Thoracic Cancer
Open Access
Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Survival comparison of right and left side non-small cell lung cancer in stage I–IIIA patients: A Surveillance Epidemiology and End Results (SEER) analysis

Bo Jia[1*], Qiwen Zheng[2*], Xinmeng Qi[3], Jun Zhao[1], Meina Wu[1], Tongtong An[1], Yuyan Wang[1], Minglei Zhuo[1], Jianjie Li[1], Xinghui Zhao[1], Xue Yang[1], Jia Zhong[1], Hanxiao Chen[1], Zhi Dong[1], Youwu Shi[4], Feng Du[4], Jingjing Wang[1], Yujia Chi[1], Xiaoyu Zhai[1] & Ziping Wang[1]

1 Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Thoracic Medical Oncology, Peking University Cancer Hospital and Institute, Beijing, China
2 Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China
3 Department of Otolaryngology Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University Key Laboratory of Otolaryngology Head and Neck Surgery (Capital Medical University), Ministry of Education, Beijing, China
4 Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), The VIPII Gastrointestinal Cancer Division of Medical Department, Peking University Cancer Hospital and Institute, Beijing, China

Keywords
Left side; NSCLC; right side; SEER; survival.

Correspondence
Ziping Wang, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Thoracic Medical Oncology, Peking University Cancer Hospital and Institute, 52 Fucheng Road, Haidian District, Beijing 100142, China.
Tel: +86 10 8819 6660
Email: wangzp2007@126.com

*These authors contributed equally to this work and should be considered co-first authors.

Parts of these results were presented at the 2018 American Society of Clinical Oncology Annual Meeting (Abstract #8524).

Received: 29 October 2018;
Accepted: 6 December 2018.

doi: 10.1111/1759-7714.12959

Thoracic Cancer **10** (2019) 459–471

Abstract

Background: Primary tumors located in the right and left side have distinctive prognoses, but the details have not been fully identified in non-small cell lung cancer (NSCLC). This study investigated the impact of primary tumor side on long-term survival in NSCLC patients.

Methods: Data of 90 407 patients from the Surveillance, Epidemiology, and End Results (SEER) Program were analyzed. To avoid bias between groups, we used innovative propensity score matching (PSM) analysis.

Results: There was no significant distinction in overall survival (OS) between right (n = 53 496) and left (n = 36 911) side tumors (hazard ratio [HR] 0.993, 95% confidence interval [CI] 0.9756–1.011; P = 0.432). Left side was associated with superior five-year cancer-specific survival (CSS) compared to right side NSCLC (HR 0.977, 95% CI 0.9574–0.9969; P = 0.024). No significant difference was observed in OS (P = 0.689) or CSS (P = 0.288) after PSM analysis. In the 51 319 patients who underwent surgery, left side (n = 21 245) was associated with poor OS compared to right side (n = 30 074) NSCLC (HR 1.039, 95% CI 1.011–1.067; P = 0.006), while CSS was similar (HR 1.031, 95% CI 0.997–1.065; P = 0.069). In patients who underwent surgery, there was also no significant difference in OS (P = 0.986) or CSS (P = 0.979) after PSM analysis.

Conclusion: The prognosis between right and left side NSCLC in stage I–IIIA was similar regardless of whether patients underwent surgery. Primary tumor side cannot be considered a prognostic factor when choosing appropriate treatment.

Introduction

Lung cancer is the leading cause of cancer morbidity and mortality in China and worldwide, with an estimated 0.7 million new cases and 0.6 million deaths per year in China.[1,2] Non-small cell lung cancer (NSCLC) accounts for approximately 75–80% of all lung cancer cases,[3] thus NSCLC is a major health problem worldwide.

Several studies have reported distinctions in cancer mortality between primary tumors located on different sides. Differences in regard to factors such as epidemiology, clinical characteristics, genetic mutations, and prognosis have been reported in right and left side colon cancer. The prognosis of right versus left side lung cancer might be different because of several factors. First, the left lung consists of

two lobes and eight segments, whereas the right lung includes three lobes and 10 segments; thus the right lung is thought to make a greater contribution to overall lung function than the left lung.[4] As a result, remaining lung function after surgery might be different, which could affect long-term survival. Previous studies have shown that the risk of death after right pneumonectomy is higher than that after left.[5,6] Second, it has been reported that lung cancer located in different sides follow different routes and skip metastasis to mediastinal lymph nodes. For instance, a tumor located in the left upper lobe first metastasizes to station 5, whereas a tumor in the right upper lobe first metastasizes to station 4. Lymph node metastasis patterns could affect prognosis because patients with single skipping metastasis to mediastinal lymph nodes show better survival outcomes than patients with mediastinal lymph node metastases.[7] Third, left and right side lung cancer might have different biological and gene mutation features. Tumors with *EGFR* L858R mutation are most commonly located on the right side, whereas tumors without *EGFR* mutation are found on the left. Male smokers aged > 50 with primary a tumor on the right are more likely to harbor *KRAS* mutations.[8] Fourth, the vascular supply between right and left side may vary. As a result of these factors, it is reasonable to hypothesize that long-term survival may vary between right and left side lung cancer, and thus require different treatment strategies. However, these variations have not yet been fully identified.

Previous studies have mainly focused on the impact of pneumonectomy on cancer mortality between right and left side NSCLC, but less information on patients receiving other types of surgical procedures is available.[9,10] Because surgery is the most important treatment method for stage I–IIIA NSCLC, illustrating the survival difference in such patients is of great value. The choice of surgical procedure is closely related to primary tumor site, which could greatly influence survival. Moreover, primary tumor location may have a greater impact on survival in patients without distant metastasis, and this information will be useful for physicians to develop appropriate treatment strategies. Therefore, the purpose of this study was to investigate the impact of primary tumor side on long-term survival in patients with stage I–IIIA NSCLC in order to further develop the best treatment strategies.

Methods

Data source

Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute across 18 cancer registries in the United States were used for the present study.[11] The database was accessed using SEER* Stat 8.3.4 (https://seer.cancer.gov/seerstat, 23 March 2017). The North American Association of Central Cancer Registries (NAACCR) documented the data and codes.[12] Primary cancer site and histology were coded using the third edition of the International Classification of Diseases for Oncology (ICD-O-3).

Cohort selection

Data of patients with lung tumors (site codes, C34.0-C34.9) at stage I–IIIA according to the sixth edition of the American Joint Committee on Cancer (AJCC) classification and aged ≥ 18 years were extracted from the SEER database between 2004 and 2014. The following histologic codes were designated as NSCLC: 8010, 8012, 8013, 8014,8015, 8020,8021,8022,8031,8032, 8046, 8050–8052, 8070–8078, 8140–8147, 8250–8255, 8260, 8310,8323, 8430, 8480, 8481,8482, 8490, 8560, and 8570–8575. Patients diagnosed with small cell lung cancer (ICD-0-3 8041–8045) and those with unknown primary tumor location were excluded. The research ethics board of Beijing Cancer Hospital exempted ethical review as the authors could not access patient's identities. However, according SEER database requirements, we obtained data agreement and files were downloaded directly from the SEER website (Fig S1).13

Statistical analysis

Patients were categorized into two cohorts: left and right side lung cancer. Categorical variables are presented as counts and frequencies. The chi-square test was used to compare categorical data between independent groups. After descriptive analysis, the impact of lung cancer location on overall survival (OS) and cancer-specific survival (CSS) was assessed by Cox proportional hazard models with and without risk-adjustment for tumor stage, T-stage, N-stage, original site, histology, type of operation, number of lymph nodes dissected, radiation, chemotherapy, year of diagnosis, age, gender, and ethnicity.

