Evaluation of Different Treatment Strategies Between Right-sided and Left-sided Pneumonectomy for Stage I-IIIA Non-small Cell Lung Cancer Patients

Bo Jia
Beijing Cancer Hospital
Qiwen Zheng
School of public health, Peking University
Jianjie Li
Beijing Cancer Hospital
Jun Zhao
Beijing Cancer Hospital
Meina Wu
Beijing Cancer Hospital
Tongtong An
Beijing Cancer Hospital
Yuyan Wang
Beijing Cancer Hospital
Minglei Zhuo
Beijing Cancer Hospital
Xue Yang
Beijing Cancer Hospital
Hanxiao Chen
Beijing Cancer Hospital
Yujia Chi
Beijing Cancer Hospital
Jingjing Wang
Beijing Cancer Hospital
Xiaoyu Zhai
Beijing Cancer Hospital
Ziping Wang (wangzp2007@126.com)
Beijing Cancer Hospital https://orcid.org/0000-0002-6763-7431

Primary research

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Abstract

Background

This study aimed to assess the different survival outcome of stage I-IIIA NSCLC patients who received right-sided and left-sided pneumonectomy, and to further develop the most appropriate treatment strategies.

Methods

We accessed data from the Surveillance, Epidemiology, and End Results database in the United States for the present study. An innovative propensity score matching analysis was used to minimize the variance between groups.

Results

For 2,683 patients who received pneumonectomy, cancer-specific survival (HR=0.863, 95%CI: 0.771 to 0.965, P=0.010) and overall survival (OS) (HR=0.875, 95%CI: 0.793 to 0.967, P=0.008) were significantly superior of left-sided pneumonectomy compared with right-sided pneumonectomy. Cancer-specific survival (HR=0.847, 95%CI: 0.745 to 0.963, P=0.011) and OS (HR=0.858, 95%CI: 0.768 to 0.959, P=0.007) were also significantly longer with left-sided over opposite-sided pneumonectomy after matching analysis for 2,050 patients. Adjuvant therapy could significantly prolong cancer-specific survival (67 versus 51 months, HR=1.314, 95%CI: 1.093 to 1.579, P=0.004) and OS (46 versus 30 months, HR=1.458, 95%CI: 1.239 to 1.715, P<0.001) among left-sided pneumonectomy patients after matching procedure. While adjuvant therapy did not increase cancer-specific survival for right-sided pneumonectomy patients (46 versus 42 months, HR=1.112, 95%CI: 0.933 to 1.325, P=0.236). Subgroup analysis showed that adjuvant chemotherapy could significantly improve cancer-specific survival and OS for all pneumonectomy patients. But radiotherapy was associated with worse survival for patients with right-sided pneumonectomy.

Conclusions

Pneumonectomy side could be deemed as an important factor when physicians choosing the most optimal treatment strategies.

Introduction

Lung cancer has been the most common cancer in China and globally [1, 2]. About 75–80% lung cancer patients belong to non-small cell lung cancer (NSCLC) [3]. Pneumonectomy can approximately affect quality of life and long-term survival for several reasons. First, there are some complications of pneumonectomy including decreased respiratory function, bronchopleural fistulas, progressive pulmonary hypertension and elevated right-heart pressure, etc[4, 5]. Second, it has been reported that patients received right or left-sided pneumonectomy may have different prognosis [6, 7], and patients with pneumonectomy in right lung were associated with higher incidence of mortality and morbidity than that in left side[8]. mainly due to the reason that right lung contributes more to overall lung function than that in the opposite side[9]. Third, the anatomical structure, blood supply and metastatic lymph node routes of bilateral lungs are not totally identical. Therefore, right and left-sided pneumonectomy may have distinctive long-term survival, but this problem has not been fully identified..

Although adjuvant chemotherapy has been the standard treatment for II-IIIA patients with surgery, few of them have examined patients undergoing pneumonectomy. Besides, the long-term risks and benefits of adjuvant radiotherapy after pneumonectomy remain controversial. It is of great value to illustrate the influence of adjuvant therapy for patients who received pneumonectomy. Therefore, the purpose of this study was to assess whether primary tumor sidedness could influence long-term survival in stage I-IIIA NSCLC patients who received pneumonectomy, and to further develop the best treatment strategies for these patients.

Patients And Methods

Data source

We access data from the Surveillance, Epidemiology, and End Results (SEER) database in the United States for the present study[10]. Data codes were recorded by the North American Association of Central Cancer Registries (NAACCR)[11]. The 3rd edition of the International Classification of Diseases for Oncology (ICD-O-3) was used to code primary tumor histology..

Cohort Selection

NSCLC patients aged 18 years or older from the year 2004 to 2014 were included in this study. Patients with primary tumor location unknown were excluded. All patients received pneumonectomy. The study was exempted from ethical review by the Beijing Cancer Hospital. We obtained the data agreement and data files were downloaded directly from the SEER website[12]. Flow chart of patients' selection in this study was shown in **eFigure1**.

