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Role of chemotherapy for survival in patients with second primary non-small cell lung cancer

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Keywords
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Abstract

Background: The therapeutic effect of chemotherapy is still unclear for clinical usage among second primary non-small cell lung cancer (NSCLC) patients. The aim of this study was to verify the therapeutic effect of chemotherapy and identify the prognostic factors among patients who had received chemotherapy for second primary NSCLC.

Methods: A retrospective cohort was constructed based on the Surveillance, Epidemiology and End Results (SEER) database. Through least absolute shrinkage and selection operator regression, univariate Cox and multivariate Cox regression, we identified the prognostic factors among clinicopathological features. Propensity score matching analysis was used to verify the therapeutic effect of chemotherapy. Survival curves were plotted among the subgroups of the selected factors. We further selected clinicopathological features that would affect the prognosis among patients who had received chemotherapy through a similar process.

Results: A total of 769 patients were enrolled to verify the therapeutic value of chemotherapy for second primary lung cancer. Significant differences were observed between the chemotherapy and nonchemotherapy group for cancer-specific survival. 215 patients who had received chemotherapy were analyzed to identify the factors that might influence outcome on the therapeutic effect of chemotherapy. Age, tumor size, histology and treatment were selected as significant factors.

Conclusions: The therapeutic effect of chemotherapy for second primary NSCLC was found to be significant. Age, tumor size and histology were significant prognostic factors among patients who had received chemotherapy for second primary NSCLC.

Key points

Significant findings of the study

- A significant therapeutic effect of chemotherapy for second primary non-small cell lung cancer was proven through univariate Cox regression and propensity score matching analysis.
- Prognostic factors for second primary non-small cell lung cancer patients who had received chemotherapy.

What this study adds

- Chemotherapy could be applied in clinical practice as an additional therapeutic method for second primary non-small cell lung cancer patients.
- We selected prognostic factors for patients who had received chemotherapy to identify patients who were appropriate for chemotherapy.

Introduction

Multiple primary lung cancer (MPLC) has been previously widely reported with the first study published in 1975.[1] Multiple primary lung cancer refers to the independent occurrence of multiple primary lung cancers, as defined by Martini and Melamed and the ACCP criteria in Shen *et al.*[1,2] Based on the definition of multiple primary lung cancer, second primary lung cancer (SPLC) refers to a specific kind of multiple primary lung cancer that second unrelated lung cancer occurred after the diagnosis of initial primary lung cancer (IPLC). The overall incidence of second primary lung cancer has been estimated to be 1% to 2% per patient-year.[3,4] In another study, among patients who underwent resection of stage I non-small cell lung cancer (NSCLC) of initial primary lung cancer, the incidence of second primary lung cancer has been reported to be 12%.[5] Another recent study also supported the finding that there is a relatively high risk of occurrence of second primary lung cancer among initial primary lung cancer patients.[6] The relatively high incidence of second primary lung cancer is not the only challenge for treatment. Due to the usage of low-dose CT screening, the incidence[7] and ratio of small lung cancer in second primary lung cancer has also been reported to be increasing.

Currently, the predominant therapeutic strategy for second primary lung cancer is still surgery. Surgical resection has been reported to be feasible and effective in the management of second primary lung cancer patients, with sublobar resection being highly recommended.[8] In another study, surgery was particularly recommended in patients found to have bronchopulmonary carcinoid tumors or multiple lesions in the lung.[9,10] With the increasing number of second primary lung cancer patients, other therapeutic strategies may become complementary treatment in addition to surgical resection. However, few studies have so far focused on the role of chemotherapy in SPLC. A recent study reported a single case of the therapeutic effect of chemotherapy on a specific second primary lung cancer patient.[11] The therapeutic effect of chemotherapy among second primary lung cancer patients should be verified in a larger population.

The aim of this study was to focus on verifying the therapeutic effect of chemotherapy among second primary NSCLC patients. We explored the prognostic factors among patients who had received chemotherapy for diagnosed second primary lung cancer in order to provide clinical recommendations for patients receiving chemotherapy in the future. The relevant clinicopathological characteristics of second primary lung cancer patients were collected based on the data in the Surveillance, Epidemiology, and End Results (SEER) database.

Methods

SEER database

The study was designed to retrospectively enroll patients diagnosed with second primary lung cancer from the SEER database. The initial selection criteria were set as follows: (i) Limiting the number of tumors to two; (ii) setting the tumor site as "lung and bronchus" (site and morphology. Site recode ICD-O-3/WHO 2008); (iii) the diagnosis year of second primary lung cancer was later than 2004, and the diagnosis of second lung cancer was earlier than 2015; and (iv) the sequence number of "multiple primary fields" was first and second of two or more primaries. The exclusion criteria were: (i) histology was reported to be small cell lung cancer (SCLC); (ii) not diagnosed with second primary lung cancer according to Martini and Melamed and the ACCP criteria in Shen *et al.*[1,2]; (iii) loss of key information, including survival time and status of the patients. The SEER definition of multiple primaries was based on: (i) Tomography; (ii) histology code; (iii) solitary tumor diagnosed in each lung; (iv) interval period time for diagnosis more than three years; or (v) period of more than two months between the diagnosis of invasive carcinoma and in situ carcinoma.[12,13]

Clinical features

Relevant clinicopathological characteristics were collected from the SEER database after the enrollment of patients, including age at diagnosis, race, sex, laterality for both IPLC and SPLC, tumor size for SPLC, histology, grade, clinical stage, T stage and treatment including surgery, chemotherapy and radiotherapy. The survival data was recorded as overall survival and cancer-specific survival conditions after a diagnosis of IPLC and SPLC, and the latest survival status information was updated in December 2016. The diagnostic interval was defined as the interval months between diagnosis of the initial primary lung cancer and diagnosis of the second primary lung cancer. Surgery were divided into sublobar resection, lobectomy, pneumonectomy and no-surgery subgroups. According to the histology code in the SEER database, patients were divided into three groups: (i) Squamous cell carcinoma (SQCC) group; (ii) adenocarcinoma (ADC) group; and (iii) other-NSCLC (large cell carcinoma, carcinoid tumor, oat cell carcinoma, etc) group.

Overall survival and cancer-specific survival

In the study, the definition of overall survival was that living patients (according to the latest follow-up information)

would be recorded as "alive" regardless of tumor progression or recurrence of the tumor. Death for any reason would be recorded as "dead".

The definition of cancer-specific survival was that living patients would be recorded as "alive". The patients who died from a tumor or during the process of treatment would be recorded as "cancer-specific death". Patients who died from other causes (such as traffic accident) would be recorded as "lost" according to the latest follow-up status.

Statistical analysis

All statistical analyses were performed using R software version 4.0.1 (http://www.r-project.org/) and IBM SPSS 25.0 (SPSS Inc.; Chicago, IL, USA). A two-sided *P*-value <0.05 was considered statistically significant in the study.

Continuous variables (age and tumor size) were classified into different subgroups by a cutoff value which was calculated through the maximally selected rank statistics from the "maxstat" R package. The least absolute shrinkage and selection operator (LASSO) regression ("glmnet" R package) was applied to screen optimal prognostic factors among all the collected clinicopathological features of all enrolled patients. Univariate Cox proportional regression model ("survival" R package) was used to verify the prognostic factors. Multivariate Cox proportional regression model ("survival" R package) was used to reduce the influence of confounding bias. The restricted mean survival time (RMST) values were calculated among different subgroups for comparison of differences in prognosis. Propensity score matching (PSM) analysis was conducted using the propensity score as constructed in 1:1 nearest-neighbor matching within calipers without replacement, through SPSS software.[14] Propensity scores were calculated through probit regression with the clinicopathological features among all enrolled patients. The caliper value for propensity score was set as 0.02. Survival curves were plotted using the Kaplan-Meier method and compared by log-rank test ("survival" R package).

Results

Demographic features

A total of 769 patients were finally enrolled into the study. Table 1 shows the demographic features of selected factors. Among all enrolled patients, 307 patients (39.9%) were younger than 64 years, and 462 patients (60.1%) were equal to, or older than, 64 years. A total of 332 patients (43.2%) were male, and 437 patients (56.8%) were female. A total of 84.8% (652/769) of all enrolled patients were white, 9.0% (69/769) were black, with 6.2% (48/769) patients of other races. There was 301 patients (39.1%) with ipsilateral tumors, and 468 patients (60.9%) had contralateral tumors. With regard to the histology code of IPLC and SPLC, 435 patients (56.6%) were diagnosed with adenocarcinoma for IPLC, and 217 patients (28.2%) were diagnosed with squamous cell carcinoma for IPLC. A total of 117 patients (15.2%) were diagnosed with other NSCLCs, and small cell lung cancer patients had previously been excluded from the study. For second primary lung cancer, 432 patients (56.2%) were adenocarcinoma. A total of 199 patients (25.9%) had squamous cell carcinoma, and 138 patients (17.9%) were diagnosed with other NSCLCs. Patients were classified into different subgroups according to the size of the second primary lung cancer (SPLC), including "0–3 cm", "3–5 cm" and "≥5 cm" subgroups. The total number of patients in each subgroup was 414 (53.8%), 77 (10.0%) and 60 (7.8%), respectively, with 218 patients (28.3%) without valid tumor size information. For the treatment of SPLC, 533 patients (69.3%) did not receive surgery. There were 107 patients (13.9%) who received wedge resection for second primary lung cancer, 17 patients (2.2%) received segmentectomy and 18 patients (2.3%) received inseparable resection. A total of 87 patients (11.3%) accepted lobectomy, and seven patients (0.9%) received pneumonectomy for second primary lung cancer. As for chemotherapy, 215 patients (28.0%) accepted chemotherapy to treat second primary lung cancer lesions, while 554 patients (72.0%) refused chemotherapy for SPLC after diagnosis.

Survival analysis

LASSO regression was applied to screen the clinicopathological features for possible prognostic factors based on both overall survival (OS) and cancer-specific survival (CSS) condition (Fig 1). A total of 14 clinicopathological factors were selected as possible prognostic factors within the minimum error criterion according to the coefficient variation plot and cross validation plot for OS (Fig 1a,b), including age, sex, relative location, laterality of IPLC, surgery for IPLC, tumor size of SPLC, T stage for SPLC, N stage for SPLC, grade for SPLC, histology for SPLC, surgery for SPLC, chemotherapy for SPLC, radiotherapy for SPLC and treatment for SPLC. For CSS, 15 factors were selected (Fig 1c,d). Selected factors were further screened through univariate Cox regression (Table 1) and multivariate Cox regression (Table 2).