Propensity score matching (PSM) was used to match the treatment groups as closely as possible.

Logistic regression was used to estimate the probability of cancer location as the function of the following baseline characteristics: T-stage, N-stage, original site, histology, number of lymph nodes dissected, radiation, chemotherapy, year of diagnosis, age, gender, and ethnicity. Under the stratification of tumor stage, PSM (1:1) was then performed using a nearest neighbor-matching algorithm with a maximum caliper distance of 0.25 of the standard deviation of the propensity score. To assess

Table 1 Characteristics of all stage I–IIIA NSCLC patients

Characteristic	Patient characteristics			
	Total N = 90 407	Right-side N = 53 496	Left-side N = 36 911	*P* †
Tumor stage (AJCC 6th ed.)				
Stage I	52 409 (58.0)	30 628 (57.3)	21 781 (59.0)	< 0.001
Stage II	12 906 (14.3)	7307 (13.7)	5599 (15.2)	
Stage IIIA	25 092 (27.8)	15 561 (29.1)	9531 (25.8)	
T-stage				
T1	34 756 (38.4)	20 574 (38.5)	14 182 (38.4)	< 0.001
T2	45 061 (49.8)	26 579 (49.7)	18 482 (50.1)	
T3	8712 (9.6)	5123 (9.6)	3589 (9.7)	
TX	1878 (2.1)	1220 (2.3)	658 (1.8)	
N-stage				
N0	56 467 (62.5)	32 925 (61.5)	23 542 (63.8)	< 0.001
N1	10 084 (11.2)	5708 (10.7)	4376 (11.9)	
N2	23 856 (26.4)	14 863 (27.8)	8993 (24.4)	
Original site				
Lung lobe	85 247 (94.3)	50 254 (93.9)	34 993 (94.8)	< 0.001
Main bronchus	2048 (2.3)	1169 (2.2)	879 (2.4)	
Overlapping lesion of lung	1030 (1.1)	786 (1.5)	244 (0.7)	
NOS	2082 (2.3)	1287 (2.4)	795 (2.2)	
Histology				
Adenocarcinoma	45 172 (50.0)	27 458 (51.3)	17 714 (48.0)	< 0.001
Squamous cell carcinoma	30 153 (33.4)	17 065 (31.9)	13 088 (35.5)	
Large cell carcinoma	2629 (2.9)	1552 (2.9)	1077 (2.9)	
Other	2110 (2.3)	1235 (2.3)	875 (2.4)	
NSCLC NOS	10 343 (11.4)	6186 (11.6)	4157 (11.3)	
Operation				
Lobectomy	40 245 (44.5)	24 236 (45.3)	16 009 (43.4)	< 0.00.
Pneumonectomy	2683 (3.0)	1150 (2.1)	1533 (4.2)	
Segmental resection/wedge resection	7629 (8.4)	4237 (7.9)	3392 (9.2)	
Local tumor excision	312 (0.3)	181 (0.3)	131 (0.4)	
Other	450 (0.5)	270 (0.5)	180 (0.5)	
Surgery NOS	39 088 (43.2)	23 422 (43.8)	15 666 (42.4)	
Lymph node dissection				
1–3 removed	9104 (10.1)	5718 (10.7)	3386 (9.2)	< 0.001
≥ 4 removed	37 080 (41.0)	21 384 (40.0)	15 696 (42.5)	
None/unknown	44 223 (48.9)	26 394 (49.3)	17 829 (48.3)	
Radiation				
None/unknown	59 861 (66.2)	35 297 (66.0)	24 564 (66.5)	0.062
Other (isotope, implant, or combination)	698 (0.8)	396 (0.7)	302 (0.8)	
Beam radiation	29 848 (33.0)	17 803 (33.3)	12 045 (32.6)	
Chemotherapy				
Yes	30 619 (33.9)	18 317 (34.2)	12 302 (33.3)	0.005
No/unknown	59 788 (66.1)	35 179 (65.8)	24 609 (66.7)	
Year				
2004–2007	30 861 (34.1)	18 321 (34.2)	12 540 (34.0)	0.655
2008–2011	33 086 (36.6)	19 565 (36.6)	13 521 (36.6)	
2012–2014	26 460 (29.3)	15 610 (29.2)	10 850 (29.4)	
Age				
≤ 40 years	445 (0.5)	254 (0.5)	191 (0.5)	0.004
41–69 years	45 062 (49.8)	26 904 (50.3)	18 158 (49.2)	
70+ years	44 900 (49.7)	26 338 (49.2)	18 562 (50.3)	
Gender				
Male	46 379 (51.3)	27 327 (51.1)	19 052 (51.6)	0.116
Female	44 028 (48.7)	26 169 (48.9)	17 859 (48.4)	

Table 1 Continued

Characteristic	Patient characteristics			
	Total N = 90 407	Right-side N = 53 496	Left-side N = 36 911	*P* †
Ethnicity				
Caucasian	74 701 (82.6)	43 992 (82.2)	30 709 (83.2)	0.001
African-American	9656 (10.7)	5889 (11.0)	3767 (10.2)	
Asian	5067 (5.6)	3020 (5.6)	2047 (5.5)	
Other/unknown	983 (1.1)	595 (1.1)	388 (1.1)	

†The chi-square test was used to compare categorical data between independent groups. AJCC, American Joint Committee on Cancer; NSCLC, non-small cell lung cancer; NOS, not otherwise specified.

matching performance, baseline categorical variables were compared between the matched groups, and standardized differences were calculated for which a difference between −0.1 and 0.1 is generally considered negligible. Statistical analysis was performed using R software (version 3.3.3; http://www.r-project.org). The reported significance levels were all two-sided, with statistical significance set at 0.05.

Results

Patient characteristics

Data of 90 407 out of 254 525 stage I–IIIA NSCLC patients between 2004 and 2014 were included. Of these patients, 53 496 had right side and 36 911 patients had left side NSCLC. Table 1 compares the patient characteristics between the groups. Before matching, these two groups were imbalanced in tumor stage, T-stage, N-stage, original site, histology, operation method, lymph node dissection, chemotherapy, age, and ethnicity. Characteristics in NSCLC patients with right side tumors were: more advanced stages ($P < 0.001$); less T2 and T3 ($P < 0.001$); higher N-stage ($P < 0.001$); fewer patients had ≥ 4 lymph nodes dissected ($P < 0.001$); and more often had overlapping lung lesions ($P < 0.001$), adenocarcinomas ($P < 0.001$), underwent lobectomy ($P < 0.001$), were administered chemotherapy, ($P = 0.005$), aged > 70+ ($P = 0.004$), and were Asian ($P = 0.001$). Of the 51 319 patients who underwent surgery, 30 074 had right side and 21 245 had left side NSCLC. These two groups were also imbalanced in tumor stage, N-stage, original site, histology, operation method, lymph node dissection, chemotherapy, and gender. Left side NSCLC patients had: more advanced stages ($P < 0.001$); higher N-stage ($P < 0.001$); and more often had main bronchus tumors ($P < 0.001$), ≥ 4 regional lymph nodes dissected ($P < 0.001$), squamous cell carcinoma ($P < 0.001$), underwent lobectomy ($P < 0.001$), administered chemotherapy ($P = 0.020$), and were male ($P = 0.036$) (Table S1).

