Effect of laterality on the postoperative survival of non-small cell lung cancer patients undergoing pneumonectomy

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Background: Pneumonectomy is one of the important surgical methods for non-small cell lung cancer (NSCLC). This study evaluated the effects of laterality on the short- and long-term survival of NSCLC patients undergoing pneumonectomy.

Methods: We reviewed the Surveillance, Epidemiology, and End Results database to retrieve the data of patients who underwent pneumonectomy for stage I–III NSCLC from 2004 to 2015. Propensity score matching (PSM) was used to reduce the selection bias. Logistic regression was used to analyze the correlation between laterality and mortality at 3, 6, and 9 months. The Kaplan-Meier curve was used to further assess the effect of laterality on overall survival (OS).

Results: A total of 4,763 patients met the enrollment criteria [right-sided, 1,988 (41.7%); left-sided, 2,775 (58.3%)]. After PSM, 1,911 patients for each side were included in the further analysis. The first 6 months following pneumonectomy was the main period of death, with 32.0% (428/1,336) and 19.9% (250/1,258) of right- and left-sided deaths occurring during this period. The logistic regression analysis showed that right-sided pneumonectomy was an independent risk factor for 3- (P<0.001) and 6-month (P<0.001) mortality. However, laterality had no significant effect on postoperative death at 7–9 months (P=0.82). In the total cohort, right-sided patients had worse OS (P<0.001), but the subgroup survival analysis of patients with a follow-up period >6 months revealed that laterality had no statistically significant effect on OS (P=0.75).

Conclusions: Right-sided pneumonectomy was associated with a higher perioperative mortality risk that lasted about 6 months. After that period, laterality was not observed to have a significant prognostic effect on

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the OS of patients undergoing pneumonectomy.

Introduction

As one of the most common cancers and the leading cause of cancer-related death worldwide for several decades, lung cancer severely affects human life and health (1). Graham performed the first successful one-stage left-sided pneumonectomy to treat lung cancer in 1933 (2). For a long time, pneumonectomy remained the standard surgical procedure for treating lung cancer. However, technological advances and improved medical concepts have led to the widespread acceptance of lobectomy and sleeve resection in the treatment of non-small cell lung cancer (NSCLC) (3). As a result, in recent decades, much fewer patients with resectable lung cancer have undergone pneumonectomy (4). Nevertheless, current guidelines recommend that patients with locally advanced diseases, such as those with centrally located tumors or tumors with hilum invasion, undergo

pneumonectomy to achieve radical resection and improve their long-term survival (5). Unilateral pneumonectomy can completely remove the lesion, but it always leads to a greater proportion of pulmonary function loss and has a significant effect on the patient's respiratory and circulatory systems. Thus, optimal perioperative evaluation and management will facilitate accelerated patient recovery.

Studies on the survival prognosis of NSCLC patients undergoing pneumonectomy have shown that gender, age, tumor stage, laterality, and lymph node dissection are independently associated with perioperative mortality and long-term prognosis (6,7). Previous studies have suggested that laterality affects the short-term prognosis but not the long-term prognosis of patients undergoing a pneumonectomy (8). However, the exact extent of the effect of laterality on the short-term prognosis of patients after pneumonectomy has not yet been determined (9,10).

This study analyzed data from the Surveillance, Epidemiology, and End Results (SEER) database, which has a large sample size and relatively complete follow-up data related to patients after pneumonectomy. This study aimed to explore the effect of laterality on the prognosis of NSCLC patients undergoing pneumonectomy and to quantify the approximate timing and magnitude of this effect. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-700/rc).

Highlight box

Key findings

• Patients who undergo right-sided pneumonectomy for non-small cell lung cancer (NSCLC) have a higher risk of mortality during the initial 6 months post-surgery, with the impact of laterality on long-term prognosis leveling off after this critical period.

What is known and what is new?

• It is widely acknowledged that patients with NSCLC who undergo right-sided pneumonectomy often experience a poorer prognosis. However, the precise impact of laterality remains unclear.

• This study reveals that the high-risk period for patients following right-sided pneumonectomy is primarily within the initial 6 months post-operation. The influence of laterality on prognosis diminishes beyond this high-risk phase.