Through univariate Cox regression, factors were selected for both OS and CSS. Age (≥64 years vs. <64 years: hazard ratio [HR]: 1.277, $P < 0.001$), sex (female vs. male: HR 0.739, $P = 0.003$), surgery for IPLC (sublobar resection: HR 0.541, $P < 0.001$; lobectomy: HR 0.565, $P < 0.001$), tumor size of SPLC (3–5 cm: HR 2.094, $P < 0.001$; ≥ 5 cm: HR 4.777, $P < 0.001$), grade of SPLC (poorly differentiated: HR

Table 1 Demographic characteristics and univariate Cox regression analysis for overall survival (OS) and cancer-specific survival (CSS) among all the 769 enrolled patients

			Overall survival			Cancer-specific survival		
Factors	Classification	Number %	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	< 64 years	307 (39.9)	-	Reference	-	-	Reference	-
	≥ 64 years	462 (60.1)	1.277	1.035–1.574	**<0.001**	1.132	0.895–1.430	0.301
Sex	Male	332 (43.2)	-	Reference	-	-	Reference	-
	Female	437 (56.8)	0.739	0.605–0.902	**0.003**	0.782	0.623–0.982	**0.034**
Race	White	652 (84.8)	-*	-	-	-	Reference	-
	Black	69 (9.0)	-*	-	-	1.359	0.925–1.997	0.118
	Others	48 (6.2)	-*	-	-	0.759	0.458–1.259	0.286
Relative Location	Ipsilateral	301 (39.1)	-	Reference	-	-*	-	-
	Contralateral	468 (60.9)	1.048	0.853–1.287	0.657	-*	-	-
Initial primary lung carcinoma								
Laterality	Right	456 (59.3)	-	Reference	-	-*	-	-
	Left	313 (40.7)	1.092	0.892–1.338	0.395	-*	-	-
Histology	SQCC	217 (28.2)	-*	-	-	1.388	1.072–1.796	**0.013**
	ADC	435 (56.6)	-*	-	-	-	Reference	-
	Other NSCLCs	117 (15.2)	-*	-	-	0.980	0.708–1.357	0.902
Surgery	None	144 (18.7)	-	Reference	-	-	Reference	-
	Sublevel resection	114 (14.8)	0.541	0.384–0.763	**<0.001**	0.431	0.287–0.646	**<0.001**
	Lobectomy	485 (63.1)	0.565	0.443–0.722	**<0.001**	0.525	0.400–0.687	**<0.001**
	Pneumonectomy	26 (3.4)	0.885	0.512–1.530	0.662	0.853	0.463–1.568	0.608
Radiotherapy	None	578 (75.2)	-*	-	-	-	Reference	-
	Accepted	191 (24.8)	-*	-	-	1.386	1.083–1.773	**0.010**
Second primary lung carcinoma								
Tumor size, cm	0–3 cm	414 (53.8)	-	Reference	-	-	Reference	-
	3–5 cm	77 (10.0)	2.094	1.537–2.852	**<0.001**	2.020	1.409–2.896	**<0.001**
	≥ 5 cm	60 (7.8)	4.777	3.493–6.533	**<0.001**	5.470	3.885–7.702	**<0.001**
	Unknown	218 (28.3)	2.208	1.709–2.855	**<0.001**	2.322	1.737–3.105	**<0.001**
T stage	T1	336 (43.7)	-	Reference	-	-	Reference	-
	T2	298 (38.8)	1.102	0.882–1.378	0.393	1.152	0.893–1.487	0.275
	T3	36 (4.7)	1.133	0.712–1.804	0.599	1.126	0.658–1.927	0.665
	T4	73 (9.5)	1.246	0.887–1.751	0.204	1.467	1.014–2.122	**0.042**
	Unknown	26 (3.4)	1.082	0.626–1.869	0.779	1.023	0.536–1.952	0.945
N stage	N0	563 (73.2)	-	Reference	-	-	Reference	-
	N1	86 (11.2)	1.125	0.825–1.532	0.457	1.242	0.882–1.749	0.215
	N2	109 (14.2)	1.046	0.791–1.384	0.750	1.180	0.868–1.603	0.290
	Unknown	11 (1.4)	0.246	0.061–0.989	0.048	0.163	0.023–1.165	0.071
Grade	I	97 (12.6)	-	Reference	-	-	Reference	-
	II	197 (25.6)	1.839	1.196–2.826	0.005	2.016	1.197–3.396	**0.008**
	III	163 (21.2)	2.748	1.794–4.209	**<0.001**	3.417	2.049–5.698	**<0.001**
	IV	5 (0.7)	3.692	0.875–15.584	0.075	5.619	1.298–24.335	**0.021**
	Unknown	307 (39.9)	2.645	1.758–3.979	**<0.001**	3.133	1.911–5.138	**<0.001**
Histology	SQCC	199 (25.9)	1.543	1.224–1.944	**<0.001**	1.406	1.078–1.833	**0.012**
	ADC	432 (56.2)	-	Reference	-	-	Reference	-
	Other NSCLCs	138 (17.9)	1.731	1.332–2.251	**<0.001**	1.668	1.240–2.244	**0.001**
Surgery	None	533 (69.3)	-	Reference	-	-	Reference	-
	Sublevel resection	142 (18.5)	0.374	0.278–0.504	**<0.001**	0.361	0.257–0.508	**<0.001**
	Lobectomy	87 (11.3)	0.397	0.272–0.581	**<0.001**	0.355	0.226–0.558	**<0.001**
	Pneumonectomy	7 (0.9)	0.587	0.219–1.576	0.290	0.557	0.178–1.743	0.315
Chemotherapy	None	554 (72.0)	1.452	1.175–1.794	**0.001**	1.839	1.457–2.321	**<0.001**
	Accepted	215 (28.0)	-	Reference	-	-	Reference	-
Radiotherapy	None	441 (57.3)	-	Reference	-	-	Reference	-
	Accepted	328 (42.7)	1.033	0.840–1.272	0.757	0.937	0.739–1.189	0.594
Treatment	Radiotherapy	309 (40.2)	-	Reference	-	-	Reference	-
	Surgery	217 (28.2)	0.472	0.355–0.628	**<0.001**	0.469	0.336–0.656	**<0.001**
	Combined	19 (2.5)	1.364	0.718–2.591	0.343	1.707	0.863–3.377	0.124

Table 1 Continued

Factors	Classification	Number %	Overall survival			Cancer-specific survival		
			HR	95% CI	*P*-value	HR	95% CI	*P*-value
	None	224 (29.1)	1.871	1.490–2.351	**<0.001**	2.196	1.695–2.845	**<0.001**

95% CI, 95 percent confidence interval; ADC, adenocarcinoma; HR, hazard ratio; Grade I, II, III, IV, well differentiated, moderately differentiated, poorly differentiated and undifferentiated individually; NSCLC, non-small cell lung cancer; SQCC, squamous cell cancer. Bold values represent a *P*-value <0.05 among subgroups. *The clinicopathological factors were excluded by the least absolute shrinkage and selection operator (LASSO) test for prognostic factors.

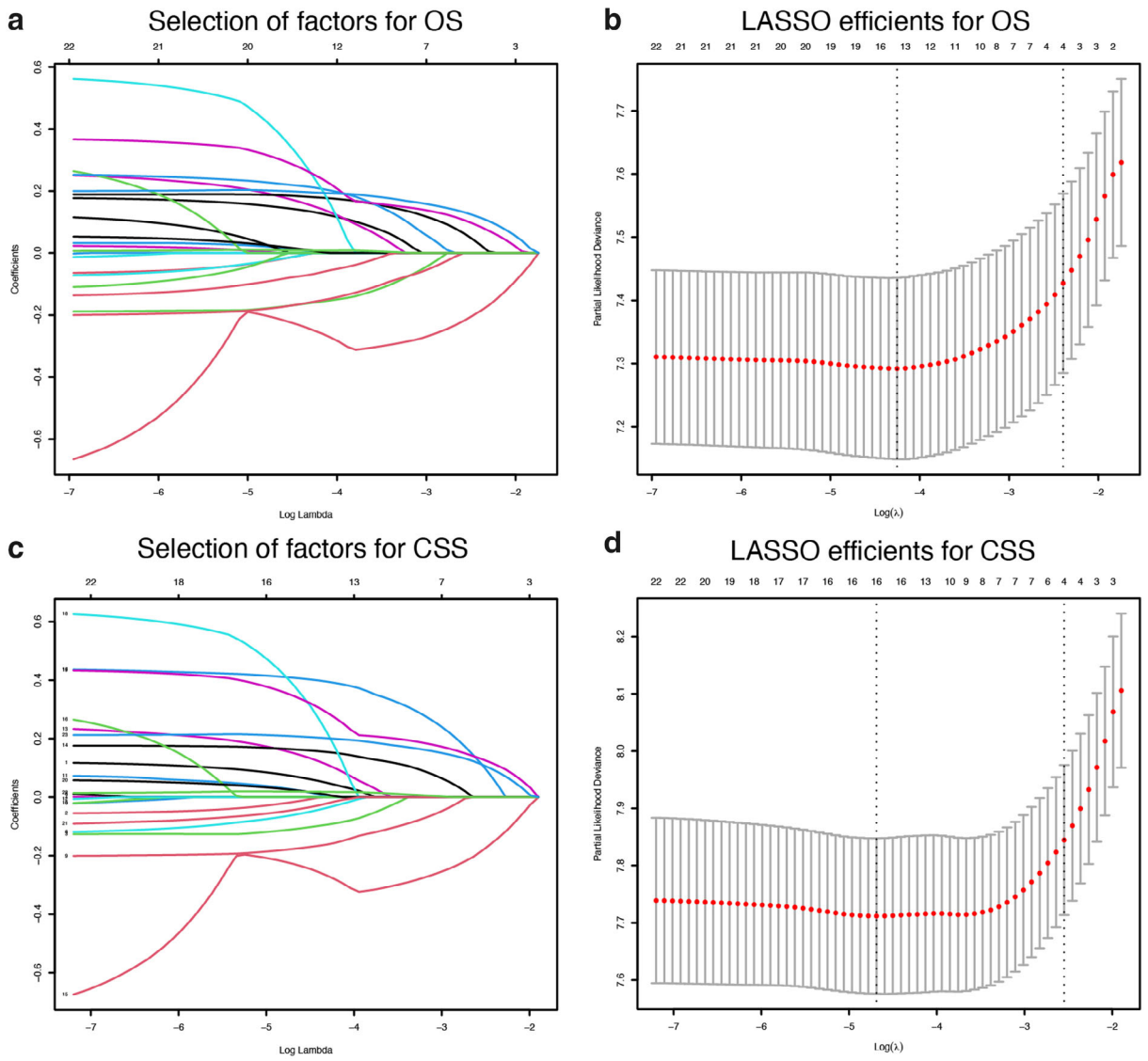

Figure 1 The least absolute shrinkage and selection operator (LASSO) regression on screening prognostic factors among 769 enrolled patients. (**a**) the selection of prognostic factors by 10-fold cross validation for overall survival (OS). (**b**) LASSO coefficients of variables for overall survival (OS). (**c**) the selection of prognostic factors by 10-fold cross validation for cancer-specific survival (CSS). (**d**) LASSO coefficients of variables for cancer-specific survival (CSS).

