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Prognostic study for survival outcome following the treatment of second primary lung cancer in patients with previously resected non-small cell lung cancer

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Keywords
LASSO regression; non-small cell lung cancer; second primary lung cancer; survival analysis.

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Abstract

Background: Patients who have previously undergone surgical resection of initial primary lung cancer (IPLC) are at high risk of developing second primary lung cancer (SPLC). There are still no standard treatments for SPLC. This study aimed to identify the prognostic factors and compare survival between the different SPLC treatment groups.

Methods: SPLC patients in the Surveillance, Epidemiology, and End Results (SEER) database between 2007 and 2016 were retrospectively reviewed. Prognostic factors for SPLC were identified, using the least absolute shrinkage and selection operator (LASSO) regression and univariate Cox analysis to select variables for multivariate Cox analysis. Kaplan-Meier method plus log-rank test and restricted mean survival time (RMST) were used to compare survival outcome.

Results: A total of 665 SPLC patients were finally enrolled into the study. Multivariate Cox regression analysis revealed that male vs. female (HR = 1.82, 95% CI: 1.29–2.59, $P = 0.001$), tumor size of SPLC ≥1 cm vs. <1 cm (HR = 1.80, 96% CI: 1.07–3.02, $P = 1.028$), IPLC characteristics of squamous cell carcinoma vs. adenocarcinoma (HR = 1.89, 95% CI: 1.17–3.04, $P = 0.009$), clinical stage II vs. stage I (HR = 2.60, 95% CI: 1.08–6.27, $P = 0.033$), and T2 stage vs. T1 stage (HR = 1.68, 95% CI: 1.04–2.72, $P = 0.034$) indicated worse survival. SPLC patients demonstrated a five-year survival rate of 68.6% and a five-year RMST of 49.4 months. The choice of surgical procedure (wedge resection, segmentectomy and lobectomy) for both IPLC and SPLC had no significant effect on prognosis ($P > 0.05$). Patients that received radiotherapy for SPLC also demonstrated similar survival when compared with those that underwent surgery ($P > 0.05$).

Conclusions: Radiotherapy and sublobar resection can be considered reasonable alternative treatments for SPLC, especially when patients are unable to tolerate lobectomy.

Introduction

Multiple primary lung cancer (MPLC) refers to the occurrence of ≥2 primary lung cancers at the same time, or at different times for the same patient.[1] Specifically, second primary lung cancer (SPLC), with an estimated incidence rate of 12% among patients undergoing initial resection of stage I non-small cell lung cancer (NSCLC),[2] occurs more frequently with the improvements made in diagnostic tools. It has also been reported that SPLC was observed in 1.5% of patients with lung cancer in the Surveillance, Epidemiology, and End Results (SEER) database.[3] Patients who have previously undergone surgical resection of initial

lung cancer are reported to be at a higher risk of developing SPLC.[4] However, the increase in SPLC patients has brought new challenges and discussions to clinical management, including resectability evaluation, surgical procedure selection, follow-up advice and prognosis prediction. It is inappropriate to treat SPLC as initial primary lung cancer (IPLC), although some similarities between them are shared. Thus, diagnostic and therapy guidelines for SPLC are urgently required and a prognostic study on SPLC would be of significant importance.

In the past decade, the possible therapeutic strategies for SPLC have mainly included surgery, radiotherapy and chemotherapy, but there is still a lack of evidence-based guidelines. It is unknown whether the current empirical treatments are effective and which one is more beneficial to patient survival. Additionally, distinguishing MPLC from intrapulmonary metastasis is critical for clinical management and prognosis, but limited diagnostic preciseness has been observed for the widely used criteria, initially proposed by Martini and Melamed in 1975.[1] In 2007, the American College of Chest Physicians (ACCP) revised the diagnostic criteria and more factors or conditions became available for consideration.[5] Therefore, in this study, based on the Martini and Melamed and ACCP criteria, SPLC patients were identified from the SEER database to compare the survival outcome following treatment of SPLC. The prognostic factors were also determined by analyzing the clinicopathological characteristics that related to both primary carcinomas.

Methods

Study population

The SEER database was searched for identifying patients with two primary lung cancers. The initial search criteria were set as follows: (i) the number of tumors were limited to two using the Person Selection session in SEER*Stat software; (ii) tumor site for two tumors: "Lung and Bronchus" (Site and Morphology. Site recode ICD-O-3/WHO 2008); (iii) year of diagnosis for both tumors: 2007–2016; and (iv) the sequence number in multiple primary fields for two tumors: first and second of two or more primaries, respectively. The definition in SEER of multiple primaries for lung cancer is based on: (i) tomography; (ii) histology code; (iii) a solitary tumor located in each lung; (iv) a diagnosis time interval of more than three years between tumors; or (v) an invasive carcinoma diagnosed more than two months after the initial diagnosis of an in situ carcinoma.[6, 7] Thus, to obtain a better study SPLC population, further evaluation and screening were performed (as shown in Fig 1), which was based on the criteria in the studies by Martini and Melamed and Shen *et al.*[1, 5]

Study variables and survival data

The clinicopathological characteristics directly collected from the SEER database included age at diagnosis for IPLC, race, sex, location lobe, laterality, tumor size, clinical stage, T stage, pleural invasion, histology and grade (Table 1). TNM staging was based on the eighth edition of the TNM staging system.[8]The treatment information involved surgery, radiotherapy, chemotherapy and the number of examined lymph nodes for the first NSCLC. The survival data was recorded as the survival status and overall survival after the diagnosis of both tumors, with the latest information update in December 2016. All the variables' names and codes used in SEER database are summarized in Table S1. In addition, the sum of tumor size means the sum of two primary size tumors, and the diagnosis interval was defined as the time interval between the diagnoses of both primary tumors.