Statistical analysis

Patients were categorized into left-sided and right-sided pneumonectomy. We used chi-square test or Fisher's exact test between groups to perform univariate analysis. A propensity score was constructed to reduce potential bias. A multivariable logistic regression model was constructed including variables such as age, gender, race, year of diagnosis, tumor stage, T stage, N stage, original site, histology, number of lymph node dissection, radio therapy and chemotherapy. Matching (1:1) across the two groups was achieved with a 0.2-width caliper of the standard deviation of the logit of the propensity score. To evaluate the matching performance, baseline variables were compared using the McNemar's test between the matched groups, and a difference between −0.1 and 0.1 is generally considered negligible to calculate standardized differences..

We assessed overall survival (OS) and cancer-specific survival using Kaplan-Meier curves in the matched groups. Relationships between pneumonectomy laterality and OS or cancer-specific survival was evaluated by Cox regression model stratified on matched pairs.

R software (version 3.3.3; http:// www.r-project.org) was used for statistical analysis. The significance levels were all two-sided, with statistical significance set at 0.05.

Results

Patients' characteristics

In this study, 2,683 NSCLC patients with stage I-IIIA who received pneumonectomy between 2004 and 2014 were collected. In these patients, 1,150 patients received right-sided pneumonectomy and 1,533 patients with left-sided pneumonectomy. Patients' characteristics between the two groups were illustrated in **Table 1**. More patients with right-sided pneumonectomy patients had stage I (P=0.006), N0 (P=0.005), had overlapping lesion (P=0.007), and had adenocarcinomas (P<0.001). Less patients with pneumonectomy in right side received chemotherapy (P=0.025).

Table 1
Comparison of Baseline Characteristics Between Right-sided and Left-sided Pneumonectomy in the Original and Matched Data Sets.

Variable	Original Data Set				Matched Data Set			
	Right-sided (n=1150)	Left-sided (n=1533)	Sdiff	P*	Right-sided (n=1025)	Left-sided (n=1025)	Sdiff	P†
Age								
Up to 40 years	17 (1.5)	13 (0.8)	-0.059	0.283	11 (1.1)	12 (1.2)	-0.009	0.748
41 to 69 years	862 (75.0)	1146 (74.8)	-0.005		775 (75.6)	788 (76.9)	-0.030	
70+ years	271 (23.6)	374 (24.4)	0.019		239 (23.3)	225 (22.0)	0.033	
Gender								
Male	792 (68.9)	1020 (66.5)	-0.050	0.217	707 (69.0)	703 (68.6)	0.008	0.882
Female	358 (31.1)	513 (33.5)	0.050		318 (31.0)	322 (31.4)	-0.008	
Race/ethnicity								
Caucasian	990 (86.1)	1328 (86.6)	0.016	0.251	893 (87.1)	887 (86.5)	0.017	0.364
African-American	97 (8.4)	128 (8.3)	-0.003		86 (8.4)	91 (8.9)	-0.017	
Asian	53 (4.6)	54 (3.5)	-0.055		37 (3.6)	39 (3.8)	-0.010	
Other/Unknown	10 (0.9)	23 (1.5)	0.058		9 (0.9)	8 (0.8)	0.011	
Year of diagnosis								
2004 - 2007	510 (44.3)	655 (42.7)	-0.033	0.694	453 (44.2)	429 (41.9)	0.047	0.196
2008 - 2011	400 (34.8)	545 (35.6)	0.016		359 (35.0)	381 (37.2)	-0.045	
2012 - 2014	240 (20.9)	333 (21.7)	0.021		213 (20.8)	215 (21.0)	-0.005	
Tumor stage‡								
Stage I	389 (33.8)	437 (28.5)	-0.115	0.006	330 (32.2)	336 (32.8)	-0.012	0.148
Stage II	403 (35.0)	613 (40.0)	0.102		374 (36.5)	336 (32.8)	0.078	
Stage IIIA	358 (31.1)	483 (31.5)	0.008		321 (31.3)	353 (34.4)	-0.066	
Clinical T stage								
T1	135 (11.7)	161 (10.5)	-0.039	0.204	121 (11.8)	118 (11.5)	0.009	0.647
T2	797 (69.3)	1100 (71.8)	0.054		711 (69.4)	712 (69.5)	-0.002	