2.748, $P < 0.001$), histology for SPLC (SQCC: HR 1.543, $P < 0.001$; other NSCLCs: HR 1.731, $P < 0.001$), surgery for SPLC (sublobar resection: HR 0.374, $P < 0.001$; lobectomy: HR 0.397, $P < 0.001$), chemotherapy for SPLC (accepted vs. none: HR 1.452, $P = 0.001$) and treatment for SPLC (surgery only: HR 0.472, $P < 0.001$; no treatment: HR 1.871, $P < 0.001$) were chosen as prognostic factors for OS status. Similarly, sex, histology for IPLC, surgery for IPLC, radiotherapy for IPLC, tumor size of SPLC, T stage for SPLC, grade for SPLC, histology for SPLC, surgery for SPLC, chemotherapy for SPLC and treatment for SPLC were selected as significant prognostic factors for CSS.

Multivariate Cox regression was further conducted for both OS and CSS to minimize confounding among selected factors (Table 2). For OS status, age ($P = 0.032 < 0.05$), surgery for IPLC (lobectomy: $P = 0.001 < 0.05$), tumor size of SPLC (3–5 cm: $P < 0.001$; ≥ 5 cm: $P < 0.001$), grade for SPLC (moderately differentiated: $P = 0.015 < 0.05$; poorly differentiated: $P = 0.004 < 0.05$) and treatment for SPLC (surgery only: $P = 0.030 < 0.05$; None: $P < 0.001$) were selected as independent prognostic factors. For cancer-specific survival status, radiotherapy for IPLC ($P = 0.049 < 0.05$), surgery for IPLC (sublobar resection: $P = 0.001 < 0.01$; lobectomy: $P < 0.001$), tumor size of SPLC (3–5 cm: $P = 0.004 < 0.05$; ≥ 5 cm: $P < 0.001$), grade for SPLC (moderately differentiated: $P = 0.013 < 0.05$; poorly differentiated: $P = 0.001 < 0.05$) and treatment for SPLC (none: $P < 0.001$) were identified as independent prognostic factors.

Propensity score matching

Propensity score matching was designed to minimize the influence of selection and confounding bias through patient-pairing among all enrolled patients. Through propensity score matching 1:1 analysis, 185 patients who had received chemotherapy for SPLC were matched with another 185 patients who rejected chemotherapy for SPLC and had the nearest clinicopathological features. Baseline characteristics and distribution of cases are shown in Table 3. As shown, significant differences in age ($P < 0.001$, calculated through *t*-test or Mann-Whitney test according to the type of variables) and chemotherapy for IPLC ($P < 0.001$) were observed among patients in the chemotherapy and nonchemotherapy groups. After propensity score matching, the baseline characteristics of cases between the chemotherapy and nonchemotherapy groups were not significantly different ($P > 0.05$). The survival curves of the chemotherapy and nonchemotherapy groups are shown in Fig 2. Among all the 769 patients enrolled (not filtered through propensity score matching), the differences between the chemotherapy and nonchemotherapy groups were significant for both OS and CSS ($P < 0.001$) (Fig 2a, b). Among 370 patients who were selected by propensity score matching, we observed significant differences in survival probability among patients in the chemotherapy and nonchemotherapy groups for CSS status (P 0.028 < 0.05) (Fig 2c), while no significant difference was observed in survival probability among patients in the chemotherapy and nonchemotherapy groups considering OS status (Fig 2d).

Prognostic features

To identify the prognostic factors for patients who had received chemotherapy for second primary lung cancer (SPLC), 215 patients who had received chemotherapy for second primary lung cancer (SPLC) were chosen from all 769 enrolled patients for further analysis. Table 4 shows the distribution of clinicopathological factors among the selected 215 patients. A total of 114 patients (53.0%) were younger than 64 years. There were 101 patients (47.0%) older than 64 years. A total of 182 patients (84.7%) were white, and 23 patients (10.7%) were black, with 10 patients (4.7%) of other races. With regard to the size of the SPLCs, 99 patients (46.0%) had 0–3 cm SPLC, 29 patients (13.5%) had 3–5 cm SPLC, and 31 patients (14.4%) had SPLC of more than 5 cm. Histology codes for SPLC were collected from the SEER database for the 215 patients who had received chemotherapy. A total of 121 patients (56.3%) were diagnosed with adenocarcinoma for SPLC, and 59 patients (27.4%) were diagnosed with squamous cell carcinoma for SPLC. An additional 35 patients (16.3%) were diagnosed with other NSCLCs. SCLC patients were excluded from the study. Patients were classified into right and left subgroups according to laterality for SPLC. The number of patients in each subgroup was 123 (57.2%) and 89 (41.4%), respectively with three patients (1.4%) having unknown second primary lung cancer laterality details. The surgery group was classified according to surgical strategies. A total of 165 patients (76.7%) did not receive any surgery for SPLC, while 24 patients (11.2%) received sublobar resection. There were 24 patients (11.2%) who underwent lobectomy, and two patients (0.9%) who received pneumonectomy for SPLC. When radiotherapy was taken into consideration, 79 patients (36.7%) only accepted radiotherapy for SPLC. A total of 40 patients (18.6%) received only surgery for SPLC, and 10 patients (4.7%) received both surgery and radiotherapy to treat second primary lung cancer lesions. A total of 86 patients (40.0%) refused both therapeutic strategies after diagnosis.

LASSO + regression selected 12 prognosis-related clinicopathological features among 215 patients who had received chemotherapy for SPLC (Fig 3) including age, race, surgery for IPLC, tumor size for SPLC, laterality for SPLC, histology for SPLC, surgery for SPLC and treatment

Table 2 Multivariate Cox regression analysis for selecting prognostic factors for overall survival (OS) and cancer-specific survival (CSS) among all the 769 enrolled patients

		Overall survival			Cancer-specific survival		
Characteristic	Classification	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	<64 years	-	Reference	-	-*	-	-
	≥64 years	1.283	1.021–1.611	**0.032**	-*	-	-
Sex	Male	-	Reference	-	-	Reference	-
	Female	0.892	0.722–1.100	0.285	0.942	0.740–1.199	0.628
Initial primary lung carcinoma							
Histology	SQCC	-*	-	-	1.042	0.768–1.416	0.79
	ADC	-*	-	-	-	Reference	-
	Other NSCLCs	-*	-	-	0.728	0.506–1.048	0.088
Radiotherapy	None	-*	-	-			
	Accepted	-*	-	-	0.651	0.425–0.999	**0.049**
Surgery	None	-	Reference	-	-	Reference	-
	Sublevel resection	0.699	0.474–1.029	0.070	0.387	0.224–0.667	**0.001**
	Lobectomy	0.616	0.459–0.825	**0.001**	0.389	0.249–0.610	**<0.001**
	Pneumonectomy	0.906	0.509–1.614	0.738	0.600	0.304–1.184	0.141
Second primary lung carcinoma							
Tumor size, cm	0–3 cm	-	Reference	-	-	Reference	-
	35 cm	1.796	1.300–2.481	**<0.001**	1.748	1.200–2.546	**0.004**
	≥ 5 cm	3.407	2.417–4.802	**<0.001**	4.020	2.753–5.870	**<0.001**
	Unknown	1.591	1.215–2.084	**0.001**	1.671	1.227–2.277	**0.001**
T stage	T1	-*	-	-	-	Reference	-
	T2	-*	-	-	1.118	0.859–1.455	0.405
	T3	-*	-	-	0.930	0.515–1.681	0.811
	T4	-*	-	-	0.878	0.572–1.348	0.552
	Unknown	-*	-	-	1.191	0.601–2.358	0.616
Grade	I	-	Reference	-	-	Reference	-
	II	1.737	1.111–2.714	**0.015**	1.977	1.151–3.396	**0.013**
	III	1.957	1.242–3.085	**0.004**	2.692	1.562–4.638	**<0.001**
	IV	1.005	0.226–4.470	0.995	1.679	0.357–7.894	0.512
	Unknown	1.467	0.948–2.269	0.085	1.782	1.050–3.022	**0.032**
Histology	SQCC	1.111	0.864–1.428	0.413	0.981	0.709–1.356	0.906
	ADC	-	Reference	-	-	Reference	-
	Other	1.291	0.961–1.735	0.090	1.136	0.810–1.593	0.459
Chemotherapy	None	1.121	0.885–1.421	0.344	1.25	0.969–1.613	0.086
	Accepted	-	Reference	-	-	Reference	-
Surgery	None	-	Reference	-	-	Reference	-
	Sublevel resection	1.323	0.667–2.626	0.423	1.509	0.715–3.184	0.280
	Lobectomy	1.079	0.507–2.295	0.844	1.078	0.465–2.498	0.861
	Pneumonectomy	0.950	0.313–2.881	0.927	0.822	0.238–2.841	0.756
Treatment	Radiotherapy only	-	Reference	-	-	Reference	-
	Surgery only	0.467	0.235–0.930	**0.030**	0.415	0.196–0.881	**0.022**
	Combined treatment	NA	NA	NA	NA	NA	NA
	None	1.708	1.343–2.174	**<0.001**	1.920	1.459–2.526	**<0.001**