Survival

For all 90 407 patients, the mean follow-up was 31.25 ± 30.90 months and the median follow-up was 20 (interquartile range [IQR] 8–46) months. At the end of the follow-up period, 39 340 (43.51%) patients were alive, 39 054 (43.20%) had died from lung cancer, and 12 013 (13.29%) had died as the result of other causes. The five-year OS rate for patients with right side NSCLC was 36.3% (95% CI 35.8–36.8%) compared to 36.5% (95% CI 35.9–37.1%) for patients with left side NSCLC. The OS curve showed no significant difference between groups with an HR of 0.993 (95% CI 0.9756–1.011; $P = 0.432$). The five-year CSS rate in patients with right side NSCLC was 45.9% (95% CI 45.4–46.5%) compared to 46.7% (95% CI 46.1–47.3%) in patients with left side NSCLC. CSS was significantly longer in left side versus right side lung cancer patients (HR 0.977, 95% CI 0.9574–0.9969; $P = 0.024$) (Fig 1). However, after multivariable adjustment, no significant difference was observed in OS (HR 1.002, 95% CI 0.985–1.020; $P = 0.801$) or CSS (HR 1.000, 95% CI 0.980–1.021; $P = 0.972$) (Table 2).

In the 51 319 patients who underwent surgery, the mean follow-up was 41.19 ± 33.73 months and the median follow-up was 32 (IQR 13–63) months. At the end of the follow-up period, 29 991 (58.44%) patients were alive, 14 659 (28.56%) had died from lung cancer, and 6669 (13.00%) had died as a result of other causes. The five-year OS rate in patients with right side NSCLC was 54.6% (95% CI 53.9–55.3%) compared to 53.6% (95% CI 52.8–54.4%) in patients with left side NSCLC. OS was significantly longer in patients with right side versus left side lung cancer (HR 1.039, 95% CI 1.011–1.067; $P = 0.006$). The five-year CSS rate for patients with right side NSCLC was 65.0% (95% CI 64.4–65.7%) compared to 64.3% (95% CI 63.5–65.1%) for patients with left side NSCLC. CSS was similar between the groups (HR 1.031, 95% CI 0.997–1.065; $P = 0.069$) (Fig 2). No significant difference was observed in OS (HR 0.988, 95% CI 0.961–1.016; $P = 0.403$) or CSS (HR 0.983, 95% CI 0.951–1.016; $P = 0.331$) after multivariable adjustment.

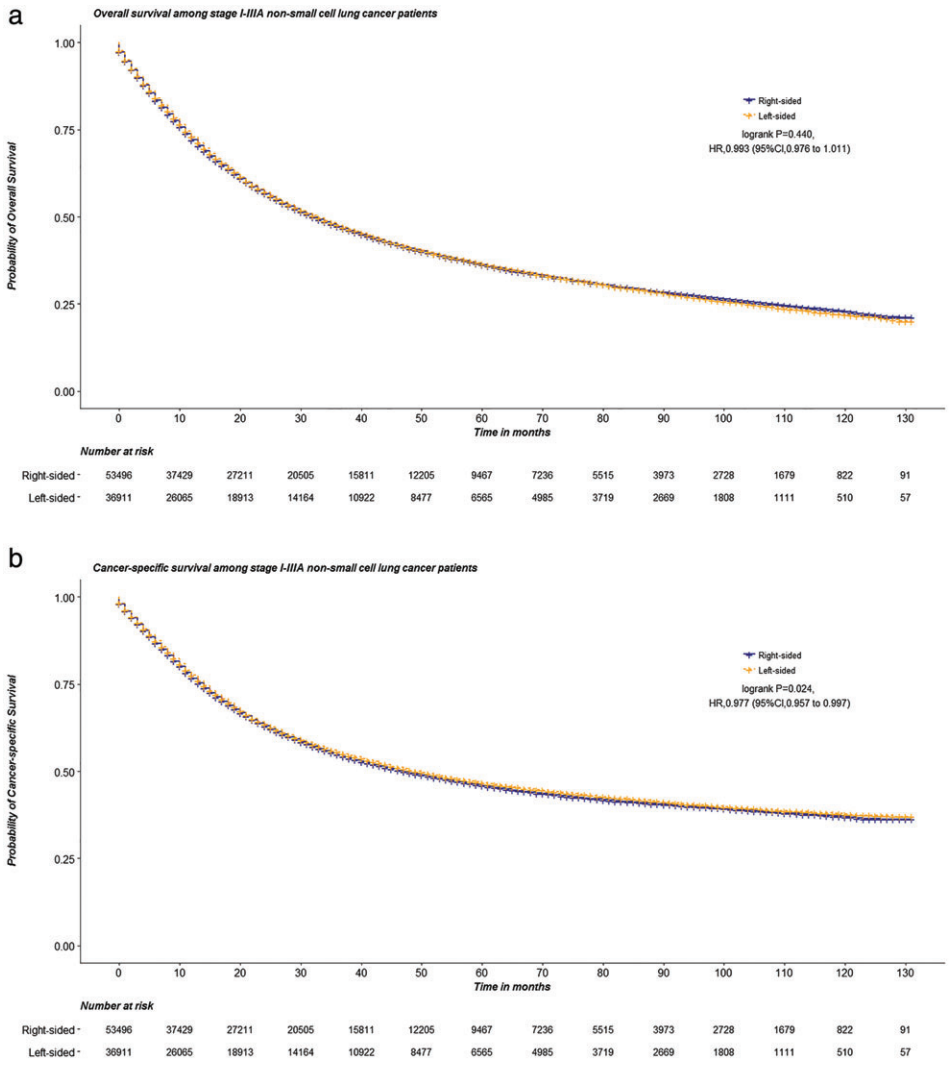

Figure 1 Overall survival (OS) and cancer-specific survival (CSS) among stage I–IIIA non-small cell lung cancer (NSCLC) patients. The five-year OS rate for patients with right side NSCLC was 36.3% (95% confidence interval [CI] 35.8–36.8%) compared to 36.5% (95% CI 35.9–37.1%) for patients with left side NSCLC. The OS curve showed no significant difference between groups (hazard ratio [HR] 0.993 (95% CI 0.9756–1.011; P = 0.432). The five-year CSS rate for patients with right side NSCLC was 45.9% (95% CI 45.4–46.5%) compared to 46.7% (95% CI 46.1–47.3%) in patients with left side NSCLC. CSS was significantly longer in patients with left side than right side lung cancer (HR 0.977, 95% CI 0.9574–0.9969; P = 0.024). (**a**) (—+—) Right side, (···+···) left side, logrank P = 0.440, HR 0.993 (95% CI 0.976–1.011) and (**b**) (—+—) Right side, (···+···) left side, logrank P = 0.024, HR 0.977 (95% CI 0.957–0.997).