Statistical analysis

All statistical analyses were performed using IBM SPSS 25.0 (SPSS Inc.; Chicago, IL, USA) and R software version 3.6.3. For continuous variables (age, tumor size, time interval, number of examined lymph nodes), as well as considering clinical significance, a k-adaptive partitioning algorithm ("kaps" R package) was used for identifying the optimal cutoff points, which performed well by reducing information loss in subgrouping continuous variables into categorical ones in prognostic studies.[9] The least absolute shrinkage and selection operator (LASSO) regression was first used to select optimal predictive variables for overall survival following the diagnosis of SPLC. Univariate and multivariate Cox proportional hazard models were also developed for identifying possible prognostic factors that influenced survival outcome. Survival curves were plotted using Kaplan-Meier method and compared by log-rank test. In addition, using "survRM2" R package, the restricted mean survival time (RMST) was also calculated and compared for further survival evaluation. A two-sided P value < 0.05 was considered statistically significant.

Results

Demographic characteristics

A total of 665 patients who met the inclusion criteria were finally enrolled in our study, including 272 males and 393 females (Table 1). The median age of the study population was 68 (25–88) years. For study rigor, only patients

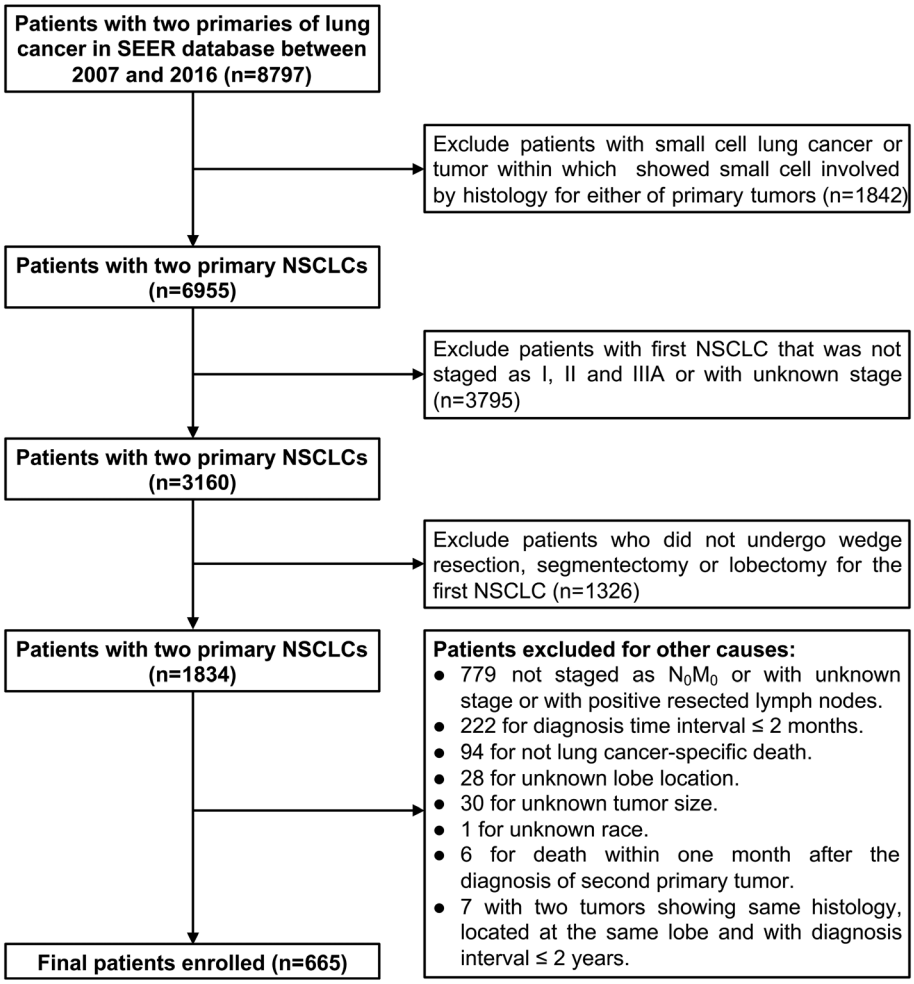

Figure 1 The flowchart of study cohort for identifying patients with second primary non-small lung cancer (NSCLC) from the Surveillance, Epidemiology, and End Results (SEER) database.

who underwent IPLC resection and histology examination were included. Among them, 527 (79.2%) patients were recorded as stage I, 119 (17.9%) as stage II and 19 (2.9%) as stage IIIA. The median tumor size for IPLC was 2.4 (IQR: 1.4–3.5) cm. Lobectomy was performed for most patients (72.2%, 480/665), with wedge resection for 149 (22.4%) patients and segmentectomy for 36 (5.4%) patients. According to the histology code for IPLC, the study cohort consisted of 466 (70.1%) adenocarcinomas (ADC), 135 (20.3%) squamous cell carcinomas (SCC) and 64 (9.6%) others. In addition to surgical treatment, 98 (14.7%) patients also received chemotherapy and 34 (5.1%) also received radiotherapy. There were 16 (2.4%) patients who underwent combined treatments of surgery, chemotherapy and radiotherapy for IPLC. For SPLC, wedge resection, segmentectomy and lobectomy were performed in 241 (36.2%), 45 (6.8%) and 145 (21.8%) patients, respectively, while none of the surgical procedures were performed in 186 (28.0%) patients. Of all patients, 156 (23.5%) received radiotherapy and 73 (11.0%) received chemotherapy.

Feature selection

First, to obtain reliable prognostic factors for SPLC, LASSO regression was performed for feature selection. Among the 29 variables in Table 1, one variable (diagnosis interval) was identified when following one-standard error criterion, while eight variables were identified when following the minimum error criterion, which included IPLC characteristics as age at diagnosis, lobe location, histology, grade and pleural invasion, tumor size of SPLC, the sum of tumor size and diagnosis interval (Fig 2).