95% CI, 95 percent confidence interval; ADC, adenocarcinoma; HR, hazard ratio; Grade I, II, III, IV, well differentiated, moderately differentiated, poorly differentiated and undifferentiated individually; NSCLC, non-small cell lung cancer; SQCC, squamous cell cancer. Bold values represent a *P*-value <0.05 among subgroups. *Clinicopathological factors were excluded by the least absolute shrinkage and selection operator (LASSO) test for prognostic factors.

for SPLC (Fig 3a,b). When analyzing CSS instead of OS, only four features (age, tumor size for SPLC, histology for SPLC and treatment for SPLC) were selected (Fig 3c,d). Six variables were selected with two-sided *P*-values <0.05 as prognostic factors for OS through univariate Cox regression (Table 4). Univariate Cox regression selected four factors for CSS. Further multivariate Cox regression checked these factors for both OS and CSS. Finally, four factors were chosen for both OS and CSS (Table 5 and Fig 4), including age (< 64 years vs. ≥ 64 years, CSS: hazard ratio, HR 1.784, $P < 0.05$), tumor size for SPLC (≥5 cm vs. 0–3 cm, CSS: HR 2.174, $P < 0.05$), histology for SPLC

Table 3 Baseline characteristics and distribution of cases before and after propensity score matching

		All patients				Propensity score matched patients			
Covariates	Classification	Chemo	None	*P*-value	ASD	Chemo	None	*P*-value	ASD
Overall propensity		-	-	-	0.867	0.361 ± 0.175	0.360 ± 0.174	0.933	0.008
Age (years)		63.25 ± 8.36	66.57 ± 9.14	0.000*	0.398	64.00 ± 8.27	63.24 ± 9.42	0.409*	0.091
Race	White	182 (84.7%)	470 (84.8%)	0.956	0.005	156 (84.3%)	158 (85.4%)	0.785	0.030
	Black	23 (10.7%)	46 (8.3%)		0.077	19 (10.3%)	17 (9.2%)		0.035
	Others	10 (4.7%)	38 (6.9%)		0.105	10 (5.4%)	10 (5.4%)		0.000
Sex	Male	105 (48.8%)	227 (41.0%)	0.048	0.157	84 (45.4%)	81 (43.8%)	0.754	0.032
	Female	110 (51.2%)	327 (59.0%)		-	101 (54.6%)	104 (56.2%)		-
Laterality, IPLC	Right	135 (62.8%)	321 (57.9%)	0.220	0.100	120 (64.9%)	114 (61.6%)	0.518	0.067
	Left	80 (37.2%)	233 (42.1%)		-	65 (35.1%)	71 (38.4%)		-
Histology, IPLC	ADC	122 (56.7%)	313 (56.5%)	0.868	0.005	103 (55.7%)	111 (60.0%)	0.357	0.087
	SQCC	62 (28.8%)	155 (28.0%)		0.019	55 (29.7%)	52 (28.1%)		0.036
	Other NSCLCs	31 (14.4%)	86 (15.5%)		-	27 (14.6%)	22 (11.9%)		-
Grade, IPLC	I	22 (10.2%)	79 (14.3%)	0.301	0.133	20 (10.8%)	28 (15.1%)	0.656	0.142
	II	82 (38.1%)	212 (38.3%)		0.003	75 (40.5%)	66 (35.7%)		0.100
	III	71 (33.0%)	154 (27.8%)		-	53 (28.6%)	57 (30.8%)		-
	IV	3 (1.4%)	15 (2.7%)		0.112	3 (1.6%)	2 (1.1%)		0.046
	Unknown	37 (17.2%)	94 (17.0%)		0.006	34 (18.4%)	32 (17.3%)		0.029
Surgery, IPLC	None	42 (19.5%)	102 (18.4%)	0.915	0.028	36 (19.5%)	35 (18.9%)	0.636	0.014
	Sublevel resection	30 (14.0%)	84 (15.2%)		0.035	24 (13.0%)	18 (9.7%)		0.093
	Lobectomy	136 (63.3%)	349 (63.0%)		-	119 (64.3%)	128 (69.2%)		-
	Pneumonectomy	7 (3.3%)	19 (3.4%)		0.010	6 (3.2%)	4 (2.2%)		0.061
Chemotherapy, IPLC	Yes	95 (44.2%)	164 (29.6%)	0.000	0.293	73 (39.5%)	73 (39.5%)	1.000	0.000
	No	120 (55.8%)	390 (70.4%)		-	112 (60.5%)	112 (60.5%)		-
Radiotherapy, IPLC	Yes	53 (24.7%)	138 (24.9%)	0.941	0.006	42 (22.7%)	43 (23.2%)	0.902	0.013
	No	162 (75.3%)	416 (75.1%)		-	143 (77.3%)	142 (76.8%)		-
Laterality, SPLC	Right	123 (57.2%)	304 (54.9%)	0.629	-	104 (56.2%)	108 (58.4%)	0.679	-
	Left	89 (41.4%)	247 (44.6%)		0.065	79 (42.7%)	75 (40.5%)		0.044
	Unknown	3 (1.4%)	3 (0.5%)		0.073	2 (1.1%)	2 (1.1%)		0.000
Relative location	Ipsilateral	93 (43.3%)	208 (37.5%)	0.146	-	80 (43.2%)	76 (41.1%)	0.674	-
	Contralateral	122 (56.7%)	346 (62.5%)		0.115	105 (56.8%)	109 (58.9%)		0.044
Interval (months)		72.79 ± 22.40	73.77 ± 20.58	0.562*	0.044	72.39 ± 22.57	72.78 ± 20.29	0.860*	0.018
Histology, SPLC	ADC	121 (56.3%)	311 (56.1%)	0.785	0.003	105 (56.8%)	116 (62.7%)	0.354	**0.120**
	SQCC	59 (27.4%)	140 (25.3%)		0.049	54 (29.2%)	42 (22.7%)		**0.145**
	Other NSCLCs	35 (16.3%)	103 (18.6%)		-	26 (14.1%)	27 (14.6%)		-
Surgery, SPLC	None	165 (76.7%)	368 (66.4%)	0.016	0.244	139 (75.1%)	134 (72.4%)	0.629	0.064
	Sublevel resection	24 (11.2%)	118 (21.3%)		-	23 (12.4%)	29 (15.7%)		-
	Lobectomy	24 (11.2%)	63 (11.4%)		0.007	21 (11.4%)	20 (10.8%)		0.017
	Pneumonectomy	2 (0.9%)	5 (0.9%)		0.003	2 (1.1%)	2 (1.1%)		0.000
Radiotherapy, SPLC	Yes	89 (41.4%)	239 (43.1%)	0.661	0.035	80 (43.2%)	75 (40.5%)	0.599	0.055

Table 3 Continued

Covariates	Classification	All patients				Propensity score matched patients			
		Chemo	None	*P*-value	ASD	Chemo	None	*P*-value	ASD
	No	126 (58.6%)	315 (56.9%)		-	105 (56.8%)	110 (59.5%)		-
T stage, SPLC	T1	84 (39.1%)	252 (45.5%)	0.168	0.131	76 (41.1%)	83 (44.9%)	0.542	0.077
	T2	92 (42.8%)	206 (37.2%)		-	79 (42.7%)	72 (38.9%)		-
	T3	8 (3.7%)	28 (5.1%)		0.070	6 (3.2%)	6 (3.2%)		0.000
	T4	24 (11.2%)	49 (8.8%)		0.073	19 (10.3%)	22 (11.9%)		0.051
	Unknown	7 (3.3%)	19 (3.4%)		0.010	5 (2.7%)	2 (1.1%)		0.091
N stage, SPLC	N0	152 (70.7%)	411 (74.2%)	0.369	-	131 (70.8%)	134 (72.4%)	0.644	-
	N1	27 (12.6%)	59 (10.6%)		0.057	23 (12.4%)	25 (13.5%)		0.033
	N2	34 (15.8%)	75 (13.5%)		0.062	29 (15.7%)	25 (13.5%)		0.059
	Unknown	2 (0.9%)	9 (1.6%)		0.072	2 (1.1%)	1 (0.5%)		0.056
Grade, SPLC	I	24 (11.2%)	73 (13.2%)	0.063	0.064	21 (11.4%)	29 (15.7%)	0.297	**0.137**
	II	35 (16.3%)	162 (29.2%)		0.350	32 (17.3%)	32 (17.3%)		0.000
	III	66 (30.7%)	97 (17.5%)		-	54 (29.2%)	53 (28.6%)		-
	IV	4 (1.9%)	1 (0.2%)		0.124	1 (0.5%)	1 (0.5%)		0.000
	Unknown	86 (40.0%)	221 (39.9%)		0.002	77 (41.6%)	70 (37.8%)		0.077
Size, SPLC	0–3 cm	99 (46.0%)	315 (56.9%)	0.105	-	90 (48.6%)	89 (48.1%)	0.992	-
	3–5 cm	29 (13.5%)	48 (8.7%)		0.141	23 (12.4%)	27 (14.6%)		0.063
	≥ 5 cm	31 (14.4%)	29 (5.2%)		0.261	21 (11.4%)	18 (9.7%)		0.046
	Unknown	56 (26.0%)	162 (29.2%)		0.073	51 (27.6%)	51 (27.6%)		0.000

ADC, adenocarcinoma; ASD, absolute standardized differences; Chemo, chemotherapy group; NSCLC, non-small cell lung cancer; SQCC, squamous cell cancer. Bold values represent an absolute standardized difference value <0.1 among subgroups. **P*-values were calculated through the *t*-test, and the other *P*-values were calculated through Mann-Whitney tests.