T3	214 (18.6)	271 (17.7)	-0.024		193 (18.8)	195 (19.0)	-0.005	
TX	4 (0.3)	1 (0.1)	-0.062		-	-	-	
Clinical N stage								
N0	466 (40.5)	533 (34.8)	-0.119	0.005	400 (39.0)	401 (39.1)	-0.002	0.507
N1	412 (35.8)	631 (41.2)	0.109		380 (37.1)	355 (34.6)	0.051	
N2	272 (23.7)	369 (24.1)	0.010		245 (23.9)	269 (26.2)	-0.054	
Original site								
Lung lobe	892 (77.6)	1250 (81.5)	0.098	0.007	817 (79.7)	792 (77.3)	0.059	0.544
Main bronchus	102 (8.9)	140 (9.1)	0.009		91 (8.9)	113 (11.0)	-0.072	
Overlapping lesion of lung	121 (10.5)	108 (7.0)	-0.123		93 (9.1)	91 (8.9)	0.007	
NOS	35 (3.0)	35 (2.3)	-0.047		24 (2.3)	29 (2.8)	-0.031	
Histology								
Adenocarcinoma	411 (35.7)	417 (27.2)	-0.183	<0.001	328 (32.0)	317 (30.9)	0.023	0.774
Squamous cell carcinoma	563 (49.0)	882 (57.5)	0.171		537 (52.4)	540 (52.7)	-0.006	
Large cell carcinoma	38 (3.3)	66 (4.3)	0.052		38 (3.7)	38 (3.7)	0.000	
Other	48 (4.2)	60 (3.9)	-0.013		43 (4.2)	46 (4.5)	-0.014	
NSCLC NOS	90 (7.8)	108 (7.0)	-0.030		79 (7.7)	84 (8.2)	-0.018	
Lymph node dissection								
1 to 3 removed	66 (5.7)	65 (4.2)	-0.069	0.106	53 (5.2)	49 (4.8)	0.018	0.811
4 or more removed	994 (86.4)	1364 (89.0)	0.077		898 (87.6)	907 (88.5)	-0.027	
None/Unknown	90 (7.8)	104 (6.8)	-0.040		74 (7.2)	69 (6.7)	0.019	
Radiotherapy								
None/Unknown	918 (79.8)	1201 (78.3)	-0.036	0.335	811 (79.1)	798 (77.9)	0.031	0.301
Other§	4 (0.3)	11 (0.7)	0.051		2 (0.2)	1 (0.1)	0.026	
Beam radiation	228 (19.8)	321 (20.9)	0.028		212 (20.7)	226 (22.0)	-0.033	
Chemotherapy								
Yes	555 (48.4)	808 (52.7)	0.089	0.025	501 (48.9)	540 (52.7)	-0.076	0.061
No/Unknown	595 (51.7)	725 (47.3)	-0.089		524 (51.1)	485 (47.3)	0.076	

Abbreviations: AJCC, American Joint Committee on Cancer; Sdiff, standardized difference.

*P value for chi-square test or Fisher's exact test.

†P value for McNemar's test or general McNemar's test.

‡The 6th Edition of the AJCC Cancer Staging Manual.

§Isotope, implant or the combination.

Survival

The median follow-up was 25 months. Cancer-specific survival (HR=0.863, 95%CI: 0.771 to 0.965, P=0.010) and OS (HR=0.875, 95%CI: 0.793 to 0.967, P=0.008) were significantly superior with left-sided pneumonectomy compared with right-sided pneumonectomy with the 5-year OS rate of 36.4% (95%CI: 33.4% to 39.6%) and 40.2% (95%CI: 37.5% to 43.1%) for patients received right-sided and left-sided pneumonectomy respectively **(eFigure 2).** After multivariable adjustment, differences were also significant between left-sided and right-sided pneumonectomy both in cancer-specific survival (HR=0.836, 95%CI :0.746 to 0.937, P=0.002) and OS (HR=0.841, 95%CI: 0.760 to 0.929, P□0.001) **(Table 2).**

Table 2
Prognostic Factors for Overall and Cancer-specific Survival in All Stage I-IIIA NSCLC Patients with Pneumonectomy in Original Data Set

Variable	Overall Survival				Cancer-specific Survival			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age								
Up to 40 years	Reference		Reference		Reference		Reference	
41 to 69 years	1.944(1.073-3.520)	0.028	2.104(1.158-3.825)	0.015	1.694(0.908-3.159)	0.098	1.918(1.024-3.591)	0.042
70+ years	3.143(1.728-5.717)	<0.001	3.333(1.824-6.090)	<0.001	2.421(1.290-4.542)	0.006	2.726(1.446-5.140)	0.002
Gender								
Male	Reference		Reference		Reference		Reference	
Female	0.817(0.734-0.910)	<0.001	0.809(0.723-0.905)	<0.001	0.895(0.794-1.009)	0.070	0.861(0.759-0.975)	0.019
Race/ethnicity								
Caucasian	Reference		Reference		Reference		Reference	
African-American	0.909(0.756-1.093)	0.310	0.967(0.802-1.166)	0.726	0.921(0.748-1.133)	0.437	0.952(0.771-1.176)	0.652
Asian	0.977(0.755-1.265)	0.861	0.918(0.707-1.192)	0.523	1.050(0.791-1.395)	0.735	0.956(0.718-1.274)	0.763
Other/Unknown	0.561(0.325-0.968)	0.038	0.597(0.345-1.035)	0.066	0.454(0.226-0.910)	0.026	0.480(0.238-0.966)	0.039
Year of diagnosis								
2004 - 2007	Reference		Reference		Reference		Reference	
2008 - 2011	0.811(0.726-0.905)	<0.001	0.817(0.731-0.914)	<0.001	0.771(0.681-0.872)	<0.001	0.773(0.682-0.877)	<0.001
2012 - 2014	0.779(0.658-0.922)	0.004	0.880(0.741-1.044)	0.143	0.709(0.585-0.859)	<0.001	0.785(0.646-0.954)	0.015
Tumor stage‡								
Stage I	Reference		Reference		Reference		Reference	
Stage II	1.147(1.014-1.298)	0.029	0.861(0.622-1.193)	0.369	1.355(1.171-1.568)	<0.001	1.070(0.750-1.526)	0.706
Stage IIIA	1.455(1.283-1.649)	<0.001	0.744(0.423-1.308)	0.304	1.824(1.576-2.111)	<0.001	0.960(0.520-1.771)	0.897
Clinical T stage								
T1	Reference		Reference		Reference		Reference	
T2	1.210(1.026-1.427)	0.023	1.267(1.070-1.499)	0.006	1.443(1.179-1.767)	<0.001	1.484(1.207-1.824)	<0.001
T3	1.347(1.113-1.632)	0.002	1.723(1.293-2.296)	<0.001	1.749(1.393-2.196)	<0.001	2.002(1.45-2.766)	<0.001