What is the implication, and what should change now?

• Patients with NSCLC who undergo right-sided pneumonectomy often have a higher risk of mortality during the initial 6 months post-surgery. Therefore, those patients planning to undergo this procedure should undergo a thorough preoperative evaluation. Additionally, patients undergoing right-sided pneumonectomy should receive extended perioperative follow-up, including no less than 6 months of postoperative monitoring.

Methods

Data source

This retrospective observational cohort study was based on the SEER program, which was established in 1973 (11). Anonymized information is made available to medical researchers upon formal request. The requirement of informed consent was waived due to the anonymous, observational, and registry-based nature of this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The investigators

consecutively reviewed and obtained the Incidence-SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975–2016 varying) data set through SEER*Stat (Version 8.4.0) software (https://seer.cancer.gov/data-software/documentation/seerstat/).

To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have been diagnosed between 2004 and 2015 (because of the staging standards modification); (II) have undergone pneumonectomy (surgical primary site codes: 55, 56, 65, 66, and 70); (III) have the lung as the primary site (primary site-labelled: C34.0–C34.9); (IV) have a pathological confirmation of NSCLC; and (V) have stage I–III disease (American Joint Committee on Cancer, 6th ed.) (12). Patients were excluded from the study if they met any of the following exclusion criteria: (I) had an autopsy as the reporting source; (II) had an unknown laterality side; (III) had been diagnosed with (an)other malignant tumor(s); and/or (IV) had incomplete follow-up data.

Variables

The general demographic characteristics encompassed age, sex, racial identity, year of disease diagnosis, marital status, vital condition, and duration of survival in months. Tumor characteristics such as laterality, histopathological subtypes, tumor grade, tumor dimensions, N (lymph node) stage, and treatment strategies (operation type, additional chemotherapy, or additional radiotherapy) were included in this research. The SEER variables directory specified radical pneumonectomy as pneumonectomy with mediastinal lymph node dissection, whereas extended pneumonectomy was radical pneumonectomy with additional dissection of surrounding structures, including the diaphragm, pleura, or chest wall. The primary study endpoint focused on overall survival (OS).

Statistical analysis

All the statistical analyses in this study were performed using R software 4.0.5 (The R foundation, Vienna, Austria) and SPSS Statistics 24.0 (IBM Corp., Armonk, NY, USA). Propensity score matching (PSM) was conducted using the *MatchIt* R package to reduce selection bias. To examine the balance between the left- and right-sided pneumonectomy groups, a 1:1 matching protocol was used without replacement with a caliper width of 0.02 standard deviations (SDs) of the logit of the propensity score. A stepwise

logistic regression model analysis was employed to analyze the correlation of laterality and other potential variables with postoperative mortality at 0–3, 4–6, and 7–9 months using the *rms* R package.

All the research variables were included in the univariable logistic analysis and odds ratios (ORs) with 95% confidence intervals (CIs) were compared. The factors significantly associated with postoperative mortality ($P<0.1$) in the univariable analysis were included in the multivariable analysis to identify the independent risk factors associated with mortality. Kaplan-Meier (KM) curves were used to further assess the effect of laterality on OS.

Numbers and proportions were calculated for the categorical variables, and the groups were compared using the Chi-squared test or Fisher's exact test. The normally distributed continuous variables were analyzed using the independent samples Student's *t*-test or paired Student's *t*-test, and are expressed as the mean ± SD. The non-normally distributed variables were analyzed using the Mann-Whitney *U* test or Wilcoxon signed-rank test, and are presented as the median with interquartile range (IQR). Two-sided P values <0.05 were considered statistically significant.

Results

A total of 4,763 patients met the enrollment criteria, including 1,988 (41.7%) and 2,775 (58.3%) patients who underwent right-sided and left-sided pneumonectomies, respectively. The screening scheme for the subjects is provided in *Figure 1*. The median age of the included patients was 63 [56–70] years. Squamous cell carcinoma (N=2,423; 50.9%) was a more common diagnosis than adenocarcinoma. The median tumor size was 4.9 (3.3–7.0) cm, and 62.2% (N=2,962) of the patients had lymph node metastasis. Radical or extended pneumonectomy was performed in 62.2% (N=2,962) of the patients, while 50.5% (N=2,407) and 22.3% (N=1,060) of the patients underwent chemotherapy and radiotherapy, respectively.