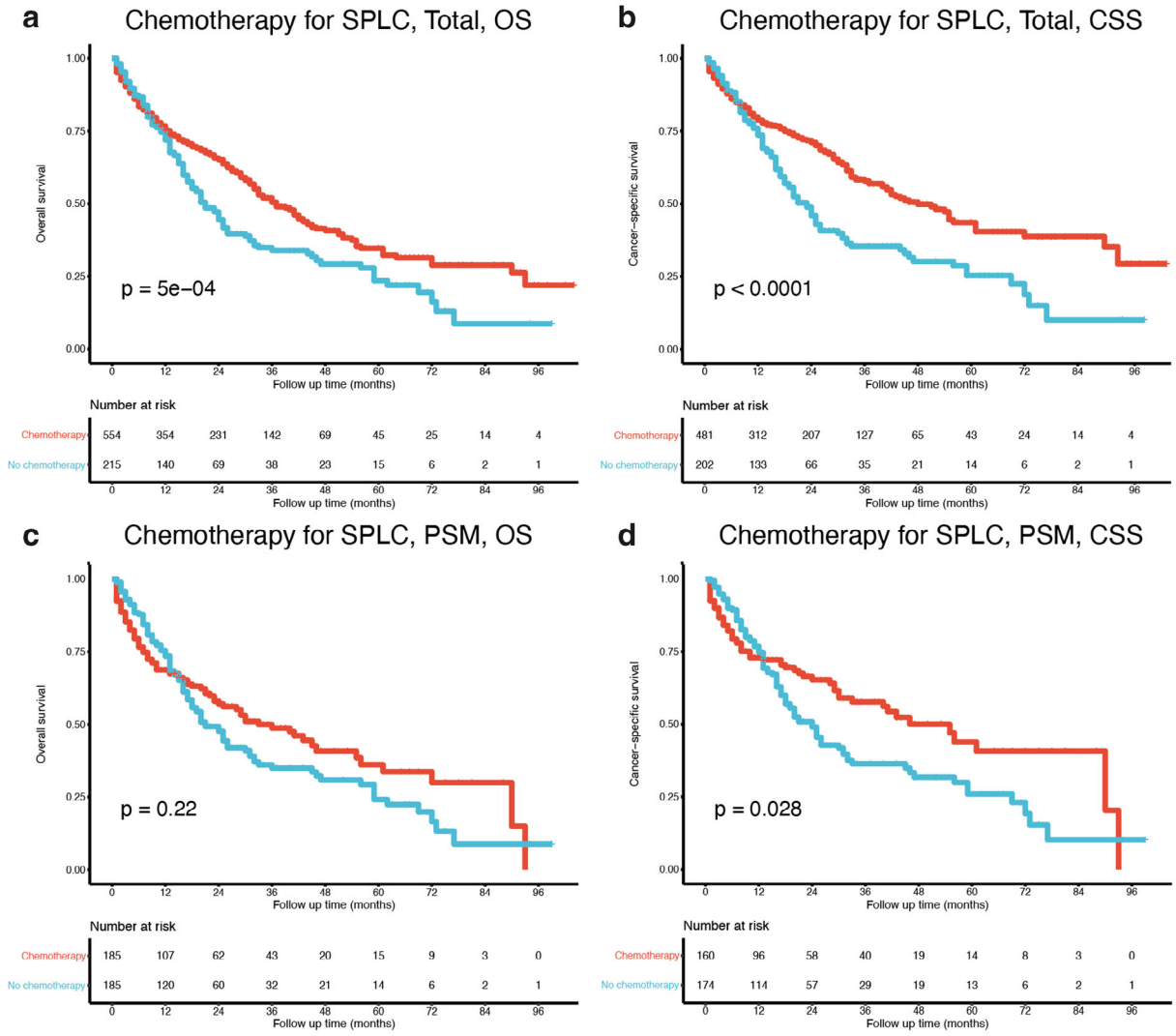

Figure 2 The overall survival (OS) and cancer-specific survival (CSS) curves of chemotherapy group versus nonchemotherapy group before (A and B) (——) Chemotherapy (——) No chemotherapy (——) Chemotherapy (——) No chemotherapy and after propensity score matching (C and D) (——) Chemotherapy (——) No chemotherapy (——) Chemotherapy (——) No chemotherapy.

(other NSCLCs vs. adenocarcinoma, CSS: HR 1.775, $P < 0.05$) and treatment for SPLC (none vs. radiotherapy, CSS: HR 1.836, $P < 0.05$). None of the factors violated the proportional hazards assumption ($P > 0.05$).

The restricted mean survival time values of each subgroup within the truncation time of one-, three- and five-years were calculated based on the four prognostic factors (Tables 6 and 7). Significant differences were observed in restricted mean survival time among age, tumor size for SPLC, histology for SPLC and treatment for SPLC subgroups ($P < 0.05$). The comparisons were conducted between a specific subgroup and all the other subgroups. None of the patients in "tumor size ≥ 5 cm" subgroup, "squamous cell cancer" subgroup and "combined treatment" subgroup reached the truncation time, leaving a null value in restricted mean survival time. For all the patients enrolled, the one-, three- and five-year restricted mean survival time were 10.4 (95% confidence interval [CI]: 10.0–10.8), 21.9 (95% CI: 20.2–23.7) and 29.3 (95% CI: 26.0–32.5) individually.

Relationship of survival probability and selected prognostic factors were analyzed for OS and CSS (Fig 5 and Fig 6). The one-, three- and five-year overall survival probabilities for all the patients enrolled were 2.0%, 33.9% and 23.5%, respectively. The one-, three- and five-year cancer-specific survival probabilities were 74.8%, 37.3% and 27.4%, respectively. The median survival time were 20 and 23 months for OS and CSS individually. All the subgroups

Table 4 Demographic characteristics and univariate Cox regression analysis for overall survival (OS) and cancer-specific survival (CSS) among 215 patients who had accepted chemotherapy for SPLC

			Overall survival			Cancer-specific survival		
Factors	Classification	Number %	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	<64 years	114 (53.0)	-	Reference	-	-	Reference	-
	≥64 years	101 (47.0)	1.559	1.098–2.212	**0.013**	1.661	1.147–2.405	**0.007**
Race	White	182 (84.7)	-	Reference	-	-†	-	-
	Black	23 (10.7)	1.621	0.970–2.709	0.065	-†	-	-
	Others	10 (4.7)	0.570	0.232–1.404	0.222	-†	-	-
Initial primary lung carcinoma								
Surgery	None	42 (19.5)	-	Reference	-	-†	-	-
	Sublevel resection	30 (14.0)	0.607	0.333–1.109	0.104	-†	-	-
	Lobectomy	136 (63.3)	0.607	0.400–0.919	**0.018**	-†	-	-
	Pneumonectomy	7 (3.3)	0.840	0.326–2.165	0.718	-†	-	-
Second primary lung carcinoma								
Tumor size, cm	0–3 cm	99 (46.0)	-	Reference	-	-	Reference	-
	3–5 cm	29 (13.5)	1.488	0.891–2.486	0.129	1.338	0.772–2.318	0.299
	≥5 cm	31 (14.4)	2.838	1.760–4.575	**<0.001**	2.660	1.610–4.395	**<0.001**
	Unknown	56 (26.0)	1.440	0.890–2.330	0.138	1.361	0.818–2.266	0.235
Laterality	Right	123 (57.2)	-	Reference	-	-†	-	-
	Left	89 (41.4)	1.201	0.849–1.701	0.301	-†	-	-
	Unknown	3 (1.4)	1.141	0.279–4.662	0.854	-†	-	-
Histology	SQCC	59 (27.4)	1.408	0.926–2.139	0.109	1.260	0.808–1.967	0.308
	ADC	121 (56.3)	-	Reference	-	-	Reference	-
	Other NSCLCs	35 (16.3)	2.194	1.414–3.404	**<0.001**	2.014	1.262–3.212	**0.003**
Surgery	None	165 (76.7)	-	Reference	-	-†	-	-
	Sublevel resection	24 (11.2)	0.403	0.219–0.742	**0.004**	-†	-	-
	Lobectomy	24 (11.2)	0.542	0.291–1.009	0.053	-†	-	-
	Pneumonectomy	2 (0.9)	-*	-	0.995	-†	-	-
Treatment	Radiotherapy	79 (36.7)	-	Reference	-	-	Reference	-
	Surgery	40 (18.6)	0.499	0.288–0.867	**0.014**	0.552	0.311–0.982	**0.043**
	Combined	10 (4.7)	0.999	0.395–2.528	0.998	1.146	0.449–2.923	0.775
	None	86 (40.0)	1.634	1.107–2.412	**0.013**	1.707	1.128–2.584	**0.011**

95% CI, 95 percent confidence interval; ADC, adenocarcinoma; HR, hazard ratio; NSCLC, non-small cell lung cancer; SQCC, squamous cell cancer. Bold values represent a *P*-value < 0.05 among subgroups. *The number of patients in the subgroups was too low to calculate a reliable value for univariate Cox regression. †Clinicopathological factors were excluded by the least absolute shrinkage and selection operator (LASSO) test for prognostic factors.

of the identified four prognostic factors showed significant differences in survival probability (Fig 5b–e and Fig. 6b–e, $P < 0.05$).

Discussion

Previous studies on second primary lung cancer have been mainly focused on the incidence of second primary lung cancer rather than the prognosis.[3,4,15,16] Age, sex, race, clinical stage and surgery resection of initial primary lung cancer have been proven to be important prognostic factors in the occurrence of second primary lung cancer.[15,16] After a relatively high incidence of second primary lung cancer was reported among initial primary lung cancer patients,[3,4] the importance of prognostic study among second primary lung cancer patients caught the attention of researchers. Smoking, atypical histology, lymph node metastasis and expression of Ki-67 have been proven to be significant risk factors among patients diagnosed with carcinoid as a second primary lung cancer.[17] However, a recent study claimed that histology could not be proven to be a prognostic factor.[9] Furthermore, the treatment strategy among second primary lung cancer patients has also been a major focus for researchers. Surgical resection has been recommended for all second primary lung cancer patients, regardless of other clinicopathological features.[8,18] However, the therapeutic effect of chemotherapy has not yet been verified.