TX	1.359(0.558-3.309)	0.499	1.256(0.511-3.090)	0.619	1.264(0.401-3.984)	0.688	0.946(0.297-3.008)	0.925
Clinical N stage								
N0	Reference		Reference		Reference		Reference	
N1	1.175(1.046-1.320)	0.006	1.593(1.152-2.202)	0.005	1.308(1.143-1.497)	<0.001	1.454(1.024-2.063)	0.036
N2	1.484(1.307-1.684)	<0.001	2.370(1.399-4.016)	0.001	1.780(1.542-2.054)	<0.001	2.165(1.225-3.826)	0.007
Original site								
Lung lobe	Reference		Reference		Reference		Reference	
Main bronchus	0.889(0.745-1.062)	0.195	0.894(0.746-1.072)	0.227	0.915(0.749-1.117)	0.381	0.931(0.759-1.141)	0.492
Overlapping lesion of lung	0.888(0.738-1.069)	0.209	0.852(0.706-1.027)	0.094	0.958(0.782-1.175)	0.684	0.909(0.739-1.118)	0.367
NOS	1.507(1.148-1.979)	0.003	1.508(1.146-1.986)	0.003	1.467(1.074-2.006)	0.016	1.440(1.051-1.974)	0.023
Histology								
Adenocarcinoma	Reference		Reference		Reference		Reference	
Squamous cell carcinoma	1.041(0.929-1.165)	0.485	0.979(0.868-1.104)	0.737	0.914(0.805-1.037)	0.164	0.863(0.754-0.988)	0.032
Large cell carcinoma	1.474(1.155-1.882)	0.002	1.373(1.072-1.758)	0.012	1.593(1.231-2.061)	<0.001	1.469(1.131-1.907)	0.004
Other	1.348(1.045-1.738)	0.021	1.337(1.034-1.729)	0.026	1.329(1.004-1.759)	0.046	1.302(0.981-1.727)	0.067
NSCLC NOS	1.011(0.830-1.232)	0.912	0.977(0.799-1.195)	0.824	0.989(0.794-1.233)	0.928	0.918(0.733-1.149)	0.456
Lymph node dissection								
1 to 3 removed	Reference		Reference		Reference		Reference	
4 or more removed	0.846(0.685-1.045)	0.120	0.845(0.682-1.047)	0.125	0.942(0.732-1.212)	0.642	0.916(0.709-1.184)	0.506
None/Unknown	0.964(0.737-1.260)	0.788	0.989(0.754-1.297)	0.936	1.128(0.827-1.539)	0.448	1.153(0.842-1.578)	0.374
Radiotherapy								
None/Unknown	Reference		Reference		Reference		Reference	
Other§	1.714(0.992-2.961)	0.053	2.278(1.310-3.962)	0.003	1.884(1.040-3.415)	0.037	2.256(1.236-4.118)	0.008
Beam radiation	1.162(1.033-1.306)	0.012	1.238(1.083-1.416)	0.002	1.280(1.124-1.457)	<0.001	1.217(1.050-1.411)	0.009
Chemotherapy								
Yes	Reference		Reference		Reference		Reference	
No/Unknown	1.479(1.340-1.633)	<0.001	1.741(1.555-1.950)	<0.001	1.255(1.123-1.404)	<0.001	1.577(1.388-1.791)	<0.001
Cancer side								

Right-sided	Reference		Reference		Reference		Reference	
Left-sided	0.875(0.0.793-0.967)	0.008	0.841(0.760-0.929)	<0.001	0.863(0.771-0.965)	0.010	0.836(0.746-0.937)	0.002

Abbreviations: AJCC, American Joint Committee on Cancer; Sdiff, standardized difference.

‡The 6th Edition of the AJCC Cancer Staging Manual.

§Isotope, implant or the combination.

Patients who had T2 or T3 (P<0.001), had N1(P=0.036) or N2 (P=0.007), were large cell carcinoma (P=0.004), were diagnosed before 2008 (P<0.001), were diagnosed older than 40 (P<0.042), were male (P<0.019), did not receive chemotherapy (P<0.001), received beam radiotherapy (P=0.009) or other radiotherapy (P=0.008) were associated with significant poorer cancer-specific survival in multivariate analysis **(Table 2)**.