In addition, univariate Cox analysis is also shown in Table 1. Variables with *P*-value <0.05 were selected for multivariate analysis, combined with those identified by LASSO regression. Thus, a total of 16 variables were used for multivariate Cox regression analysis, which showed that

Table 1 Demographic characteristics and univariate Cox regression analysis for second primary lung cancer

Characteristic	Classification	Number of patients (%)	Univariate analysis		
			HR	95% CI	*P*-value
Age, years	≤72	442 (66.5)	Reference	—	—
	>72	223 (33.5)	1.03	0.73–1.47	0.854
Sex	Male	272 (40.9)	2.03	1.45–2.84	**<0.001**
	Female	393 (59.1)	Reference	—	—
Race	White	566 (85.1)	Reference	—	—
	Black	55 (8.3)	0.79	0.41–1.50	0.465
	Others	44 (6.6)	0.48	0.20–1.18	0.112
Sum of tumor size, cm	≤2.3	64 (9.6)	Reference	—	—
	>2.3	601 (90.4)	1.12	0.64–1.95	0.692
Diagnosis interval, months	≤12	355 (53.4)	Reference	—	—
	13–36	216 (32.5)	1.32	0.92–1.89	0.135
	37–48	57 (8.6)	0.90	0.41–1.97	0.795
	>48	37 (5.6)	1.94	0.88–4.27	0.102
Initial primary lung carcinoma					
Tumor size, cm	<6	616 (92.6)	Reference	—	—
	≥6	49 (7.4)	2	1.17–3.43	**0.011**
Lobe	Upper	402 (60.5)	0.8	0.56–1.12	0.190
	Middle	35 (5.3)	0.36	0.11–1.14	0.081
	Lower	228 (34.3)	Reference	—	—
Laterality	Right	379 (57.0)	Reference	—	—
	Left	286 (43.0)	1.149	0.83–1.60	0.413
Histology	Adenocarcinoma	466 (70.1)	Reference	—	—
	Squamous cell carcinoma	135 (20.3)	2.032	1.41–2.94	**<0.001**
	Others	64 (9.6)	1.27	0.73–2.20	0.395
Grade	Well differentiated	140 (21.1)	Reference	—	—
	Moderately differentiated	307 (46.2)	1.41	0.86–2.31	0.171
	Poorly differentiated	165 (24.8)	1.82	1.08–3.06	**0.025**
	Undifferentiated	7 (1.1)	<0.001	—	0.952
	Unknown	46 (6.9)	1.9	0.97–3.74	0.063
Clinical stage	I	527 (79.2)	Reference	—	—
	II	119 (17.9)	1.63	1.11–2.39	**0.013**
	IIIA	19 (2.9)	1.05	0.39–2.86	0.922
T stage	T1	330 (49.6)	Reference	—	—
	T2	226 (34.0)	1.64	1.13–2.38	**0.009**
	T3	90 (13.5)	1.73	1.08–2.78	**0.023**
	T4	19 (2.9)	1.25	0.45–3.45	0.667
Pleural invasion	Yes	119 (17.9)	1.05	0.69–1.59	0.818
	No/unknown	546 (82.1)	Reference	—	—
Surgery	Wedge resection	149 (22.4)	1.38	0.95–2.01	0.089
	Segmentectomy	36 (5.4)	1.26	0.61–2.60	0.525
	Lobectomy	480 (72.2)	Reference	—	—
Radiotherapy	Yes	34 (5.1)	Reference	—	—
	No/unknown	631 (94.9)	1.87	1.04–3.39	**0.038**
Chemotherapy	Yes	98 (14.7)	Reference	—	—
	No/unknown	567 (85.3)	1.39	0.91–2.12	0.133
Treatment	Surgery only	549 (82.6)	Reference	—	—
	Surgery + radiotherapy	18 (2.7)	1.634	0.72–3.72	0.242
	Surgery + chemotherapy	82 (12.3)	1.263	0.78–2.03	0.338
	Three combined	16 (2.4)	2.372	1.04–5.40	**0.040**
No. of examined nodes	≤22	560 (84.2)	Reference	—	—
	>22	46 (6.9)	1.57	0.87–2.85	0.138
	Unknown	59 (8.9)	0.92	0.50–1.71	0.795
Second primary lung carcinoma					
Tumor size, cm	<1	130 (19.5)	Reference	—	—
	≥1	535 (80.5)	1.78	1.11–2.87	**0.017**

Table 1 Continued

Characteristic	Classification	Number of patients (%)	Univariate analysis		
			HR	95% CI	*P*-value
Lobe	Upper	383 (57.6)	0.82	0.58–1.15	0.253
	Middle	36 (5.4)	0.628	0.27–1.46	0.279
	Lower	246 (37.0)	Reference	—	—
Laterality	Right	353 (53.1)	Reference	—	—
	Left	312 (46.9)	0.85	0.61–1.19	0.335
Histology	Adenocarcinoma	439 (66.0)			
	Squamous cell carcinoma	115 (17.3)	1.53	1.01–2.32	**0.046**
	Others/unknown	111 (16.7)	1.11	0.71–1.73	0.644
Grade	Well differentiated	155 (23.3)	Reference	—	—
	Moderately differentiated	225 (33.8)	1.364	0.85–2.20	0.203
	Poorly differentiated	113 (17.0)	1.476	0.87–2.52	0.153
	Undifferentiated	4 (0.6)	7.546	2.27–25.07	**0.001**
	Unknown	168 (25.3)	1.364	0.82–2.27	0.228
Pleural invasion	Yes	57 (8.6)	1.6	0.98–2.59	0.059
	No/unknown	608 (91.4)	Reference	—	—
Surgery	Wedge resection	241 (36.2)	0.72	0.48–1.08	0.115
	Segmentectomy	45 (6.8)	0.91	0.43–1.94	0.809
	Lobectomy	145 (21.8)	0.7	0.44–1.12	0.139
	Others	48 (7.2)	0.9	0.47–1.75	0.759
	None	186 (28.0)	Reference	—	—
Radiotherapy	Yes	156 (23.5)	1.14	0.77–1.69	0.511
	No/unknown	509 (76.5)	Reference	—	—
Chemotherapy	Yes	73 (11.0)	1.85	1.19–2.88	**0.006**
	No/unknown	592 (89.0)	Reference	—	—
Treatment	Surgery only	407 (61.2)	Reference	—	—
	Radiotherapy only	124 (18.6)	1.08	0.67–1.75	0.756
	Chemotherapy only	12 (1.8)	3.17	1.38–7.28	**0.007**
	Combined treatments	80 (12.0)	1.87	1.19–2.94	**0.007**
	None/unknown	42 (6.3)	1.87	1.02–3.45	**0.044**