In this study, a total of 769 patients were finally enrolled, and relevant clinicopathological data collected from the SEER database. To select the prognostic factors for both OS and CSS, the LASSO test, univariate and multivariate Cox regression were conducted twice (OS and CSS) to ensure the reliability of the study. The LASSO test screened

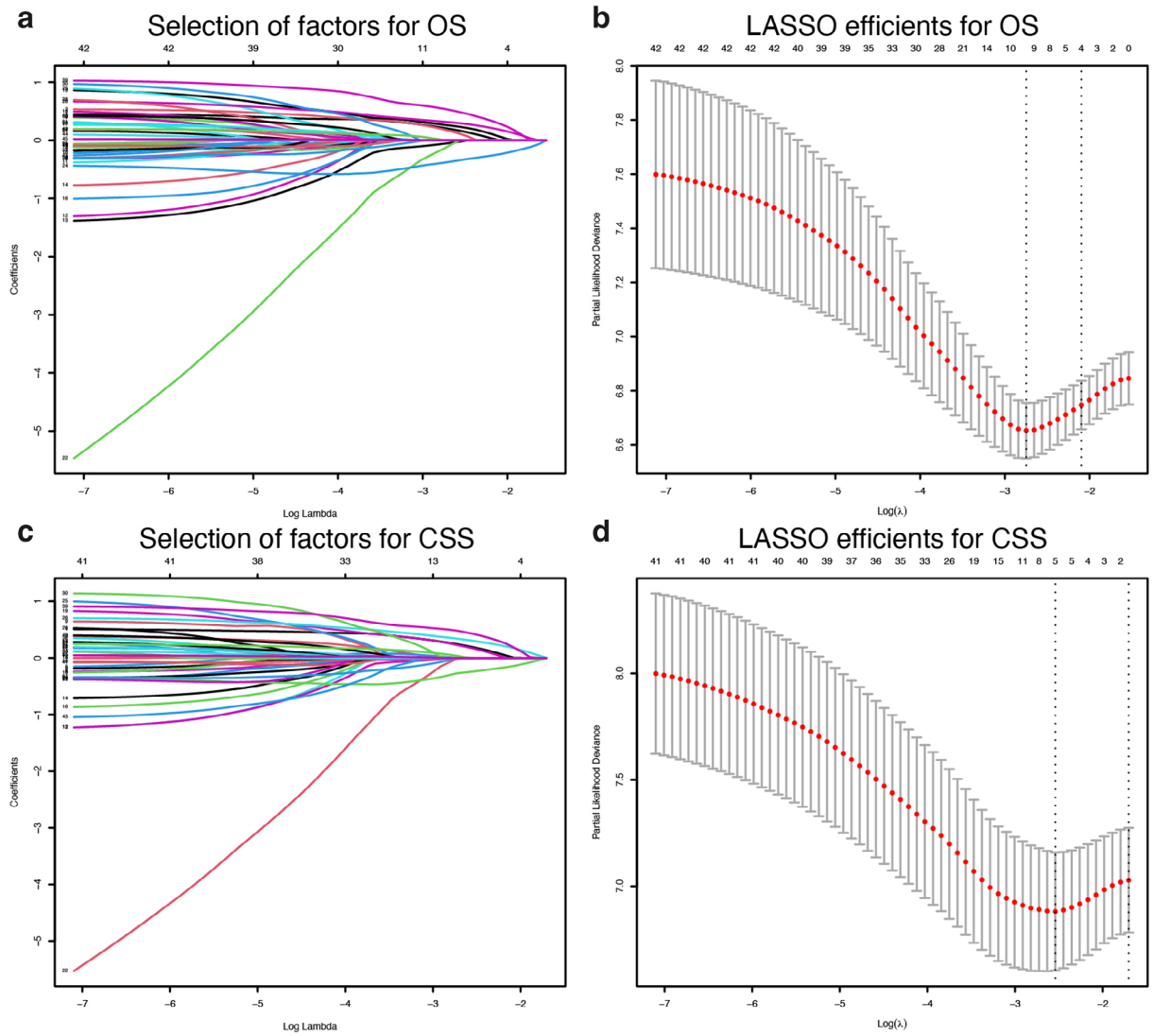

Figure 3 The least absolute shrinkage and selection operator (LASSO) regression on screening prognostic factors among selected 215 patients who had received chemotherapy for second primary lung cancer (SPLC). (**a**) the selection of prognostic factors by 10-fold cross validation for overall survival (OS). (**b**) LASSO coefficients of variables for overall survival (OS). (**c**) the selection of prognostic factors by 10-fold cross validation for cancer-specific survival (CSS). (**d**) LASSO coefficients of variables for cancer-specific survival (CSS).

the clinicopathological features of the enrolled patients. Figure 1a,c showed the relationship between coefficients of variables in the model of the LASSO test and the number of involved variables in the test considering OS and CSS individually. Figures 1b,d show the variation of partial likelihood deviance with the number of variables involved considering OS and CSS. The first dotted line (order: from left to right) highlights the maximum number of variables to reach the requirement of limitation of deviance, and the second dotted line shows the minimum number of variables within the acceptable deviance value range. A final of 14 factors were selected to reach the maximum number of variables possible for OS status (Fig 1a,b), and 15 factors were selected to reach the maximum number of variables possible considering CSS instead of OS (Fig 1c,d). Age, surgery for IPLC, tumor size of SPLC, grade for IPLC and treatment for SPLC were identified as prognostic factors for overall survival status after univariate and multivariate Cox regression (Tables 1 and 2; P-value < 0.05). When analyzing CSS instead of OS, we found that radiotherapy for IPLC, surgery for IPLC, tumor size of SPLC, grade for SPLC and treatment for SPLC were closely related to prognosis (P-value < 0.05).

Table 3 shows the baseline characteristics of the 769 patients who were enrolled in the study. According to whether the patients accepted chemotherapy for SPLC,

Table 5 Multivariate Cox regression analysis for selecting prognostic factors for overall survival (OS) and cancer-specific survival (CSS) among 215 patients who had accepted chemotherapy for SPLC

		Overall survival			Cancer-specific survival		
Characteristic	Classification	HR	95% CI	*P*-value	HR	95% CI	P-value
Age	<64 years	-	Reference	-	-	Reference	-
	≥64 years	1.609	1.110–2.331	**0.012**	1.784	1.208–2.636	**0.004**
Initial primary lung carcinoma							
Surgery	None	-	Reference	-	-†	-	-
	Sublevel resection	0.865	0.458–1.633	0.654	-†	-	-
	Lobectomy	0.701	0.449–1.093	0.117	-†	-	-
	Pneumonectomy	0.745	0.276–2.014	0.562	-†	-	-
Second primary lung carcinoma							
Tumor size, cm	0–3 cm	-	Reference	-	-	Reference	-
	3–5 cm	1.352	0.792–2.307	0.269	1.236	0.699–2.186	0.466
	≥5 cm	2.203	1.306–3.715	**0.003**	2.174	1.261–3.746	**0.005**
	Unknown	1.299	0.790–2.137	0.303	1.225	0.729–2.058	0.444
Histology	Squamous cell cancer	1.182	0.745–1.877	0.478	1.215	0.753–1.958	0.425
	Adenocarcinoma	-	Reference	-	-	Reference	-
	Other NSCLCs	1.773	1.070–2.938	**0.026**	1.775	1.044–3.016	**0.034**
Surgery	None	-	Reference	-	-†	-	-
	Sublevel resection	1.924	0.652–5.674	0.236	-†	-	-
	Lobectomy	2.375	0.829–6.805	0.107	-†	-	-
	Pneumonectomy	-*	-	0.995	-†	-	-
Treatment	Radiotherapy only	-	Reference	-	-	Reference	-
	Surgery only	0.293	0.104–0.822	**0.020**	0.716	0.388–1.319	0.284
	Combined treatment	-*	-	-	1.581	0.582–4.294	0.369
	None	1.749	1.156–2.664	**0.008**	1.836	1.192–2.827	**0.006**

95% CI, 95 percent confidence interval; HR, hazard ratio. Bold values represent a *P*-value < 0.05 among subgroups. *The numbers of patients in the subgroups were too low to calculate a reliable value for univariate Cox regression. †Clinicopathological factors were excluded by the least absolute shrinkage and selection operator (LASSO) test for prognostic factors.

769 patients were classified into the "Chemo" group (accepted chemotherapy for SPLC) and the "None" group (rejected chemotherapy for SPLC). The *P*-value was calculated based on the hypothesis that the distribution of patients between the two groups was the same. A *P*-value less than 0.05 indicated a significant difference in distribution between the "Chemo" and the "None" group. Age ($P < 0.001$), chemotherapy for IPLC ($P < 0.001$) and surgery for SPLC (P 0.016 < 0.05) showed a significant difference. Therefore, despite the fact that chemotherapy for SPLC was not an independent prognostic factor according to the multivariate Cox regression (OS: P 0.344 ≥ 0.05; CSS: P 0.086 ≥ 0.05), we further analyzed the relationship between chemotherapy for SPLC and prognosis due to the significant distribution of characteristics.

To minimize the differences of distribution between the two groups, propensity score matching was introduced into the study.[19–21] Through 1:1 matching process among the enrolled 769 patients, we selected 185 patients from the "Chemo" group and 185 patients who belonged to the "None" group and had similar characteristics to the paired patients in the "Chemo" group. No significant differences were found in the baseline characteristics among the new 370 patients ($P > 0.05$). Survival curves were plotted for both OS and CSS based on the Kaplan-Meier method among the paired 370 patients (Fig 2c,d). When focusing on CSS, we observed significant differences in survival probabilities between the chemotherapy and nonchemotherapy groups (P 0.028 < 0.05), whereas no significant differences were found when observing the survival curves for OS status (P = 0.22 > 0.05). Considering the definition of OS survival and CSS in the study, CSS was more convincible due to the specificity in tumor cases. According to the curve, we concluded that patients who had accepted chemotherapy for SPLC would have a significantly higher CSS compared to patients who had rejected chemotherapy for SPLC. For comparison, survival curves were also plotted among all enrolled patients (769 patients) (Fig 2a,b), and significant differences were observed in both curves between the chemotherapy and nonchemotherapy groups.