In multivariate analysis, regardless of primary tumor location, patients with significantly poorer CSS were characterized by: more advanced stages (P < 0.001), higher T-stage (P < 0.001), primary tumor in main bronchus or overlapping pulmonary lobes (P < 0.001), non-adenocarcinoma (P < 0.001), did not undergo lobectomy (P < 0.001), were not administered chemotherapy (P < 0.001), were administered radiotherapy (P < 0.001), diagnosed before 2008 (P < 0.001), aged > 40 years (P < 0.001), male (P < 0.001), Caucasian (P = 0.026) and received less than 4 regional lymph nodes dissection (P < 0.001).

Because there were significant imbalances in patient characteristics between right and left side NSCLC, bipartite PSM analysis was performed to further investigate whether primary tumor location had an impact on survival. In all patients, before matching, the propensity score for right side NSCLC was 0.404 ± 0.048 compared to 0.414 ± 0.051 for left side NSCLC (P < 0.001). After matching, the propensity scores of NSCLC patients with right and left side tumors were both 0.411 ± 0.045 (P = 0.932), which was well balanced by clinicopathologic characteristics (Table S2). After matching, 72 102 patients were included for further analysis and both groups included 36 051 patients. There were no significant differences in OS (HR 0.99, 95% CI 0.97–1.02; P = 0.689) or CSS (HR 0.99, 95% CI 0.96–1.02; P = 0.288) in regard to tumor location (Fig 3).

In patients who underwent surgery, before matching, the propensity score for right side NSCLC was 0.408 ± 0.057 compared to 0.422 ± 0.061 for left side NSCLC (P < 0.001). After matching, the propensity scores for right and left side NSCLC patients were both 0.417 ± 0.052 (P = 0.801) (Table S3). After matching, 40 162 patients were included for further analysis and both groups included 20 081 patients. There was no significant difference in OS (HR 0.99, 95% CI 0.96–1.02; P = 0.375) or CSS (HR 0.98, 95% CI 0.94–1.02; P = 0.263) (Fig 4).

Table 2 Prognostic factors for overall and cancer-specific mortality in all stage I–IIIA NSCLC patients

	Cox regression for overall survival				Cox regression for cancer-specific survival			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
Locations and stage	HR (95% CI)	*P*†	HR (95% CI)	*P*‡	HR (95% CI)	*P*†	HR (95% CI)	*P*‡
Cancer location								
Right side	Reference	0.432	Reference	0.801	Reference	0.024	Reference	0.972
Left side	0.993 (0.9756–1.011)		1.002 (0.985–1.020)		0.977 (0.957–0.997)		1.000 (0.980–1.021)	
Tumor stage (AJCC 6th ed)								
Stage I	Reference	< 0.001	Reference	< 0.001	Reference	<0.001	Reference	< 0.001
Stage II	1.680 (1.639–1.723)		1.598 (1.510–1.692)		2.034 (1.977–2.093)		1.771 (1.665–1.884)	
Stage IIIA	2.537 (2.489–2.587)		1.726 (1.537–1.937)		3.255 (3.185–3.328)		1.913 (1.689–2.165)	
T-stage								
T1	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
T2	1.747 (1.713–1.782)		1.498 (1.467–1.530)		2.084 (2.035–2.134)		1.689 (1.648–1.732)	
T3	2.733 (2.654–2.814)		1.693 (1.619–1.770)		3.539 (3.425–3.656)		1.953 (1.861–2.049)	
TX	3.924 (3.726–4.131)		1.445 (1.367–1.527)		5.133 (4.855–5.427)		1.600 (1.507–1.699)	
N-stage								
N0	Reference	< 0.001	Reference	0.325	Reference	< 0.001	Reference	0.136
N1	1.497 (1.457–1.539)		1.031 (0.970–1.096)		1.765 (1.711–1.821)		1.052 (0.984–1.124)	
N2	2.395 (2.349–2.441)		1.063 (0.951–1.187)		2.995 (2.931–3.060)		1.110 (0.985–1.248)	
Original site								
Lung lobe	Reference	< 0.001	Reference	0.011	Reference	< 0.001	Reference	< 0.001
Main bronchus	1.997 (1.900–2.100)		1.068 (1.015–1.125)		2.236 (2.118–2.360)		1.088 (1.030–1.150)	
Overlapping lesion of lung	1.112 (1.028–1.203)		1.083 (0.999–1.172)		1.199 (1.099–1.309)		1.125 (1.030–1.230)	
NOS	1.947 (1.851–2.048)		1.153 (1.095–1.215)		2.122 (2.008–2.243)		1.171 (1.107–1.240)	
Histology								
Adenocarcinoma	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
Squamous cell carcinoma	1.754 (1.720–1.789)		1.231 (1.206–1.257)		1.730 (1.692–1.770)		1.160 (1.133–1.188)	
Large cell carcinoma	1.630 (1.554–1.711)		1.356 (1.292–1.423)		1.721 (1.630–1.817)		1.361 (1.288–1.437)	
Other	1.235 (1.164–1.312)		1.296 (1.220–1.376)		1.251 (1.168–1.340)		1.313 (1.226–1.406)	
NSCLC NOS	2.258 (2.201–2.317)		1.196 (1.164–1.229)		2.398(2.330–2.468)		1.175 (1.140–1.211)	
Operation								
Lobectomy	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
Pneumonectomy	1.759 (1.670–1.852)		1.302 (1.234–1.374)		1.975 (1.862–2.095)		1.323 (1.244–1.407)	
Segmental resection/ wedge resection	1.259 (1.213–1.306)		1.203 (1.156–1.253)		1.131 (1.080–1.185)		1.149 (1.093–1.208)	
Local tumor excision	2.747 (2.420–3.118)		2.248 (1.974–2.560)		2.672 (2.296–3.109)		2.340 (2.004–2.733)	
Other	1.881 (1.670–2.119)		1.447 (1.282–1.634)		2.104 (1.838–2.408)		1.560 (1.360–1.790)	
Surgery NOS	3.957 (3.879–4.036)		2.937 (2.829–3.051)		4.474 (4.372–4.579)		3.172 (3.036–3.313)	