The overall postoperative mortality rates at 0 (intra-operation or in-hospital mortality), 1, 3, 6, and 12 months were 1.66%, 4.74%, 10.96%, 17.17%, and 28.15%, respectively. The postoperative mortality rates at 0, 1, 3, 6, and 12 months of the left-sided pneumonectomy group were 1.23%, 3.42%, 8.22%, 13.37%, and 24.36%, while those of the right-sided pneumonectomy group were 2.26%, 6.59%, 14.79%, 22.48%, and 33.45%, respectively.

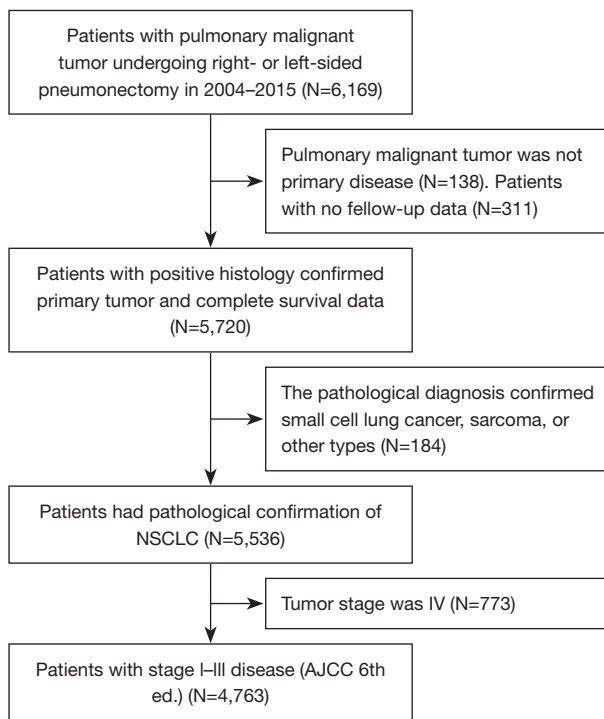After 1:1 PSM, 1,911 patients were included in each

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Patients with pulmonary malignant tumor undergoing right- or left-sided pneumonectomy in 2004–2015 (N=6,169)

Pulmonary malignant tumor was not primary disease (N=138). Patients with no fellow-up data (N=311)

Patients with positive histology confirmed primary tumor and complete survival data (N=5,720)

The pathological diagnosis confirmed small cell lung cancer, sarcoma, or other types (N=184)

Patients had pathological confirmation of NSCLC (N=5,536)

Tumor stage was IV (N=773)

Patients with stage I–III disease (AJCC 6th ed.) (N=4,763)

Figure 1 Schematic of patient screening process. NSCLC, non-small cell lung cancer; AJCC, American Joint Committee on Cancer.

matched cohort to achieve a balance in the confounding covariates between the groups (*Table 1*). Postoperative deaths occurred in 2,594 (67.9%) patients, including 1,336 (51.5%) who underwent right-sided pneumonectomies, and 1,258 (48.5%) who underwent left-sided pneumonectomies with a median follow-up time of 69 months. The mortality times for each laterality group within 3 years are shown in *Figure 2A*. Postoperative deaths were most common during the first 6 months after surgery. During this period, deaths occurred in 32.0% (428/1,336) and 19.9% (250/1,258) of the patients in the right-sided and left-sided pneumonectomy groups, respectively. The proportion of deaths in the right-sided pneumonectomy group was initially higher, but both groups showed similar trends after the initial 6 months.