sex (male vs. female, HR = 1.82, 95% CI: 1.29–2.59, $P = 0.001$), IPLC characteristics as histology (SCC vs. ADC, HR = 1.89, 95% CI: 1.17–3.04, $P = 0.009$), clinical stage (stage II vs. I) and T stage (T2 vs. T1, HR = 1.68, 95% CI: 1.04–2.72, $P = 0.034$), and tumor size of SPLC (≥1 cm vs. <1 cm, HR = 1.80, 96% CI: 1.07–3.02, $P = 1.028$) were significant prognostic factors for overall survival since the diagnosis of SPLC (Table 2). By further test, none of the variables violated the proportional hazard assumption ($P > 0.05$).

Survival analysis

The survival months since the diagnosis of both tumors were recorded. The median follow-up time was 49 (interquartile range [IQR]: 31–65) months for IPLC and 28 (IQR: 18–42) months for SPLC. As shown in Fig 3a, the one-, three- and five-year survival following the diagnosis of SPLC were 92.2%, 77.3% and 68.6%, respectively. Subgroups of all prognostic factors selected presented significantly different overall survival (Fig 3b–f; $P < 0.05$). It was noted that the survival probability of the study population was greater than 50% until the end of the last time of follow-up, and a median survival time was therefore unavailable. Then, RMST within the truncation time of one-, three- and five-years was calculated to further compare survival between the subgroups (Table 3). For example, within the next five years following a diagnosis of SPLC, on average, females would survive 6.9 months longer than males (45.4 months vs. 52.3 months, $P < 0.001$; Table 3). The patients with SPLC <1 cm or ≥ 1 cm presented similar RMST within one- or three years. However, within five years, patients with SPLC <1 would survive four months longer than those with SPLC ≥1 cm, on average (52.5 months vs. 48.5 months, $P = 0.026$; Table 3).

To analyze the impact of treatment on SPLC, 475 patients with stage I IPLC who did not receive chemotherapy or radiotherapy for IPLC were identified to compare survival between different therapeutic groups. A similar survival outcome was obtained among the three groups receiving wedge resection, segmentectomy and lobectomy for IPLC. The same similarity was also observed in surgical subgroups for SPLC (Fig 4a,b; $P > 0.05$). Additionally, after excluding those who received chemotherapy

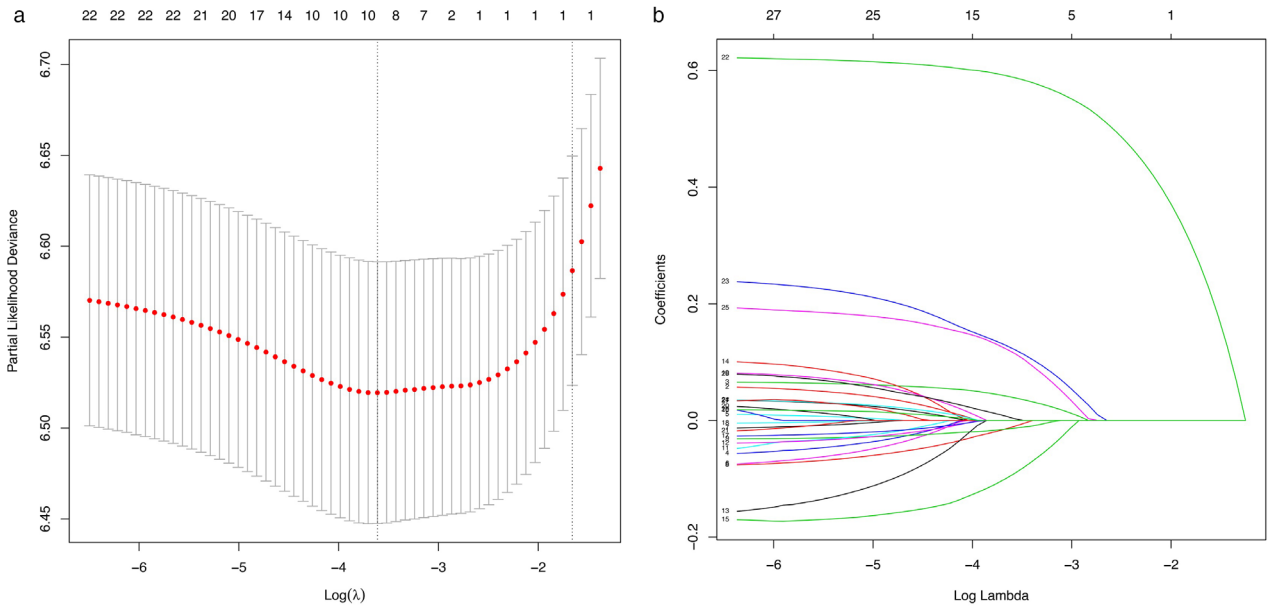

Figure 2 To select prognostic factors using the least absolute shrinkage and selection operator (LASSO) regression. (**a**) The selection of optimal prognostic factors by five-fold cross-validation. The left- and right-side dotted vertical lines represent the optimal prognostic factors of lambda when applying for the minimum criterion and the one-fold standard error of minimum criterion, respectively. (**b**) LASSO coefficients of the 29 variables.

or radiotherapy, patients were divided into four subgroups according to surgery combinations for IPLC and SPLC (Fig 4c). No significant survival and RMST difference were observed between the four surgical combinations (Fig 4c and Table 3; $P > 0.05$). Furthermore, there was not a significantly different survival outcome in our study in patients that underwent only surgery or only radiotherapy for SPLC (Fig 4d and Table 3; $P > 0.05$).