Table 2 Continued

	Cox regression for overall survival				Cox regression for cancer-specific survival			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
Locations and stage	HR (95% CI)	*P*†	HR (95% CI)	*P*‡	HR (95% CI)	*P*†	HR (95% CI)	*P*‡
lymph node dissection								
1–3 removed	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
≥ 4 removed	0.821 (0.794–0.849)		0.862 (0.832–0.893)		0.816 (0.784–0.849)		0.852 (0.817–0.889)	
None/unknown	2.535(2.455–2.616)		1.144 (1.101–1.188)		2.752 (2.651–2.856)		1.135 (1.086–1.186)	
Radiation								
None/unknown	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
Other (isotope, implant or combination)	1.809 (1.657–1.974)		0.861 (0.788–0.941)		1.952 (1.770–2.152)		0.842 (0.763–0.930)	
Beam radiation	1.782 (1.750–1.814)		0.718 (0.702–0.735)		1.936 (1.897–1.976)		0.696 (0.678–0.714)	
Chemotherapy								
Yes	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
No/unknown	0.805 (0.791–0.820)		1.409 (1.378–1.440)		0.664 (0.651–0.677)		1.299 (1.268–1.331)	
Year								
2004–2007	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
2008–2011	0.871 (0.854–0.888)		0.878 (0.861–0.896)		0.833 (0.815–0.852)		0.850 (0.832–0.869)	
2012–2014	0.767 (0.746–0.788)		0.798 (0.776–0.820)		0.735 (0.713–0.758)		0.778 (0.754–0.803)	
Age								
≤ 40 years	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
41–69 years	1.764 (1.502–2.071)		1.575 (1.341–1.850)		1.574(1.327–1.867)		1.425 (1.201–1.691)	
70+ years	2.809 (2.393–3.298)		2.238 (1.905–2.629)		2.257 (1.903–2.677)		1.868 (1.574–2.217)	
Gender								
Male	Reference	< 0.001	Reference	< 0.001	Reference	<0.001	Reference	< 0.001
Female	0.726 (0.714–0.739)		0.798 (0.784–0.813)		0.741 (0.723–0.755)		0.834 (0.817–0.851)	
Ethnicity								
Caucasian	Reference	< 0.001	Reference	0.327	Reference	<0.001	Reference	0.026
African-American	1.121 (1.091–1.153)		0.986 (0.959–1.014)		1.143 (1.107–1.179)		0.965 (0.935–0.996)	
Asian	0.760 (0.729–0.792)		0.785 (0.753–0.818)		0.786 (0.750–0.824)		0.806 (0.768–0.845)	
Other/unknown	0.960 (0.879–1.048)		0.947 (0.867–1.034)		0.972 (0.879–1.074)		0.942 (0.852–1.041)	

†The Cox proportional hazard model was used without risk-adjustment. ‡The Cox proportional hazard model was used with risk-adjustment. AJCC, American Joint Committee on Cancer; NSCLC, non-small cell lung cancer; NOS, not otherwise specified.

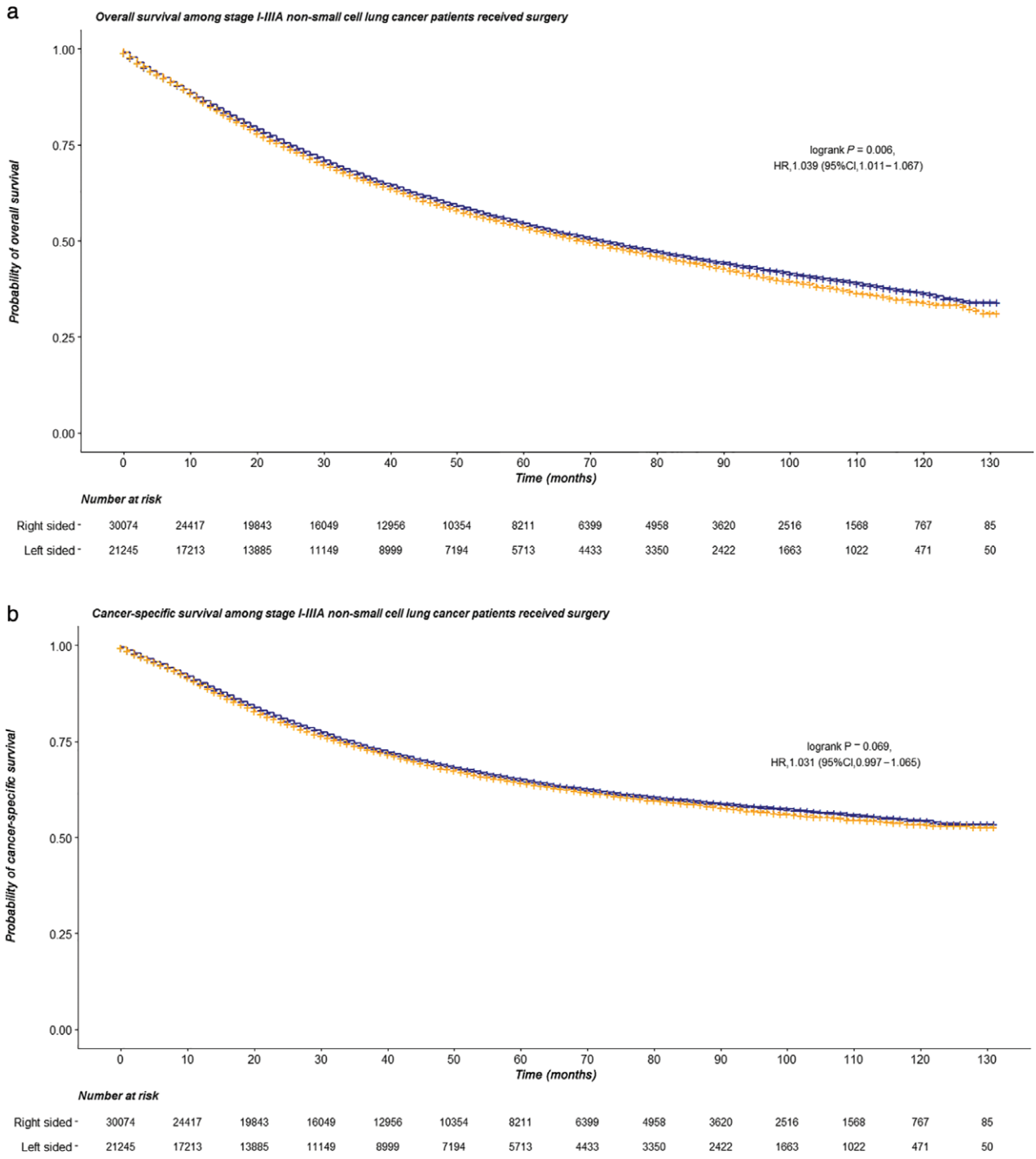

Figure 2 Overall survival (OS) and cancer-specific survival (CSS) among stage I–IIIA non-small cell lung cancer (NSCLC) patients who underwent surgery. The five-year OS rate for patients with right side NSCLC was 54.6% (95% confidence interval [CI] 53.9–55.3%) compared to 53.6% (95% CI 52.8–54.4%) in patients with left side NSCLC. OS was significantly longer in patients with right side than left side lung cancer (hazard ratio [HR] 1.039, 95% CI 1.011–1.067; $P = 0.006$). The five-year CSS rate for patients with right side NSCLC was 65.0% (95% CI 64.4–65.7%) compared to 64.3% (95% CI 63.5–65.1%) in patients with left side NSCLC. CSS was similar between the groups (HR 1.031, 95% CI 0.997–1.065; $P = 0.069$). (**a**) (—+—) Right side, (--+--) left side, logrank $P = 0.006$, HR 1.039 (95% CI 1.011–1.067) and (**b**) (—+—) Right side, (--+--) left side, logrank $P = 0.069$, HR 1.031 (95% CI 0.997–1.065).