A further analysis of postoperative mortality over 12 months revealed that the patients who underwent right-sided pneumonectomies had higher proportions of deaths during the 0–3- and 4–6-month periods (63.4% and 62.7%, respectively, P=0.85; *Figure 2B*). In the right-sided pneumonectomy group, postoperative mortality at 7–9 months was significantly lower than that at 4–6 months (P=0.01). A similar trend was also observed in the left-sided pneumonectomy group. There was no significant difference

Table 1 Patient and tumor characteristics of the enrolled patients before and after PSM

Variables	Before PSM			After PSM		
	Right-sided (N=1,988)	Left-sided (N=2,775)	P value	Right sided (N=1,911)	Left sided (N=1,911)	P value
Gender			0.057			0.34
Female	643 (32.3)	971 (35.0)		621 (32.5)	594 (31.1)	
Male	1,345 (67.7)	1,804 (65.0)		1,290 (67.5)	1,317 (68.9)	
Age (years)			0.002			0.35
≤60	843 (42.4)	1,051 (37.9)		790 (41.3)	762 (39.9)	
>60	1,145 (57.6)	1,724 (62.1)		1,121 (58.7)	1,149 (60.1)	
Race			0.20			0.24
White	1,693 (85.2)	2,399 (86.5)		1,634 (85.5)	1,659 (86.8)	
Other	295 (14.8)	376 (13.5)		277 (14.5)	252 (13.2)	
Marriage			0.93			0.23
Married	1,242 (62.5)	1,737 (62.6)		1,198 (62.7)	1,233 (64.5)	
Other	746 (37.5)	1,038 (37.4)		713 (37.3)	678 (35.5)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Before PSM			After PSM		
	Right-sided (N=1,988)	Left-sided (N=2,775)	P value	Right sided (N=1,911)	Left sided (N=1,911)	P value
Grade			0.67			0.62
I	97 (4.8)	136 (4.9)		92 (4.8)	97 (5.1)	
II	697 (35.1)	967 (34.8)		668 (35.0)	703 (36.8)	
III/IV	1,011 (50.9)	1,443 (52.0)		983 (51.4)	950 (49.7)	
Unknown	183 (9.2)	229 (8.3)		168 (8.8)	161 (8.4)	
Histology			<0.001			0.15
ADC	733 (36.9)	829 (29.9)		676 (35.4)	690 (36.1)	
SCC	940 (47.3)	1,483 (53.4)		930 (48.7)	964 (50.4)	
NEC	45 (2.3)	82 (3.0)		43 (2.3)	41 (2.1)	
Other	270 (13.6)	381 (13.7)		262 (13.7)	216 (11.3)	
Tumor size (cm)			0.006			<0.001
T ≤3	431 (21.7)	595 (21.4)		398 (20.8)	570 (29.8)	
3< T ≤5	609 (30.6)	969 (34.9)		598 (31.3)	779 (40.8)	
5< T ≤7	442 (22.2)	615 (22.2)		437 (22.9)	309 (16.2)	
T >7	457 (23.0)	533 (19.2)		441 (23.1)	204 (10.7)	
Unknown	49 (2.5)	63 (2.3)		37 (1.9)	49 (2.6)	
N stage			0.001			0.20
N0	797 (40.1)	1,004 (36.2)		764 (40.0)	815 (42.6)	
N1	690 (34.7)	1,112 (40.1)		665 (34.8)	663 (34.7)	
N2	476 (23.9)	636 (22.9)		462 (24.2)	418 (21.9)	
N3	25 (1.3)	23 (0.8)		20 (1.0)	15 (0.8)	
Surgery type			0.30			0.20
Pneumonectomy	608 (30.6)	833 (30.0)		578 (30.2)	599 (31.3)	
Radical Pneu	1,297 (65.2)	1,848 (66.6)		1,252 (65.5)	1,251 (65.5)	
Extended Pneu	83 (4.2)	94 (3.4)		81 (4.2)	61 (3.2)	
Chemotherapy			0.002			0.41
Yes	951 (47.8)	1,456 (52.5)		925 (48.4)	950 (49.7)	
No	1,037 (52.2)	1,319 (47.5)		986 (51.6)	961 (50.3)	
Radiotherapy			0.03			0.45
Yes	413 (20.8)	647 (23.3)		402 (21.0)	421 (22.0)	
No	1,575 (79.2)	2,128 (76.7)		1,509 (79.0)	1,490 (78.0)	