Discussion

There are still no reliable management guidelines for MPLC. SPLC, one common kind of MPLC, might be more capable of being resected and relieved, compared with those patients suffering a larger number of primary tumors or pulmonary metastatic tumors. Currently, it is generally thought that surgical treatment might be feasible for SPLC.[10–12] For inoperable patients where surgery is contraindicated, or those with an impaired pulmonary function reserve, commonly seen in SPLC patients who have previously undergone pulmonary surgery, other treatments such as radiotherapy and chemotherapy might be possible alternatives. Despite the fact that lobectomy remains the mainstream surgical procedure for resectable NSCLC,[13] sublobar resection (wedge resection and segmentectomy) is widely used in stage I NSCLC, and has been reported to demonstrate similar survival outcomes.[14–16] In addition, stereotactic body radiation therapy (SBRT) has also been reported to present great therapeutic effects in small cell lung cancer patients,[17] and may be a potential treatment for SPLC. However, whether the above-mentioned treatments are beneficial and which is better for survival in SPLC patients remain unknown. Therefore, this study aimed to identify possible prognostic factors and compare the survival outcome following SPLC treatment.

The unclear identification criteria of MPLC made it difficult to conduct large study cohorts. Thus, we retrospectively searched the SEER database, which recorded a special dataset of multiple primary cancers. Given that the inclusion criteria for multiple primary lung cancer were not as rigorous as those in the studies by Martini and Melamed[1] and Shen *et al.*[5] further selection was performed to narrow the inclusion population (Fig 1). The final cohort consisted 665 SPLC patients diagnosed between 2007 and 2016 that had previously received wedge resection, segmentectomy or lobectomy for IPLC.

Some clinical and pathological characteristics related to each tumor of two primary cancers are available in the SEER database. To select the possible prognostic factors for SPLC, two methods, LASSO regression and univariate Cox analysis, were used to avoid information loss. Of 16 variables selected, the multivariate Cox analysis indicated that, in addition to sex and tumor size of SPLC, the overall survival for patients with SPLC was also significantly associated with the IPLC characteristics of histology, clinical stage and T stage (Table 2). It seemed that fewer males intended to suffer SPLC after surgery for IPLC (272 vs. 393), but males showed worse overall survival than females

Table 2 Multivariate Cox regression analysis for selecting prognostic factors

Characteristic	Classification	HR	95% CI	*P*-value
Age, years	≤72	Reference	—	—
	>72	1.06	0.73–1.54	0.768
Sex	Male	1.82	1.29–2.59	**0.001**
	Female	Reference	—	—
Sum of tumor size, cm	≤2.3	Reference	—	—
	>2.3	0.58	0.31–1.01	0.085
Diagnosis interval, months	≤5	Reference	—	—
	6–34	1.19	0.81–1.76	0.381
	35–47	0.71	0.31–1.60	0.405
	≥48	1.57	0.66–3.72	0.308
Initial primary lung carcinoma				
Tumor size, cm	<6	Reference	—	—
	≥6	1.02	0.47–2.21	0.971
Histology	Adenocarcinoma	Reference	—	—
	Squamous cell carcinoma	1.89	1.17–3.04	**0.009**
	Others	1.37	0.76–2.47	0.301
Grade	Well differentiated	Reference	—	—
	Moderately differentiated	1.146	0.68–1.94	0.613
	Poorly differentiated	1.19	0.66–2.13	0.560
	Undifferentiated	<0.001	—	0.942
	Unknown	1.45	0.70–3.02	0.321
Clinical stage	I	Reference	—	—
	II	2.60	1.08–6.27	**0.033**
	IIIA	1.06	0.35–3.16	0.921
T stage	T1	Reference	—	—
	T2	1.68	1.04–2.72	**0.034**
	T3	0.66	0.26–1.72	0.397
Pleural invasion	Yes	1.36	0.83–2.21	0.224
	No/unknown	Reference	—	—
Radiotherapy	Yes	0.75	0.29–1.98	0.563
	No/unknown	Reference	—	—
Treatment	Surgery only	Reference	—	—
	Surgery + radiotherapy	0.86	0.24–3.12	0.820
	Surgery + chemotherapy	0.65	0.36–1.18	0.157
Second primary lung carcinoma				
Tumor size, cm	<1	Reference	—	—
	≥1	1.80	1.07–3.02	**0.028**
Histology	Adenocarcinoma	Reference	—	—
	Squamous cell carcinoma	0.97	0.58–1.63	0.901
	Others/unknown	1.14	0.71–1.84	0.582
Chemotherapy	Yes	0.72	0.27–1.94	0.517
	No/unknown	Reference	—	—
Treatment	Surgery only	Reference	—	—
	Radiotherapy only	0.91	0.54–1.52	0.717
	Chemotherapy only	2.37	0.60–9.46	0.221
	Combined treatments	1.60	0.68–3.77	0.285
	None/unknown	1.53	0.80–2.93	0.201

(HR = 1.82, 95% CI: 1.29–2.59, $P = 0.001$), which was similar to that reported in a previous study.[18] Surprisingly, in our study, the characteristics of resected IPLC could influence the survival outcome of SPLC patients. Patients with IPLC having SCC demonstrated a worse survival than those with ADC (HR = 1.89, 95%CI: 1.17–3.04, $P = 0.009$). Similar findings were also seen in patients with stage II (HR = 2.60, 95% CI: 1.08–6.27, $P = 0.033$) and T2 stage (HR = 1.68, 95% CI: 1.04–2.72, $P = 0.034$), when compared to those with stage I and T1 stages, respectively. Although no significance was obtained for stage IIIA and T3/T4 patients because of the limited number of patients, it could