After propensity score matching, the propensity score for NSCLC patients who received right-sided and left-sided pneumonia were both 0.566±0.073 respectively (P=0.833) (**eFigure3)**. After matching procedure, 2,050 patients were included for further analysis with 1,025 patients in both group **(Table 1).** Cancer-specific survival (HR=0.847, 95%CI: 0.745 to 0.963, P=0.011) and OS (HR=0.858, 95%CI: 0.768 to 0.959, P=0.007) were significantly longer with left-side compared with opposite side **(Figure 1).**

Adjuvant therapy

We further analyzed the impact of adjuvant therapy on survival. Among left-sided pneumonectomy patients, patients received adjuvant therapy (N=860) significantly prolonged cancer-specific survival (65 versus 44 months, HR=1.319, 95%CI: 1.134 to 1.534, P<0.001) and OS (47 versus 28 months, HR=1.489, 95%CI: 1.305 to 1.701, P<0.001) than patients received pneumonectomy alone (N=673) **(eFigure 4)**. Among right-sided pneumonectomy patients, patients received adjuvant therapy (N=582) significantly prolonged OS (36 versus 25 months, HR=1.335, 95%CI: 1.152 to 1.548, P<0.001) but did not improve cancer-specific survival (46 versus 46 months, HR=1.056, 95%CI: 0.893 to 1.249, P=0.522) compared with patients received pneumonectomy alone (N=568) **(eFigure 5)**. After matching procedure, cancer-specific survival (67 versus 51 months, HR=1.314, 95%CI: 1.093 to 1.579, P=0.004) and OS (46 versus 30 months, HR=1.458, 95%CI: 1.239 to 1.715, P<0.001) were also significantly longer for patients received adjuvant therapy (N=581) compared with patients received left-sided pneumonectomy alone (N=444) **(Figure 2).** Patients received right-sided pneumonectomy and adjuvant therapy (N=525) were not associated with superior cancer-specific survival (46 versus 42 months, HR=1.112, 95%CI: 0.933 to 1.325, P=0.236) compared with patients received pneumonectomy alone (N=500) although adjuvant therapy could improve OS (36 versus 25 months, HR=1.362, 95%CI: 1.165 to 1.592, P□0.001) **(Figure 3)**.

Subgroup analysis showed that adjuvant therapy could significantly improve cancer-specific survival and OS for stage II and stage IIIA patients with pneumonectomy in both side (P□0.05). Adjuvant therapy was not associated with prolonged cancer-specific survival (P=0.687) and OS (P=0.177) for stage I patients with right-sided pneumonectomy. Although adjuvant therapy could increase OS for stage I patents with pneumonectomy in left lung (P=0.014) but no differences of cancer-specific survival were observed(P=0.273).

Subgroup analysis showed that adjuvant chemotherapy could significantly improve cancer-specific survival and OS for all pneumonectomy patients. But radiotherapy was associated with worse OS and cancer-specific survival for patients with right-sided pneumonectomy. The median OS for right-sided pneumonectomy patients received chemotherapy alone, radiotherapy alone, chemoradiotheapy and no adjuvant therapy were 54 months, 12 months, 28 months, and 25 months, respectively (P<0.001) with the median cancer-specific survival of 68 months, 13 months, 32 months, and 46 months respectively (P<0.001). Radiotherapy did not significantly improve OS and cancer-specific survival for left-sided pneumonectomy patients either. The median OS for left-sided pneumonectomy patients received chemotherapy alone, radiotherapy alone, chemoradiotheapy and no

adjuvant therapy were 59 months, 33 months, 36 months, and 28 months, respectively (P<0.001) with the median cancer-specific survival of 94 months, 44 months, 44 months, and 44 months respectively (P<0.001).

OS was favorable for left-sided pneumonectomy across clinical subgroups including stage II or IIIA, squamous cell carcinoma, received chemoradiotherapy or radiotherapy **(Figure 4)**.

Discussion

To our knowledge, this is the largest and the first population based study using a novel propensity score matching analysis to assess the influence of pneumonectomy side on NSCLC patients survival outcome. This study indicated that pneumonectomy side could be deemed as an important factor when physicians choosing the most optimal treatment strategies.

Recent years, several studies showed that the survival outcome between right and left-sided pneumonectomy was different[6, 8]. One previous study showed that the perioperative death incidence occurred higher for patients with right-sided pneumonectomy[8]. It has also been indicated that right pneumonectomy was associated with poorer survival outcome and more postoperative complications [6, 13]. The results in our study were coincident with previous studies, indicating that OS and cancer-specific survival were significantly longer with left-sided pneumonectomy versus that in right side. Several reasons might contribute to this phenomenon. First, right lung is thought to be more vital for lung function. So pneumonectomy in right lung might lead to more loss of alveolar volume, pulmonary reserve reduction, and thus decrease respiratory function. Second, pneumonectomy is disposed to increase pulmonary artery pressure and even cause right-heart failure. Third, lung cancers located in diverse side have different skipping metastasis routes to mediastinal lymph nodes. Finally, the anatomic structures differed between right and left lung. Therefore, pneumonectomy side could be a fundamental prognostic factor and patients received right-sided pneumonectomy might need closer follow up for the risk of perioperative complications.