PSM, propensity score matching; ADC, adenocarcinoma; SCC, squamous cell carcinoma; NEC, neuroendocrine carcinoma; Pneu, pneumonectomy.
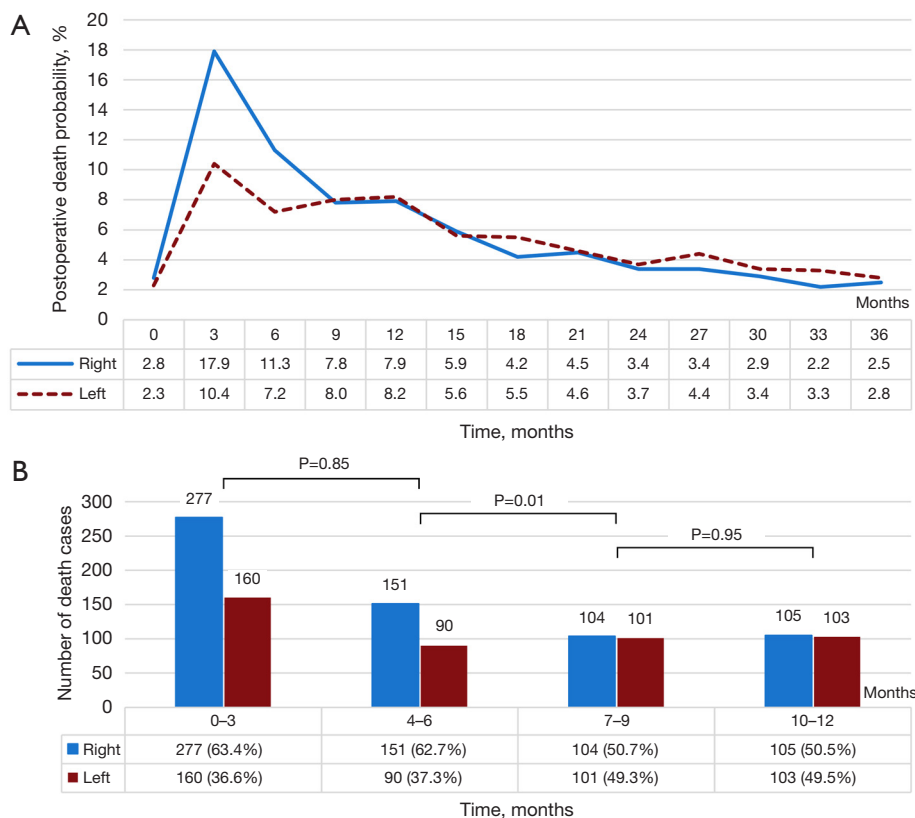
Figure 2 Postoperative mortality of enrolled patients after pneumonectomy. (A) Overall proportion of postoperative death in enrolled patients after pneumonectomy on each side. (B) Comparison of the mortality rates for left- and right-sided patients at different times within 12 months after pneumonectomy by the Chi-squared test.

in postoperative mortality between the two groups during the 7–9- and 10–12-month periods (P=0.95).

In the univariate analysis, age, laterality, pathological type, chemotherapy, and radiotherapy were found to be related to postoperative mortality at both 3 months and 4–6 months. While, gender (*Table 2*) and N stage (*Table 3*) were found to be correlated with postoperative mortality at 0–3 and 4–6 months, respectively.

The multivariable logistic regression analysis showed that right-sided pneumonectomy was an independent risk factor for postoperative mortality at 0–3 months (right *vs.* left: OR: 1.421, 95% CI: 1.269–1.592, P<0.001; *Table 2*) and 4–6 months (right *vs.* left: OR: 1.292, 95% CI: 1.122–1.488, P<0.001; *Table 3*). However, laterality was not a prognostic factor associated with postoperative death at 7–9 months (right *vs.* left: OR: 1.016, 95% CI: 0.882–1.169, P=0.82; *Table 4*).

The median follow-up time for the entire patient group was 65.0 months. The median OS of patients undergoing right- and left-sided pneumonectomy was 29.0 and 40.0 months, respectively. This survival difference between the two groups demonstrated high statistical significance (log-rank P<0.001; *Figure 3A*). The subgroup survival analysis of the patients with follow-up times >6 months demonstrated that laterality was not significantly correlated with OS (log-rank P=0.75; *Figure 3B*).