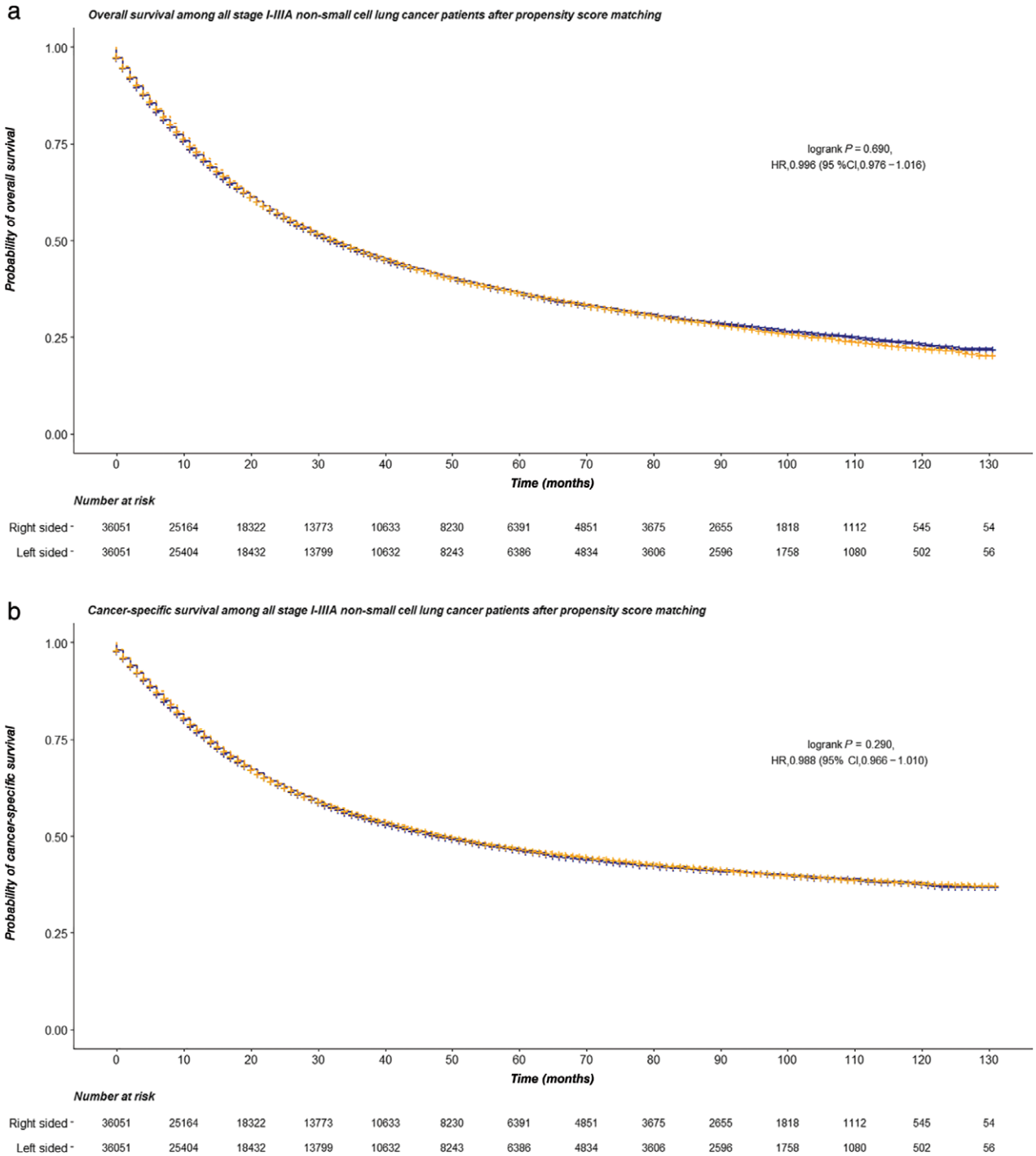

Figure 3 Overall survival (OS) and cancer-specific survival (CSS) among stage I–IIIA non-small cell lung cancer (NSCLC) patients after propensity score matching. There were no significant differences in OS (hazard ratio [HR] 0.99, 95% confidence interval [CI] 0.97–1.02; P = 0.689) or CSS (HR 0.99, 95% CI 0.96–1.02; P = 0.288). (**a**) (—+—) Right side, (--+--) left side, logrank P = 0.690, HR 0.996 (95% CI 0.976–1.016) and (**b**) (—+—) Right side, (--+--) left side, logrank P = 0.290, HR 0.988 (95% CI 0.966–1.010).

PSM analysis was also performed by surgery method and stage. Subgroup analysis showed no significant difference in OS between patients with left or right side stage I (HR 0.98, 95% CI 0.95–1.02; P = 0.424), stage II (HR 0.98, 95% CI 0.93–1.03; P = 0.468), or stage IIIA NSCLC (HR 0.97, 95% CI 0.90–1.04; P = 0.328). After matching, no significant difference in CSS was observed between right and left side NSCLC patients across all stages (stage I:

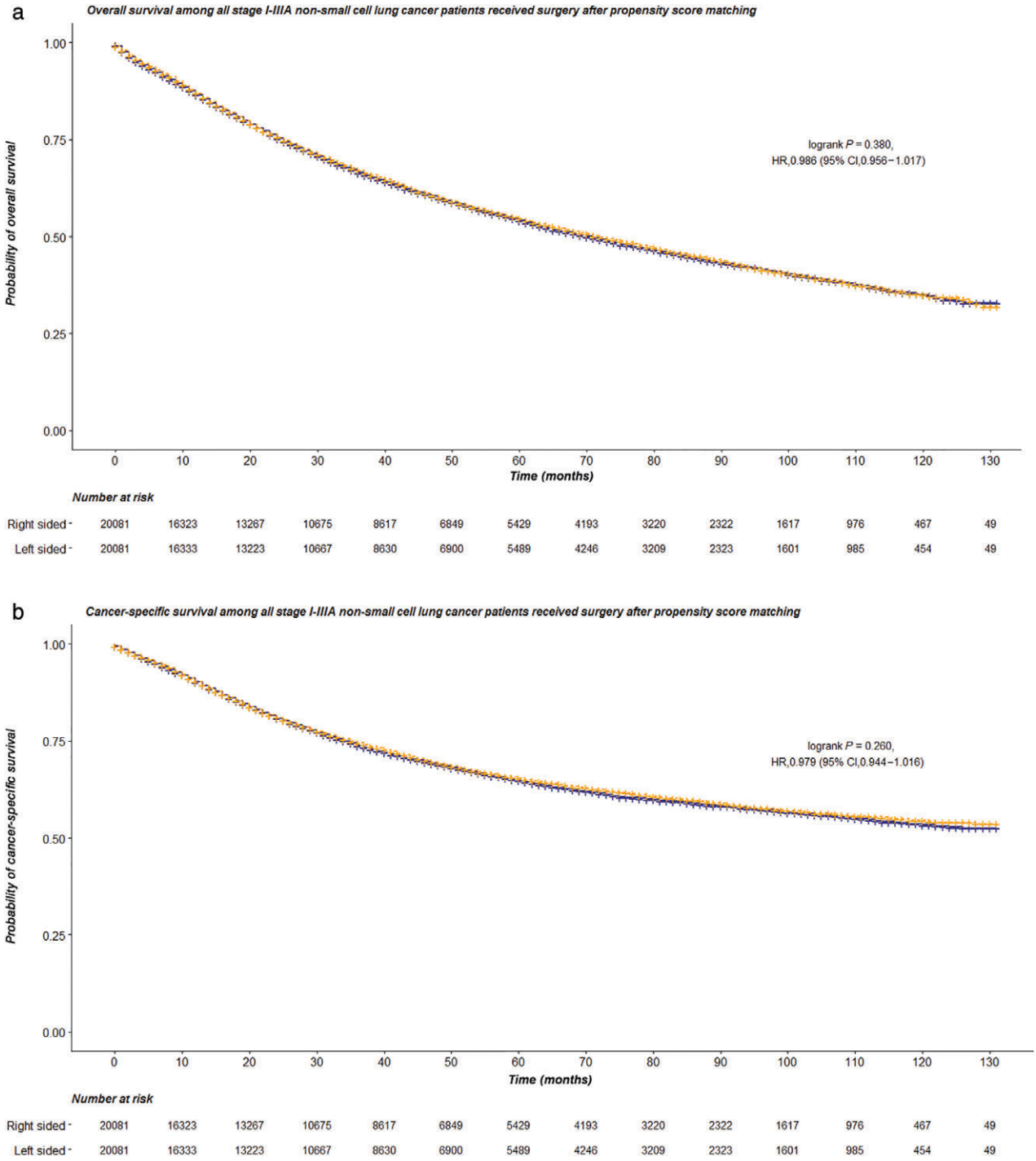

Figure 4 Overall survival (OS) and cancer-specific survival (CSS) among stage I–IIIA non-small cell lung cancer (NSCLC) patients who underwent surgery after propensity score matching. There were no significant differences in OS (hazard ratio [HR] 0.99, 95% confidence interval [CI] 0.96–1.02; $P = 0.375$) or CSS (HR 0.98, 95% CI 0.94–1.02; $P = 0.263$). (**a**) (—+—) Right side, (···+···) left side, logrank $P = 0.380$, HR 0.986 (95% CI 0.956–1.017) and (**b**) (—+—) Right side, (···+···) left side, logrank $P = 0.260$, HR 0.979 (95% CI 0.944–1.016).

HR 0.98, 95% CI 0.93–1.03, $P = 0.468$; stage II: HR 1.003, 95% CI 0.93–1.08, $P = 0.941$; stage IIIA: HR 0.95, 95% CI 0.88–1.03, $P = 0.186$) (Figs S2–S4). We further analyzed the data of stage IIIA patients administered chemoradiotherapy. No significant difference was observed in OS (HR 1.002, 95% CI 0.953–1.052; $P = 0.946$) or CSS

(HR 0.987, 95% CI 0.936–1.040; $P = 0.614$) (Fig S5). There was also no significant difference in multivariate analysis (Table S4).

In the 39 088 patients who did not undergo surgery, left side NSCLC was associated with significantly better CSS compared to right side NSCLC (HR 0.96, 95% CI 0.94–0.99; $P = 0.003$). However no difference was observed between the groups after adjusting for multivariate analysis.

Discussion

This is the first study to use a validated and innovative PSM approach to investigate the impact of primary tumor side on long-term survival in patients with stage I–IIIA NSCLC, and to our knowledge, this is the largest population-based study using the SEER database to examine this issue. The findings show no difference in cancer mortality between right and left side NSCLC regardless of whether patients underwent surgery. Moreover, there was no difference in survival outcome according to tumor location in NSCLC patients at any stage. Our results indicate that primary tumor side cannot be considered a prognostic factor when choosing appropriate treatment strategies.

After the discovery of a significant distinction between right and left side colon cancer, determining whether primary tumor location could make a difference to cancer mortality and thus influence the choice of treatment is of great importance. Several potential rationales could lead to different prognoses between right and left side NSCLC. First, the anatomic structures of the left and right lungs are not identical. The pulmonary arteries, veins, and main bronchi are arranged differently in the left and right pulmonary hilum. The upper part of the right hilum is composed of the upper pulmonary vein stem, the upper pulmonary artery, and the posterior regressive branch of the lower pulmonary artery. The lower part of the right hilum is composed of the lower pulmonary artery stem. The left hilum is mainly composed of the left pulmonary artery and the upper pulmonary vein branches. The upper part is formed by the left pulmonary artery arch, while the lower part is formed by the left lower pulmonary artery and its branches. Second, right and left lung cancers might have distinct gene mutation features. For instance, a previous study reported the case of patient with a bilateral tumor of lung adenocarcinoma composed of both ALK positive and negative rearrangement.[14] *EGFR* L858R mutations may be more common in right side lung cancer patients.[8] The mechanism of this phenomenon is unclear, but this finding indicates that patients with tumors on the right side should undergo testing for *EGFR* mutation. Third, previous studies have shown that the risk of early perioperative death and survival differs between patients who undergo right or left side pneumonectomy.[5,9] Despite these factors, large sample data with scientific and rigorous statistical methods are lacking.

Therefore, in this study, we used the SEER database, which covers almost 28% of cancer cases in the US, to collect a large sample of 90 407 patients with stage I–IIIA NSCLC to compare OS and CSS between patients with tumors located on the left and right sides. As the baseline patient characteristics between the two groups were imbalanced, which could cause substantial statistical bias, a novel and validated PSM approach was used to minimize potential confounding. Patients with tumors on the right and left sides were matched according to baseline patient characteristics to make sure any survival differences shown were the result of primary tumor location.

Our results did not show any difference between primary tumors located in the right or left side in stage I–IIIA NSCLC patients, with five-year CSS rates of 45.9% and 46.7%, respectively; this survival data is consistent with previous studies.[15–19] Several studies have compared the survival difference of right and left side NSCLC. It has been reported that the risk of early perioperative death and complications is high after right side pneumonectomy, but long-term survival did not differ between right and left side pneumonectomy.[5] Another study showed that median survival was better after pneumonectomy for stage II left tumors.[9] However, to date, no study has been designed to investigate whether primary tumor location alone is a prognostic factor of the influence of pneumonectomy or other surgical procedures. In this study, after matching according to baseline patient characteristics, including different operating procedures, primary tumor side was not a prognostic factor, regardless of whether patients underwent surgery. However it is difficult to compare the results with previous studies because the data was limited on this point.

In recent years, a significant prognostic distinction between colon cancer located in the right and left sides was discovered and the findings suggest that individualized treatment should be considered when treating colon cancer patients with tumors in different sides.[20–23] However, unlike colon cancer, primary tumor side should not be regarded as a prognostic factor for NSCLC. The poor prognostic factors found in multivariate analysis in our study were consistent with previous studies, such as patients had more advanced stages, advanced T-stage, fewer patients had ≥ 4 regional lymph nodes dissected, cases were non-adenocarcinoma, and did not undergo lobectomy. It is worthwhile to note that although primary side had no impact on survival, primary tumors located in the main bronchus or overlapping pulmonary lobes were significantly associated with poor CSS, which has not previously been reported and requires further investigation.