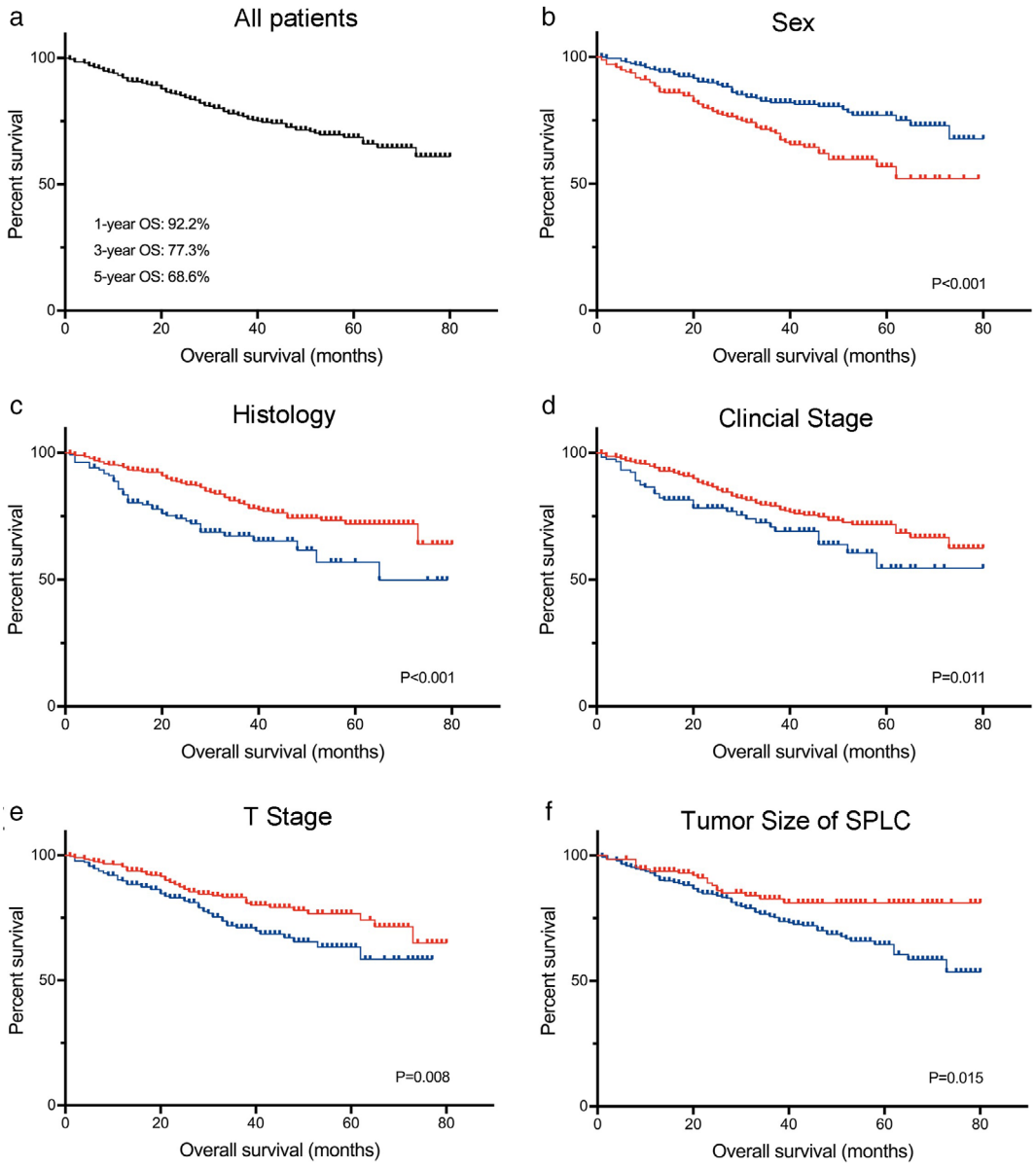

Figure 3 The overall survival (OS) rate of second primary lung cancer (SPLC) patients between the subgroups divided by the identified prognostic factors. (**a**) All patients. One-year OS: 92.2%, Three-year OS: 77.3%, Five-year OS: 68.6%. (**b**) Sex. (——) Male (N = 272), (——) Female (N = 393), P < 0.01. (**c**) Histology. (——) ADC (N = 466), (——) SCC (N = 135), P < 0.01. (**d**) Clinical stage. (——) Stage I (N = 527), (——) Stage II (N = 119), P < 0.011. (**e**) T stage. (——) T1 (N = 330), (——) T2 (N = 226), P < 0.008. (**f**) Tumor size of SPLC. (——) SPLC tumor size < 1 cm (N =130), (——) SPLC tumor size ≥ 1 cm (N = 535), P < 0.015. ADC: adenocarcinoma; SCC: squamous cell carcinoma

be inferred that a higher clinical stage or T stage of FPLC negatively influenced the prognosis of SPLC. Consistent with a previous study,[18] a larger tumor size of SPLC (≥1 cm vs. <1 cm, HR = 1.80, 96% CI: 1.07–3.02, P = 0.028) indicated poorer survival. In addition, although there was no significance, the overall size of the two primary tumors might be associated with SPLC patient survival (P = 0.085), and thus future studies should not ignore the prognostic influence of the overall tumor size.

It has previously been recommended that in MPLC patients each tumor should be separately staged, with the highest TNM stage being recommended as the patient's final stage for management.[19, 20] However, despite the special characteristics and different origins of MPLC, staging each tumor independently is not an accurate approach. This would make MPLC staging overestimated for inappropriate management decisions. Furthermore, some SPLC patients might be easily diagnosed with recurrent or

Table 3 Restricted mean survival time (RMST) for the subgroups of selected prognostic factors and treatments