Previous studies showed the occurrence of bronchopleural fistula after surgery, more advanced pathological stage and older age were the poor prognositc factors for patients with pneumonectomy[14, 15]. The poor prognostic factors found in our study included patients with T2 or T3, N1 or N2, large cell carcinoma, diagnosed before 2008, diagnostic age older than 40, male, did not receive chemotherapy, and received beam radiotherapy or other radiotherapy in multivariate analysis. It is worthwhile to note that patients did not receive chemotherapy, received beam radiotherapy or other radiotherapy had worse cancer-specific survival, which indicated that chemotherapy was essential for patients with pneumonectomy while the role of radiotherapy was controversial.

It's imperative to investigate the impact of adjuvant therapy in patients with pneumonectomy. One previous study showed that radiotherapy dose was significantly related to higher death incidence owing to cardiopulmonary disease[16]. Another study indicated that radiotherapy might cause higher death rates due to respiratory disease[5]. But several other studies showed that the mortality difference was not significant with regards to peri-operative chemotherapy and radiotherapy [17, 18]. Our study demonstrated that adjuvant therapy could significantly prolong survival for patients received left-sided pneumonectomy but did not improve survival for patients with right-sided pneumonectomy. We also found that adjuvant chemotherapy was associated with significantly improved survival both for left and right-sided pneumonectomy patients. But radiotherapy did not bring survival benefit for patients with pneumonectomy, and even worsen the prognosis of right-sided pneumonectomy patients. The complications in patients with pneumonectomy could cause cardiopulmonary insufficiency and adjuvant radiotherapy might cause further respiratory function deterioration. This might be the main cause of death for patients with pneumonectomy. Moreover, the results in our study demonstrated that adjuvant therapy were not essential for stage I patients with pneumonectomy, which was also in accordance with previous studies.

There were some limitations in this study. First, we used the 6th edition of American Joint Committee on Cancer staging rather than the 7th edition. Because we selected patients in the SEER database from 2004 to 2014 and all patients had 6th staging records in the database. If we chose the 7th version, there would be much missing values. Besides, there was no significant difference between the 6th and 7th edition stages, which had no considerable deviation on the study results. Second, some

variables such as surgical quality or R0 margin, were not actually available in the SEER database and we were unable to analyze these data.

Conclusions

Right-sided pneumonectomy was associated with worse survival compared with left-side. Adjuvant therapy could significantly prolong survival among left-sided pneumonectomy patients while adjuvant therapy did not increase cancer-specific survival for patients with right-sided pneumonectomy. Adjuvant chemotherapy could bring significant benefit for patients who received both left and right-sided pneumonectomy, but radiotherapy worsened prognosis for right-sided pneumonectomy. This study indicated that pneumonectomy side could be deemed as an important factor when physicians choosing the most optimal treatment strategies.

List Abbreviations

NSCLC：non-small cell lung cancer; SEER, Surveillance, Epidemiology, and End Results; NAACCR, North American Association of Central Cancer Registries; ICD-O, International Classification of Diseases for Oncology; OS, overall survival; HR, hazard ratio

Declarations

Ethics approval and consent to participate

The study was exempted from ethical review by the Beijing Cancer Hospital. We obtained the data agreement and data files were downloaded directly from the SEER website

Consent for publication

Each author satisfies the criteria for authorship and all authors have read it and agreed to the submission.

Availability of data and materials

Data files were downloaded directly from the SEER website

Competing interests

The Authors Declared No Potential Conflicts of Interest.

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Authors' contributions

Conceptualization, B.J. and ZP.W.; formal analysis, QW.Z.; investigation, B.J., JJ.L., J.Z., MN.W., TT.A., YY.W., ML.Z., X.Y., HX.C., YJ.C., JJ.W., XY.Z, and ZP.W; writing—original draft preparation, B.J.; writing—review and editing, B.J.; supervision, ZP.W.; funding acquisition, B.J. and ZP.W.