There were several limitations in this study. First, similar to other retrospective studies, some information was not

available in the SEER database, such as specific chemotherapy regimen, the time of disease progression or relapse, the sequence of treatment after disease progression, gene mutation information, and tobacco use. Patients who not administered chemotherapy/radiotherapy or whose chemotherapy/radiotherapy information was not recorded were categorized into one group. However, we used PSM analysis to minimize the bias between the groups. Second, we did not use the 7th AJCC staging system as it was not widely applied before 2010 in the SEER database; therefore the 6th AJCC staging system was used to ensure consistency among data. Third, approximately 40 000 NSCLC patients with stage I–IIIA did not undergo surgery and the reason was not recorded in the SEER database. Therefore, in this study, patients who underwent surgery and those who did not were compared separately; no mortality difference was observed in either group. Overall, this study provides the largest population-based survival data and prognostic factors for stage I–IIIA NSCLC patients, which is bound to be an important reference for further studies and clinical trials.

The prognosis between right and left side stage I–IIIA NSCLC was the same regardless of whether patients underwent surgery. The results of our study indicate that primary tumor side cannot be considered a prognostic factor when choosing appropriate treatment. These findings may inform further studies to improve clinical practice in the future.

Acknowledgment

We thank the SEER*Stat team at the National Cancer Institute for providing technical help in regard to formulating a SEER*Stat case-listing session in general, and specifically for the extraction of information on previous cancer history.

Disclosure

No authors report any conflict of interest.

References

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; **66**: 7–30.
2 Chen W, Zheng R, Baade PD *et al.* Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115–32.
3 Travis WD. Pathology of lung cancer. *Clin Chest Med* 2011; **32**: 669–92.
4 Kopec SE, Irwin RS, Umali-Torres CB, Balikian JP, Conlan AA. The postpneumonectomy state. *Chest* 1998; **114**: 1158–84.
5 Martin J, Ginsberg RJ, Abolhoda A *et al.* Morbidity and mortality after neoadjuvant therapy for lung cancer: The risks of right pneumonectomy. *Ann Thorac Surg* 2001; **72**: 1149–54.
6 Rodriguez M, Gomez MT, Jimenez MF *et al.* The risk of death due to cardiorespiratory causes increases with time after right pneumonectomy: A propensity score-matched analysis. *Eur J Cardiothorac Surg* 2013; **44**: 93–7.
7 Li J, Zhang DC, He J, Liu XY, Mu JW, Zhang LZ. The rule of lymph node metastasis of adenosquamous carcinoma of the lung. *Zhonghua Zhong Liu Za Zhi* 2009; **31**: 524–7.
8 Yang Y, Shi C, Sun H *et al.* Elderly male smokers with right lung tumors are viable candidates for KRAS mutation screening. *Sci Rep* 2016; **6**: 18566.
9 Simon C, Moreno N, Penalver R *et al.* The side of pneumonectomy influences long-term survival in stage I and II non-small cell lung cancer. *Ann Thorac Surg* 2007; **84**: 952–8.
10 Kim AW, Faber LP, Warren WH *et al.* Pneumonectomy after chemoradiation therapy for non-small cell lung cancer: Does "side" really matter? *Ann Thorac Surg* 2009; **88**: 937–43.
11 Surveillance, Epidemiology, and End Results (SEER) Program (www.seer. cancer.gov) Research Data (1973–2014), National Cancer Institute, DCCPS,Surveillance Research Program, Surveillance Systems Branch, released March 2017, based on the March 2017 submission. [Cited 23 March 2017.] Available from URL: www.seer.cancer.gov.
12 Wingo PA, Jamison PM, Hiatt RA *et al.* Building the infrastructure for nationwide cancer surveillance and control--a comparison between the National Program of Cancer Registries (NPCR) and the Surveillance, Epidemiology, and End Results (SEER) Program (United States). *Cancer Causes Control* 2003; **14**: 175–93.
13 Surveillance, Epidemiology, and End Results Program. *Data Use Agreement for the 1973–2014. SEER Research Data File.* [Cited 23 Mar 2017.] Available from URL: https://seer.cancer.gov/data/access.html#agreement.
14 Matsuda I, Takeuchi K, Mizuguchi S *et al.* A case of synchronous bilateral lung cancers: EML4-ALK positive adenocarcinoma in the right lung and adenocarcinoma in situ (the former bronchioloalveolar carcinoma) in the left lung. *BMC Pulm Med* 2013; **13**: 25.
15 Albain KS, Swann RS, Rusch VW *et al.* Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III randomised controlled trial. *Lancet* 2009; **374**: 379–86.
16 Timmerman R, Paulus R, Galvin J *et al.* Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010; **303**: 1070–6.
17 Scott WJ, Howington J, Feigenberg S *et al.* Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; **132**: 234S–42S.
18 Landreneau RJ, Normolle DP, Christie NA *et al.* Recurrence and survival outcomes after anatomic segmentectomy versus lobectomy for clinical stage I non-small-cell lung cancer: A propensity-matched analysis. *J Clin Oncol* 2014; **32**: 2449–55.

19 Rusch VW, Asamura H, Watanabe H *et al*. The IASLC Lung Cancer Staging Project: A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009; **4**: 568–77.
20 Brule SY, Jonker DJ, Karapetis CS *et al*. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. *Eur J Cancer* 2015; **51**: 1405–14.
21 Loupakis F, Yang D, Yau L *et al*. Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst* 2015; **107**: dju427.
22 Chen KH, Shao YY, Chen HM *et al*. Primary tumor site is a useful predictor of cetuximab efficacy in the third-line or salvage treatment of KRAS wild-type (exon 2 non-mutant) metastatic colorectal cancer: A nationwide cohort study. *BMC Cancer* 2016; **16**: 327.
23 Warschkow R, Sulz MC, Marti L *et al*. Better survival in right-sided versus left-sided stage I - III colon cancer patients. *BMC Cancer* 2016; **16**: 554.

Supporting Information

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

Figure S1. Flow chart of patient selection in this study.
Figure S2. Overall survival and cancer-specific survival among stage I non-small cell lung cancer (NSCLC) patients who underwent surgery after propensity score matching.
Figure S3. Overall survival and cancer-specific survival among stage II non-small cell lung cancer (NSCLC) patients who underwent surgery after propensity score matching.
Figure S4. Overall survival and cancer-specific survival among stage IIIA non-small cell lung cancer (NSCLC) patients who underwent surgery after propensity score matching.
Figure S5. Overall survival and cancer-specific survival among stage IIIA non-small cell lung cancer (NSCLC) patients administered chemoradiotherapy.
Table S1. Characteristics of stage I–IIIA NSCLC patients who underwent surgery.
Table S2. Characteristics of the study population in the matched cohort of all I–IIIA non-small cell lung cancer (NSCLC) patients.
Table S3. Characteristics of the study population in the matched cohort of stage I–IIIA non-small cell lung cancer (NSCLC) patients who underwent surgery.
Table S4. Cox regression of overall survival and cancer-specific survival of stage IIIA non-small cell lung cancer (NSCLC) patients administered chemoradiotherapy.