Despite all the prognostic indicators and treatment of patients with second primary lung cancer patients, the indication for therapies and the targeted population of a specific therapeutic strategy have not as yet been reported. To analyze the effect of clinicopathological features among patients who had received chemotherapy to treat second

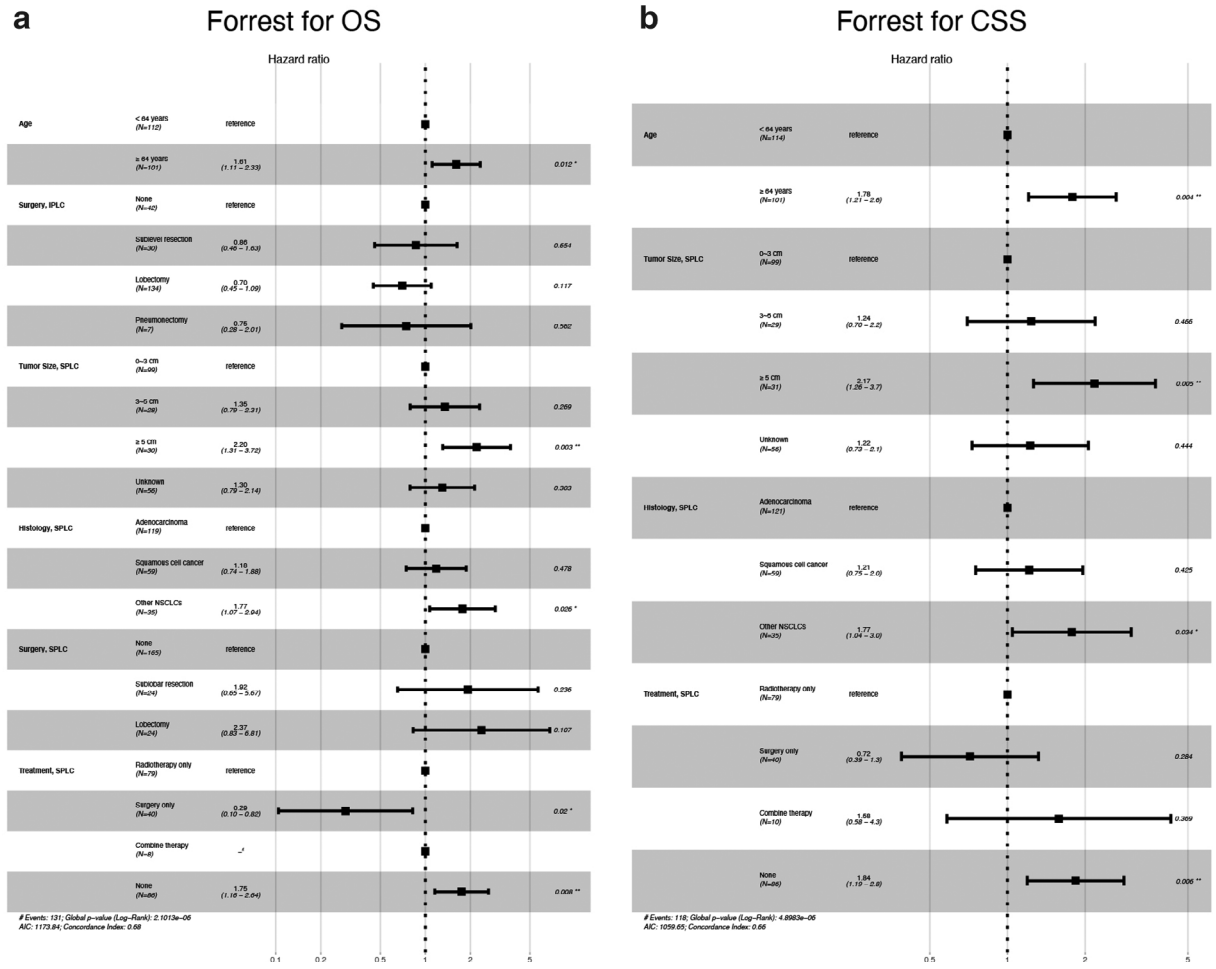

Figure 4 The Forest plot of multivariate Cox regression for overall survival (OS) (**a**) and for cancer-specific survival (CSS) (**b**).

Table 6 The restricted mean survival time (RMST) for the subgroups of selected prognostic factors and treatments for overall survival (OS) among 215 patients who had accepted chemotherapy for SPLC

			RMST, months (95% CI)					
Characteristic	Classification	N	One-year	*P*-value	Three-year	*P*-value	Five-year	*P*-value
All patients	-	215	10.6 (10.2–11.0)	-	22.9 (21.1–24.6)	-	31.0 (27.6–34.3)	-
Age	< 64 years	114	10.6 (10.0–11.1)	0.382	23.5 (21.1–26.0)	0.055	33.3 (28.6–38.0)	**0.007H**
	≥ 64 years	101	10.2 (9.6–10.8)	0.382	20.1 (17.6–22.5)	0.055	24.6 (20.4–28.8)	**0.007L**
Tumor	0–3 cm	99	11.1 (10.6–11.5)	**0.003H**	24.9 (22.5–27.3)	**0.001H**	34.6 (30.1–39.2)	**0.001H**
size, SPLC	3–5 cm	29	10.3 (9.2–11.5)	0.908	20.8 (16.6–25.1)	0.591	26.9 (19.0–34.7)	0.517
	≥ 5 cm	31	8.7 (7.1–10.2)	**0.024L**	-*	-	-	-
Histology, SPLC	Adenocarcinoma	121	10.9 (10.5–11.4)	**0.007H**	24.5 (22.2–26.8)	**0.002H**	33.5 (29.2–37.9)	**0.005H**
	Squamous cell cancer	59	10.0 (9.1–10.9)	0.304	20.5 (17.0–24.0)	0.356	-*	-
	Other NSCLCs	35	9.2 (7.9–10.5)	0.055	15.8 (12.0–19.6)	**0.003L**	18.7 (12.6–24.8)	**0.003L**
Treatment, SPLC	Radiotherapy only	79	10.0 (9.2–10.8)	0.171	21.7 (18.7–24.8)	0.877	30.6 (24.9–36.3)	0.597
	Surgery only	40	11.8 (11.4–12.2)	**<0.001H**	29.1 (25.9–32.3)	**<0.001H**	43.0 (35.9–50.1)	**<0.001H**
	Combined treatment	10	11.5 (10.7–12.2)	**0.009H**	22.5 (15.0–30.0)	0.879	-*	-
	None	86	10.0 (9.3–10.7)	0.152	18.6 (16.0–21.3)	**0.003L**	21.6 (17.6–25.5)	**<0.001L**

95% CI, 95 percent confidence interval; HR, hazard ratio; IPLC, initial primary lung cancer; SPLC, second primary lung cancer. "H" means that the RMST had a significantly higher value, "L" mean s that the RMST had a significantly lower value. Bold values represent a *P*-value <0.05 among subgroups. *None of patients in this subgroup reached the truncation time.

Table 7 The restricted mean survival time (RMST) for the subgroups of selected prognostic factors and treatments for cancer-specific survival (CSS) among 215 patients who had accepted chemotherapy for SPLC

			RMST, months (95% CI)					
Characteristic	Classification	N	One-year	*P*-value	Three-year	*P*-value	Five-year	*P*-value
All patients	-	215	10.4 (10.0–10.8)	-	21.9 (20.2–23.7)	-	29.3 (26.0–32.5)	-
Age	< 64 years	114	10.9 (10.4–11.4)	0.117	24.7 (22.3–27.1)	**0.030H**	35.2 (30.4–39.9)	**0.007H**
	≥ 64 years	101	10.3 (9.7–10.9)	0.117	20.8 (18.3–23.3)	**0.030L**	26.1 (21.6–30.5)	**0.007L**
Tumor	0–3 cm	99	11.1 (10.6–11.5)	**0.034H**	25.3 (22.9–27.7)	**0.005H**	35.6 (31.0–40.3)	**0.005H**
size, SPLC	3–5 cm	29	10.8 (9.9–11.8)	0.684	22.6 (18.3–26.9)	0.891	29.6 (21.3–38.0)	0.724
	≥ 5 cm	31	9.5 (8.0–10.9)	0.095	-*	-	-	-
Histology, SPLC	Adenocarcinoma	121	11.0 (10.6–11.4)	**0.034H**	25.0 (22.7–27.3)	**0.007H**	34.4 (30.0–38.8)	**0.030H**
	Squamous cell cancer	59	10.4 (9.6–11.2)	0.502	21.9 (18.3–25.4)	0.533	-*	-
	Other NSCLCs	35	9.6 (8.4–10.9)	0.094	17.0 (13.0–21.0)	**0.007L**	20.6 (13.8–27.3)	**0.007L**
Treatment, SPLC	Radiotherapy only	79	10.4 (9.7–11.1)	0.355	23.1 (20.0–26.1)	0.859	32.9 (26.9–38.8)	0.446
	Surgery only	40	11.8 (11.4–12.2)	**<0.001H**	29.1 (25.9–32.3)	**<0.001H**	43.0 (35.9–50.1)	**<0.001H**
	Combined treatment	10	11.5 (10.7–12.2)	**0.035H**	22.5 (15.0–30.0)	0.922	-*	-
	None	86	10.2 (9.5–10.9)	0.105	19.6 (16.9–22.3)	**0.004L**	23.2 (18.9–27.5)	**<0.001L**

95% CI, 95 percent confidence interval; HR, hazard ratio; IPLC, initial primary lung cancer; SPLC, second primary lung cancer. "H" means that the RMST had a significantly higher value, "L" mean s that the RMST had a significantly lower value. Bold values represent a *P*-value < 0.05 among subgroups. *None of patients in this subgroup reached the truncation time.

primary lung cancer, we selected 215 patients who had received chemotherapy for SPLC out of the 769 enrolled patients. Through LASSO regression screening, univariate Cox regression and multivariate Cox regression, four clinicopathological features were finally chosen as the prognostic factors for both OS and CSS, including age, tumor size for SPLC, histology for SPLC and treatment for SPLC ($P < 0.05$) (Table 4, Table 5, Fig 3 and Fig 4). Through survival curve plotting, these factors were proved to be significant prognostic factors for second primary lung cancer (Fig 5 and Fig 6). The restricted mean survival time of each group was calculated to avoid the possible bias of different follow-up time among cases. The comparison of restricted mean survival time was conducted in each subgroup to verify the prognostic factors (Table 6 and Table 7). According to the restricted mean survival time results for CSS (Table 7), an older age (≥ 64 years) was a significant risk factor during three-year and five-year truncation time ($P < 0.05$). The tumor size data showed significant differences in restricted mean survival time values among subgroups. Patients with smaller tumors (0–3 cm) acquired longer restricted mean survival time compared to other subgroups during one-, three- and five-year truncation time ($P < 0.05$). None of the patients who had tumors of ≥5 cm survived three years, making the data difficult to analyze. Similar results have been reported in a recent retrospective study among patients diagnosed with carcinoids as second primary lung cancer.[22] Among histology subgroups, patients with adenocarcinoma as second primary lung cancer reported a significantly longer restricted mean survival time during one-, three- and five-year truncation time ($P < 0.05$), and patients with other NSCLCs (such as large cell carcinoma, carcinoid tumor, oat cell carcinoma, etc) as second primary lung cancer showed significantly shorter restricted mean survival time during three- and five-year truncation time ($P < 0.05$).