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Figures

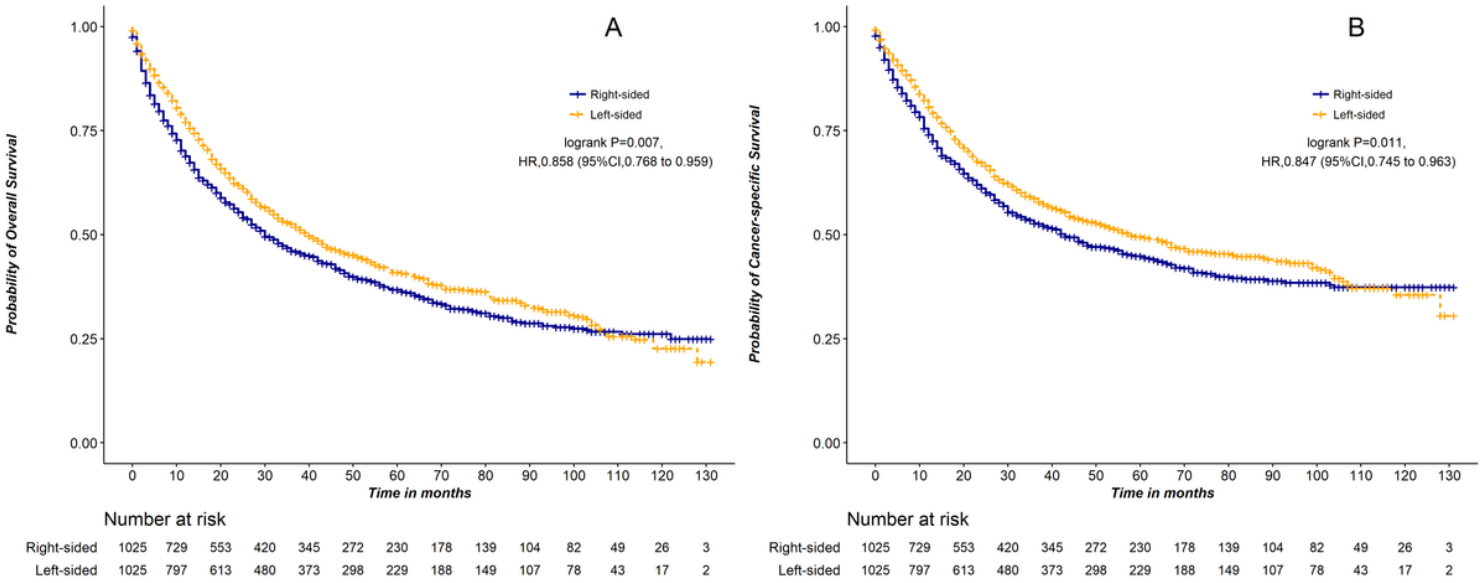

Figure 1

Overall Survival and Cancer-specific Survival among Stage I-IIIA NSCLC Patients with Pneumonectomy in the Matched Data Set. (A) Overall Survival. (B) Cancer-specific Survival.

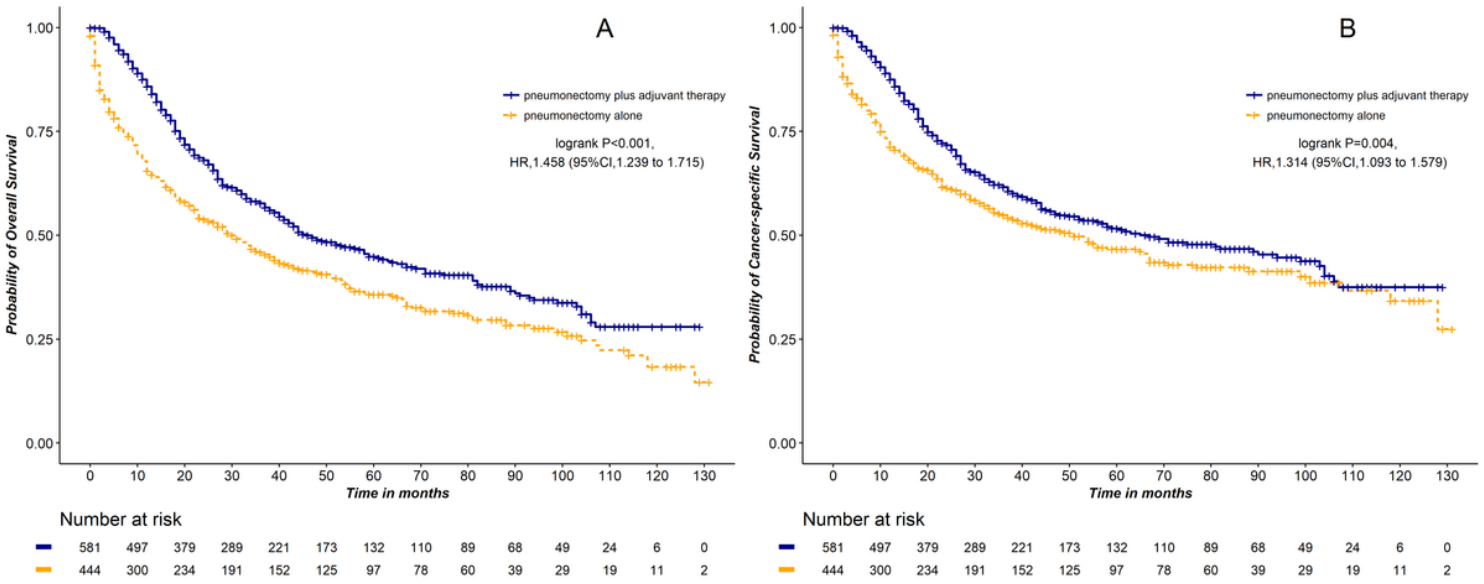

Figure 2

Overall Survival and Cancer-specific Survival among Stage I-IIIA NSCLC Patients with Pneumonectomy in Left-sided Lung in the Matched Data Set. (A) Overall Survival. (B) Cancer-specific Survival.