Characteristic	Classification	N	RMST, months (95% CI)					
			One-year	*P*-value	Three-year	*P*-value	Five-year	*P*-value
All patients	—	665	11.6 (11.5–11.7)	—	32.0 (31.3–32.7)	—	49.4 (47.9–51.0)	—
Sex	Male	272	11.4 (11.1–11.6)	0.004	30.5 (29.2–31.7)	<0.001	45.4 (42.8–48.1)	<0.001
	Female	393	11.8 (11.7–11.9)		33.2 (32.4–33.9)		52.3 (50.5–54.1)	
Histology, IPLC	ADC	466	11.7 (11.5–11.8)	0.043	32.9 (32.1–33.6)	<0.001	50.9 (49.2–52.7)	0.002
	SCC	135	11.3 (10.9–11.6)		29.0 (27.1–31.0)		43.9 (40.0–47.9)	
Clinical stage, IPLC	I	527	11.6 (11.7–11.8)	0.023	32.5 (31.8–33.2)	0.018	50.4 (48.7–52.0)	0.027
	II	119	11.2 (10.8–11.6)		29.9 (27.9–31.9)		45.4 (41.3–49.5)	
T stage, IPLC	T1	330	11.8 (11.6–11.9)	0.038	33.0 (32.1–33.8)	0.019	51.8 (49.8–53.9)	0.008
	T2	226	11.4 (11.2–11.7)		31.1 (29.8–32.4)		47.1 (44.3–50.0)	
Tumor size, SPLC	<1 cm	130	11.7 (11.4–11.9)	0.447	33.0 (31.6–34.3)	0.150	52.5 (49.5–55.5)	0.026
	≥1 cm	535	11.6 (11.4–11.7)		31.8 (31.0–32.6)		48.5 (46.7–50.3)	
Surgery-only, IPLC[†]	Wedge resection	119	11.7 (11.5–11.9)	0.715	31.5 (29.9–33.1)	0.120	47.8 (43.9–51.6)	0.103
	Segmentectomy	30	11.0 (9.8–12.1)		30.3 (25.9–34.7)		45.5 (36.6–54.5)	
	Lobectomy	326	11.7 (11.6–11.9)		33.0 (32.1–33.8)		51.4 (49.4–53.5)	
Surgery-only, SPLC[†]	Wedge resection	161	11.8 (11.7–12.0)	0.309	33.2 (32.1–34.3)	0.439	50.8 (48.0–53.6)	0.192
	Segmentectomy[‡]	29	11.8 (11.3–12.2)		32.3 (29.1–35.6)		—	
	Lobectomy	99	11.6 (11.3–12.0)		33.7 (32.3–35.2)		53.6 (50.5–56.8)	
Surgery combination	Sublobar + sublobar	82	11.7 (11.5–12.0)	0.728	31.6 (29.8–33.5)	0.534	47.6 (43.1–52.1)	0.457
	Sublobar + lobectomy	23	11.6 (10.8–12.4)		32.9 (29.5–36.3)		43.2 (51.0–58.9)	
	Lobectomy + sublobar	108	11.9 (11.6–12.1)	0.161	33.9 (32.7–35.1)	0.352	52.5 (49.3–55.7)	0.897
	Lobectomy + lobectomy	76	11.5 (11.1–11.9)		32.8 (30.9–34.7)		52.2 (48.3–56.0)	
Treatment, SPLC	Surgery only[§]	289	11.8 (11.6–12.0)	0.847	32.5 (30.8–34.2)	0.430	50.3 (45.9–54.7)	0.613
	Radiotherapy only	89	11.8 (11.6–11.9)		33.3 (32.4–34.2)		51.5 (49.4–53.6)	

[†]Minimum number of pairwise comparisons, *P*-values among subgroups of these variables. [‡]None of the patients in this subgroup reached five-year survival. [§]Surgery only included wedge resection, segmentectomy and lobectomy. Sublobar, wedge resection and segmentectomy. IPLC, initial primary lung cancer; SPLC, second primary lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma.

metastatic tumors, leading to them missing the optimal time for surgery or directly giving up surgery. It has been reported that surgical resection could be beneficial for SPLC patients.[10, 11] Zuin *et al.* enrolled 121 patients with SPLC and found that lobectomy showed a significantly better five-year survival than sublobar resection.[21] However, Lee *et al.* concluded that there were similar survival benefits between wedge resection and lobectomy for SPLC.[18] In our study, it seemed that lobectomy for IPLC performed slightly better in survival than sublobar resection, but without significance (Fig 4a). Similarly, there was also no significant difference among the three surgical procedures (wedge resection, segmentectomy and lobectomy) for SPLC (Fig 4b). Unlike previous studies, the surgery combinations of two primary tumors were also compared in our study (Fig 4c). The four subgroups demonstrated similar survival, although the survival outcome of patients with both primaries who underwent sublobar resection was slightly worse. Furthermore, given that radiotherapy also plays an important role in the management of early-stage NSCLC, the survival outcome was also compared between surgery and radiotherapy. Taioli *et al.* published a dataset of patients that demonstrated a survival benefit of surgery over radiotherapy for SPLC.[22] However, such a significant survival difference was not observed in our study, which might be attributed to the representative population of our study that was compared. The patients who had received chemotherapy or radiotherapy for IPLC were excluded, and the surgery-only and radiotherapy-only groups did not undergo other therapies. Considering that most of the SPLC patients had a history of previous surgery, the physical conditions and pulmonary function reserve might not permit another lung resection. Thus, radiotherapy would be an important alternative, especially for inoperable patients.

In addition, RMST was also used to compare survival (Table 3). On average, SPLC patients were found to survive 11.6, 32.0 and 49.4 months within the following one, three and five years, respectively. The RMST provided more detailed information to evaluate survival, although comparing results between the subgroups was similar to using the Kaplan-Meier method. It is worth noting that patients with SPLC ≥1 cm demonstrated similar one- and three-year RMST than those with SPLC <1 cm, but revealed a significantly worse five-year RMST. Thus, based on different truncation points, RMST can compare the survival within a certain period of time,[23] which is unavailable when using the Kaplan-Meier method.

