This retrospective study based on the National Cancer Institute's SEER database was approved by the institutional review board at Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. NCC201802006) and individual consent for this retrospective analysis was waived. All authors stated that the study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Comparison of clinicopathological variables between the SLR group and lobectomy group

Variables	SLR (n=62)	Lobectomy (n=14)	P value
Age at pneumonectomy (years), mean ± SD	63.45±9.22	67.14±10.58	0.192
Age at SLT (years), mean ± SD	63.06±9.57	65.86±10.16	0.333
Female sex, n (%)	26 (41.9)	3 (21.4)	0.262
Race, n (%)			0.027
White	61 (98.4)	11 (78.6)	
Black	1 (1.6)	2 (14.3)	
Other	0 (0.0)	1 (7.1)	
Interval time between pneumonectomy and SLT (months), mean ± SD	44.85±37.94	22.24±33.24	0.043
Left-sided pneumonectomy, n (%)	38 (61.3)	10 (71.4)	0.553
Histology of pneumonectomy, n (%)			0.687
Squamous cell carcinoma	38 (61.3)	10 (71.4)	
Adenocarcinoma	24 (38.7)	4 (28.6)	
Grade of pneumonectomy, n (%)			0.307
I, well	2 (3.2)	2 (14.3)	
II, moderately	22 (35.5)	3 (21.4)	
III, poorly	27 (43.5)	8 (57.1)	
IV, undifferentiated	3 (4.8)	0 (0.0)	
Unknown	8 (12.9)	1 (7.1)	
Radiation with pneumonectomy, n (%)	14 (22.6)	2 (14.3)	0.745
CT with pneumonectomy, n (%)	16 (25.8)	4 (28.6)	0.832
TNM staging of pneumonectomy, n (%)			0.154
I	14 (22.6)	2 (14.3)	
II	22 (35.5)	2 (14.3)	
III	24 (38.7)	8 (57.1)	
IV	2 (3.2)	2 (14.3)	
Lymph nodes dissection, n (%)			0.153
Yes	38 (61.3)	12 (85.9)	
No	24 (38.7)	2 (14.3)	
Number of lymph nodes dissection, mean ± SD	11.71±10.27	14.25±8.21	0.440
Number of positive lymph nodes, mean ± SD	1.00±1.71	2.92±3.40	0.083
Histology of SLT, n (%)			0.513
Squamous cell carcinoma	15 (24.2)	9 (64.3)	
Adenocarcinoma	34 (54.8)	3 (21.4)	
Neuroendocrine tumor	5 (8.1)	0 (0.0)	
Adenosquamous carcinoma	2 (3.2)	0 (0.0)	
Other/unknown	6 (9.7)	2 (14.3)	
Grade of SLT, n (%)			0.512
I, well	8 (12.9)	1 (7.1)	
II, moderately	19 (12.9)	5 (35.7)	
III, poorly	25 (40.3)	4 (28.6)	
IV, undifferentiated	2 (3.2)	0 (0.0)	
Unknown	8 (12.9)	4 (28.6)	
Tumor size of SLT, mean ± SD	27.86±13.88	27.81±13.74	0.991
TNM staging of SLT, n (%)			0.037
I	49 (79.0)	6 (42.9)	
II	3 (4.8)	3 (21.4)	
III	7 (11.3)	3 (21.4)	
IV	3 (4.8)	2 (14.3)	
Type of SLT, n (%)			0.371
Metastasis	25 (40.3)	8 (57.1)	
Metachronous	37 (59.7)	6 (42.9)	
Radiation with SLT, n (%)	18 (29.5)	3 (21.4)	0.782
CT with SLT, n (%)	20 (32.3)	4 (28.6)	0.789

SLR, sublobar resection; SD, standard deviation; SLT, second lung tumor; CT, chemotherapy; TNM, tumor-node-metastasis.