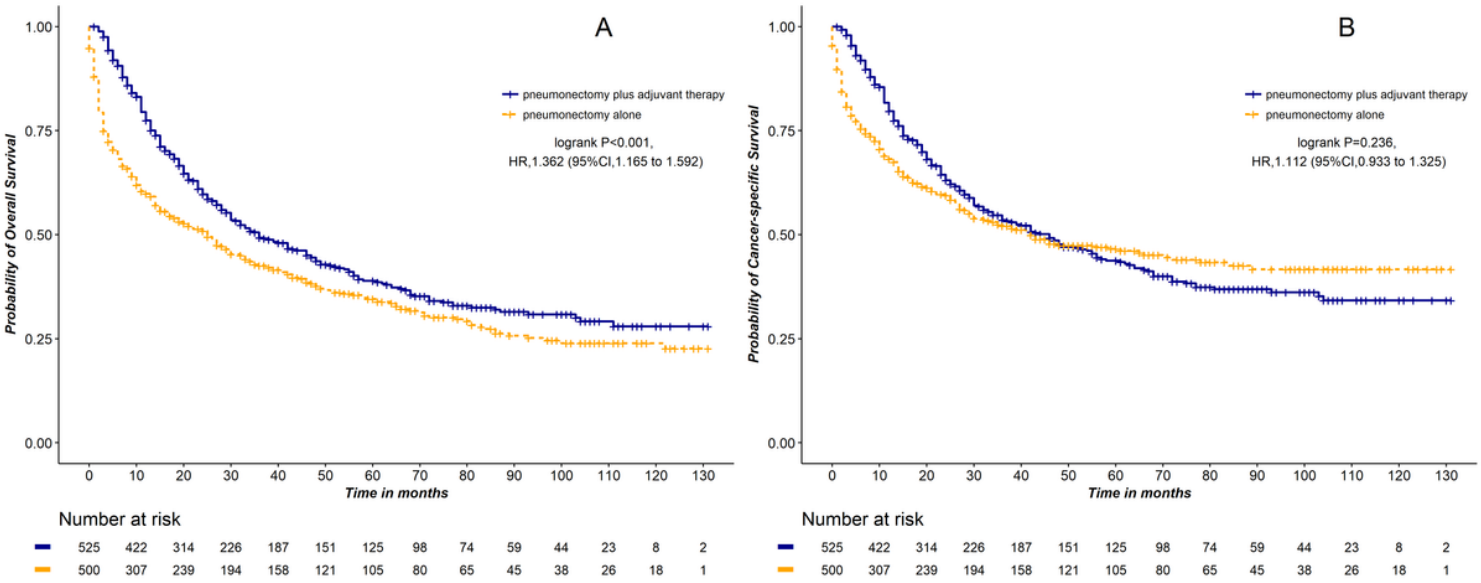

Figure 3

Overall Survival and Cancer-specific Survival among Stage I-IIIA NSCLC Patients with Pneumonectomy in Right-sided Lung in the Matched Data Set. (A) Overall Survival. (B) Cancer-specific Survival.

Subgroup	No. of Patients	Right-sided median OS	Left-sided median OS	HR_{adj} (95%)	P Value
Overall	2050	30 (27-36)	40 (35-45)	0.840(0.749-0.941)	0.002
Adjuvant therapy					
None	944	25 (18-32)	30 (23-38)	0.865(0.734-1.019)	0.084
Chemotherapy	665	56 (44-93)	81 (56-99)	0.864(0.685-1.088)	0.215
Radiotherapy	65	10 (6-21)	27 (21-62)	0.153(0.062-0.374)	<0.001
Chemoradiotheapy	376	28 (21-34)	36 (27-45)	0.747(0.576-0.969)	0.028
Histology					
Adenocarcinoma	645	40 (30-48)	41 (34-50)	0.862(0.695-1.069)	0.177
Squamous cell carcinoma	1077	30 (25-38)	41 (34-54)	0.800(0.683-0.938)	0.006
Large cell carcinoma	76	17 (12-31)	22 (16-48)	0.972(0.443-2.138)	0.945
Other	89	18 (13-32)	16 (15-NA)	0.721(0.386-1.345)	0.305
NSCLC NOS	163	24 (15-66)	54 (27-104)	0.960(0.619-1.487)	0.855
Tumor Stage					
Stage I	666	49 (38-71)	48 (40-67)	0.989(0.802-1.221)	0.920
Stage II	710	32 (25-42)	54 (39-67)	0.721(0.588-0.884)	0.002
Stage IIIA	674	21 (17-25)	28 (25-36)	0.798(0.661-0.964)	0.019

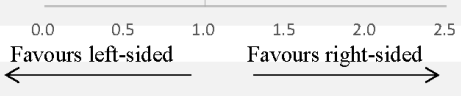

Figure 4

Overall Survival by subgroup among Stage I-IIIA NSCLC Patients with Pneumonectomy in Right-sided and Left-sided Lung in the Matched Data Set.

Supplementary Files

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- supplementmaterial.docx