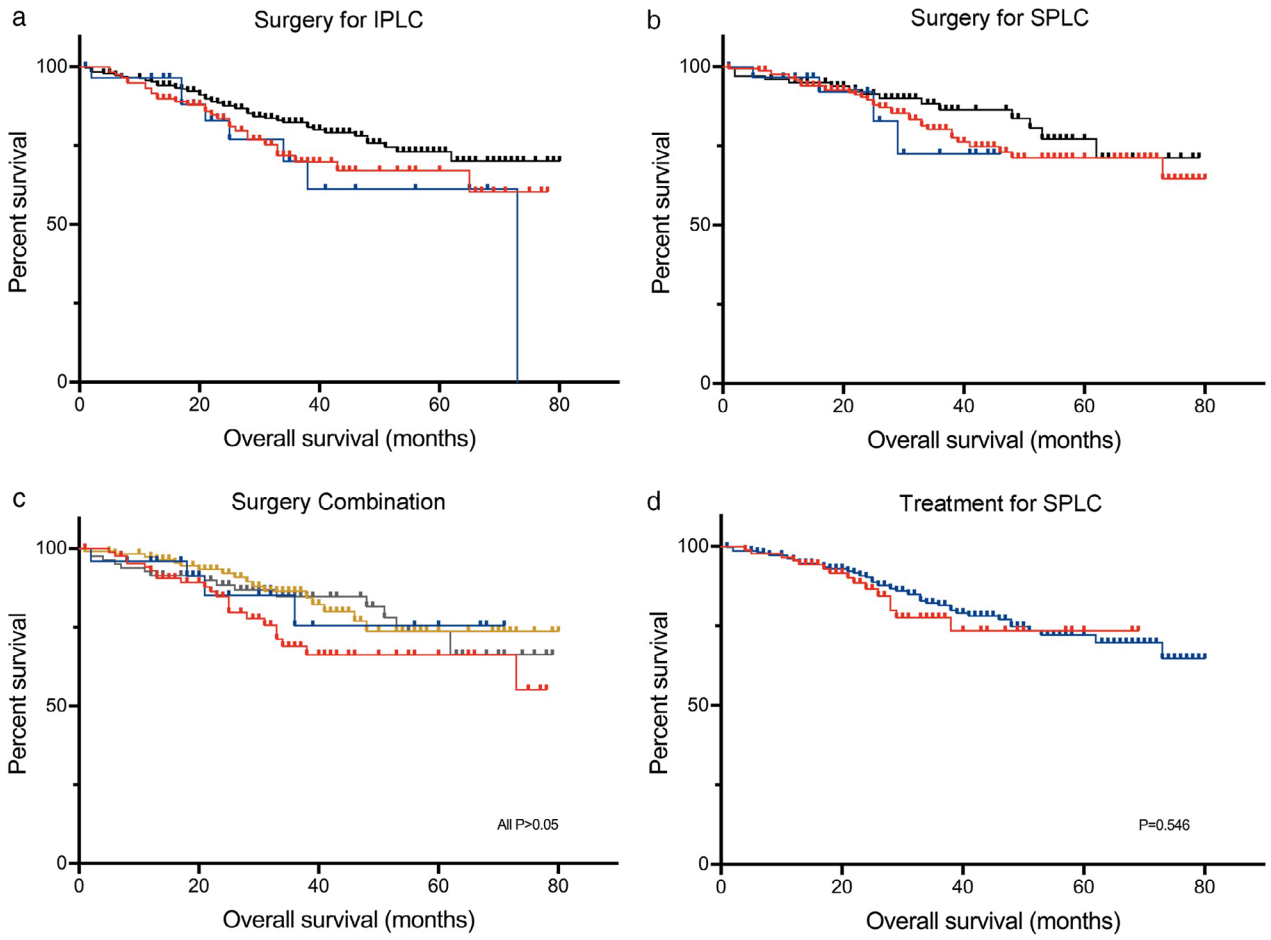

Figure 4 The overall survival (OS) rate of second primary lung cancer (SPLC) patients between different treatment groups. (**a**) Surgery for IPLC. (——) Lobectomy (*N* = 326) vs. wedge, *P* = 0.070, (——) Wedge (*N* = 119) vs. segementectomy, *P* = 0.663, (——) Segmentectomy (N = 30) vs. lobectomy, *P* = 0.119. (**b**) Surgery for SPLC. (——) Lobectomy (*N* = 99) vs. wedge, *P* = 0.280, (——) Wedge (*N* = 161) vs. segementectomy, *P* = 0.830, (——) Segmentectomy (*N* = 29) vs. lobectomy, *P* = 0.339. (**c**) Surgery combination. (——) Sublobar + sublobar (*N* = 82), (——) Sublobar + lobectomy (*N* = 23), (——) Lobectomy + sublobar (*N* = 108), (——) Lobectomy + lobectomy (*N* = 76). (**d**) Treatment for SPLC. (——) Radiotherapy (*N* = 89), (——) Surgery (*N* = 289).

There were several limitations in our study that should be taken into consideration. First, the study population was retrospectively collected from the SEER database, and thus data bias could not be totally avoided. Moreover, the database did not include all clinicopathological characteristics, such as imaging features and detailed treatment information (chemotherapy or radiotherapy). Thus, prognostic factors for SPLC deserve to be further identified in future studies. Second, there were only few patients that underwent segmentectomy. In future studies, survival following segmentectomy for SPLC should be further evaluated using a larger study population. Third, the median follow-up time for IPLC and SPLC was 49 (IQR: 31–65) and 28 (IQR: 18–42) months, respectively, which might not be enough to evaluate long-term survival. Future studies should focus more on the long-term risk of SPLC in different treatment groups.

In conclusion, SPLC patients demonstrated better survival, with a five-year survival rate of 68.6% and a five-year RMST of 49.4 months. As well as sex and tumor size of SPLC, we also identified several IPLC-related prognostic factors such as histology, clinical stage and T stage. A similar outcome was revealed in patients that underwent lobectomy, segmentectomy and wedge resection for both IPLC and SPLC. In addition, surgical procedures for SPLC did not demonstrate significantly better survival than radiotherapy. Radiotherapy and sublobar resection can be considered reasonable alternative treatments for SPLC, especially when patients are unable to tolerate lobectomy.

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Disclosure

All authors have no conflict of interest to declare.

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Supporting Information

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

Table S1. The variable names/codes used in SEER database.