As for treatment (surgery and radiotherapy condition), patients who received surgical resection for SPLC acquired significantly longer restricted mean survival time during one-, three- and five-year truncation time ($P < 0.001$), which supported the traditional conclusion.[8] Patients who received both radiotherapy and surgery for SPLC also reported longer restricted mean survival time during three-year survival time ($P < 0.05$). Patients with no treatment for SPLC reported a significantly shorter restricted mean survival time during three- and five-year truncation time ($P < 0.05$), whereas differences in restricted mean survival time were not significant for patients who received radiotherapy ($P > 0.05$).

All the restricted mean survival time findings support the view that surgery is still recommended for the treatment of second primary lung cancer among patients who have received chemotherapy. For patients age < 64 years, histological type of adenocarcinoma and tumor size <3 cm are expected to have more benefit from chemotherapy for SPLC in restricted mean survival time than the ordinary population.

There were some limitations in the study. (i) The cohort study was retrospective, and we were therefore unable to evaluate the therapeutic effect of chemotherapy. A prospective cohort study would be more convincing to clarify the therapeutic effect. (ii) The data of newest therapeutic

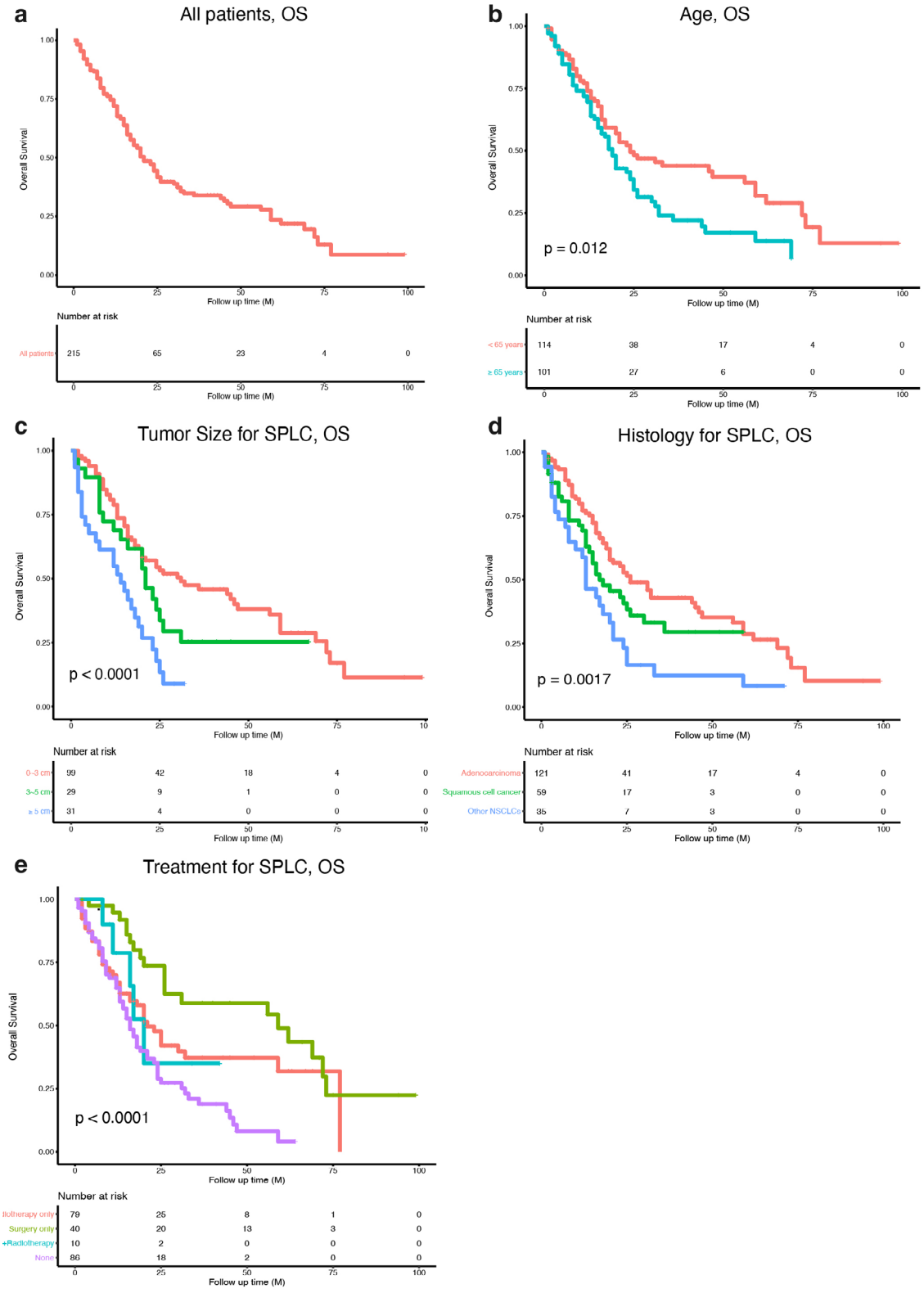

Figure 5 The overall survival (OS) curves of patients who had received chemotherapy for second primary lung cancer (SPLC) among selected prognostic factors subgroups. (**a**) The overall survival (OS) curve among all patients (——) All patients. (**b**–**e**) The overall survival (OS) curves among patients in different subgroups (——) <65 years (——) ≥65years (——) 0–3 cm (——) 3–5 cm (——) ≥5 cm (——) Adenocarcinoma (——) Squamous cell cancer (——) Other NSCLCs (——) Radiotheraphy only (——) Surgery only (——) Surgery + radiotheraphy (——) None.

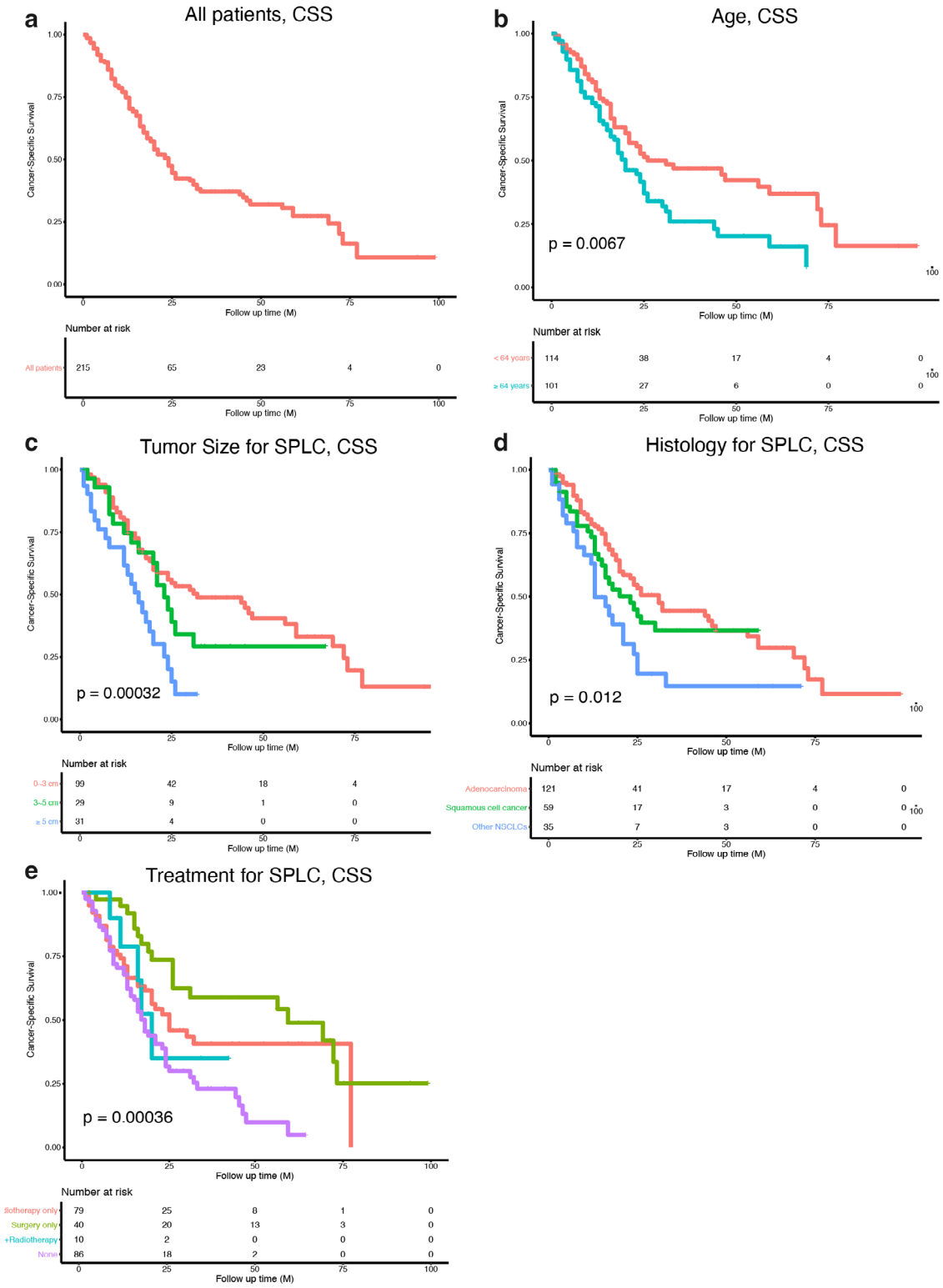

Figure 6 The cancer-specific survival (CSS) curves of patients who had received chemotherapy for second primary lung cancer (SPLC) among selected prognostic factors subgroups. (**a**) The overall survival (OS) curve among all patients (——) All patients. (**b**–**e**) The overall survival (OS) curves among patients in different subgroups (——) <64 years (——) ≥64 years (——) 0–3cm (——) 3–5 cm (——) ≥5 cm (——) Adenocarcinoma (——) Squamous cell cancer (——) Other NSCLCs (——) Radiotheraphy only (——) Surgery only (——) Surgery + radiotheraphy (——) None.

strategies were missing in the SEER database, while the effect of immunotherapy had been proven in many previous studies of NSCLC. Since immunotherapy may be an important treatment for second primary lung cancer, future studies should verify the therapeutic effect of immunotherapy by enrolling the patients who received immunotherapy for second primary lung cancer.

In conclusion, chemotherapy could significantly improve the cancer-specific survival probability. Age (< 64 years), tumor size (0–3 cm) and histology of adenocarcinoma for second primary lung cancer were determined to be protective factors among patients who had received chemotherapy as treatment for second primary NSCLC.

Disclosure

The authors confirm that there are no conflicts of interest.

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