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Table S2 Univariate Cox regression analysis of patients who underwent surgical resection for SLT after previous pneumonectomy

Variables	N	CSS		OS	
		5-year rate (%)	P value	5-year rate (%)	P value
Age at SLT			0.557		0.210
≤60 years old	27	61.2		55.6	
>60 years old	49	62.0		52.0	
Sex			0.121		0.009
Female	29	75.4		69.0	
Male	47	52.2		43.3	
Race			0.368		0.375
White	72	53.4		62.3	
Black	3	33.3		33.3	
Other	1	100.0		100.0	
Interval time between pneumonectomy and SLT			<0.001		<0.001
≤53 months	55	50.2		41.5	
>53 months	21	90.2		85.2	
Histology of pneumonectomy			0.891		0.098
Squamous cell carcinoma	48	62.7		58.1	
Adenocarcinoma	28	59.5		44.9	
Grade of pneumonectomy			0.185		0.221
I–II	29	48.9		41.4	
III–IV	38	68.2		56.9	
Unknown	9	77.8		77.8	
Radiation with pneumonectomy			0.448		0.980
Yes	16	61.9		55.6	
No	60	61.1		52.7	
CT with pneumonectomy			0.753		0.275
Yes	20	59.9		58.1	
No/unknown	56	67.4		51.5	
TNM staging of pneumonectomy			0.199		0.991
I–II	40	66.1		54.5	
III–IV	36	56.6		51.8	
Laterality of SLT			0.891		0.098
Right	48	62.7		58.1	
Left	28	59.5		44.9	
Tumor size of SLT			0.485		0.166
≤30 mm	61	61.1		51.8	
>30 mm	15	64.2		59.3	
Histology of SLT			0.458		0.859
Squamous cell carcinoma	18	67.8		55.6	
Adenocarcinoma	43	56.8		47.5	
Neuroendocrine tumor	5	40.0		20.0	
Adenosquamous carcinoma	2	100.0		50.0	
Other/unknown	8	62.5		75.0	
Grade of SLT			0.123		0.482
I–II	33	60.6		48.5	
III–IV	31	71.8		63.6	
Unknown	12	41.7		41.7	
TNM staging of SLT			<0.001		0.001
I–II	61	68.0		59.9	
III–IV	15	36.0		26.7	
Lymph nodes dissection			0.751		0.416
Yes	50	62.5		56.0	
No	26	60.5		48.4	
Radiation with SLT			0.016		0.018
Yes	21	56.2		66.3	
No	54	74.7		49.2	
CT with SLT			0.009		0.001
Yes	24	70.4		70.4	
No/unknown	52	57.3		45.3	
Type of SLT			0.019		0.026
Metastasis	33	50.1		41.7	
Metachronous	43	70.3		62.1	
Surgical procedure of SLT			0.030		0.051
SLR	62	65.8		55.5	
Lobectomy	14	42.9		42.9	

SLT, second lung tumor; CSS, cancer-specific survival; OS, overall survival; CT, chemotherapy; TNM, tumor-node-metastasis; SLR, sublobar resection.

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Table S3 Multivariate Cox regression analysis of patients who underwent surgical resection for SLT after previous pneumonectomy

Variables	CSS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex				
Male			Reference	
Female			0.346 (0.172–0.694)	0.003
Interval time between pneumonectomy and SLT				
>53 months	Reference		Reference	
≤53 months	6.157 (1.849–20.504)	0.003	4.617 (1.912–11.148)	0.001
TNM staging of SLT				
III–IV	Reference		Reference	
I–II	0.421 (0.197–0.902)	0.026	0.371 (0.173–0.796)	0.011
Radiation with SLT				
Yes	Reference		Reference	
No	0.832 (0.295–2.347)	0.728	0.848 (0.378–1.905)	0.690
CT with SLT				
Yes	Reference		Reference	
No/unknown	3.912 (1.419–10.785)	0.008	4.384 (1.867–10.293)	0.001
Type of SLT				
Metachronous	Reference		Reference	
Metastasis	1.378 (0.663–2.865)	0.728	1.222 (0.660–2.261)	0.523
Surgical procedure of SLT				
Lobectomy	Reference		Reference	
SLR	0.381 (0.176–0.827)	0.015	0.562 (0.287–1.100)	0.093

SLT, second lung tumor; CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; CT, chemotherapy; TNM, tumor-node-metastasis; SLR, sublobar resection.

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