Discussion

Pneumonectomy is associated with a greater operative risk compared to limited pulmonary resections, and its effect on long-term survival is still a subject of contention (13). Nevertheless, anatomical or technical constraints may necessitate this operation (14). In the present study, a comprehensive analysis was conducted to examine the effects of laterality on the short- and long-term survival of pneumonectomy patients. The results showed that the effect of laterality was limited to the initial 6 months

Table 2 Univariable and multivariable logistic regression analyses of the factors correlated to the 3-month postoperative mortality of patients after pneumonectomy

Variables	Univariable logistic regression		Multivariable logistic regression	
	OR (95% CI)	P value	OR (95% CI)	P value
Gender (male *vs.* female)	1.655 (1.309–2.093)	<0.001*	1.455 (1.119–1.893)	0.005
Age (>60 *vs.* ≤60 years)	2.297 (1.828–2.887)	<0.001*	1.748 (1.354–2.258)	<0.001
Race (other *vs.* White)	0.905 (0.672–1.218)	0.50		
Marriage (other *vs.* married)	1.045 (0.850–1.284)	0.67		
Laterality (right *vs.* left)	1.362 (1.229–1.510)	<0.001*	1.421 (1.269–1.592)	<0.001
Grade		0.08*		0.004
II *vs.* I	1.425 (0.819–2.480)	0.21	1.582 (0.884–2.833)	0.12
III/IV *vs.* I	1.684 (0.977–2.901)	0.06	2.142 (1.206–3.804)	0.009
Histology		0.02*		0.37
SCC *vs.* ADC	1.311 (1.048–1.639)	0.01	1.096 (0.850–1.414)	0.47
NEC *vs.* ADC	0.456 (0.164–1.264)	0.13	0.391 (0.117–1.306)	0.12
Other *vs.* ADC	1.309 (0.947–1.809)	0.10	1.034 (0.703–1.521)	0.86
Tumor size (cm)		0.23		
3< T ≤5 *vs.* T ≤3	0.982 (0.754–1.280)	0.89		
5< T ≤7 *vs.* T ≤3	1.156 (0.858–1.557)	0.33		
T >7 *vs.* T ≤3	1.281 (0.946–1.736)	0.10		
N stage		0.13		
N1 *vs.* N0	1.066 (0.851–1.336)	0.57		
N2 *vs.* N0	0.831 (0.634–1.090)	0.18		
N3 *vs.* N0	1.919 (0.826–4.456)	0.12		
Surgery type		0.07*		0.19
Radical Pneu *vs.* Pneu	0.787 (0.636–0.972)	0.02	0.878 (0.695–1.111)	0.27
Extended Pneu *vs.* Pneu	0.964 (0.572–1.626)	0.89	1.420 (0.770–2.618)	0.26
Chemotherapy (no *vs.* yes)	16.254 (11.150–23.694)	<0.001*	15.850 (10.278–24.444)	<0.001
Radiotherapy (no *vs.* yes)	4.669 (3.138–6.947)	<0.001*	1.251 (0.774–2.022)	0.36

*, these factors with P value less than 0.1 were defined as parameters significantly associated with postoperative mortality in univariable analysis. OR, odds ratio; CI, confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma; NEC, neuroendocrine carcinoma; Pneu, pneumonectomy.

following pneumonectomy. The subgroup analysis of patients with follow-up times >6 months revealed no significant difference in the long-term prognosis between the left- and right-sided pneumonectomy groups.

The study included a total of 4,763 patients who underwent surgery between 2004 and 2015. In the entire cohort, the 1-month postoperative mortality rate was 4.74%, with rates of 3.43% and 6.59% for the left- and right-sided pneumonectomy groups, respectively. Seder *et al.* analyzed data from the STS (the Society of Thoracic Surgeons) and ESTS (the European Society of Thoracic Surgeons) databases and reported that the in-hospital mortality rates for pneumonectomy patients were 4.3% and 4.9%, while the 30-day mortality rates were 6.7% and 7.3%, respectively (15). A meta-analysis reported an overall 30-day mortality rate of 7% for pneumonectomy

Table 3 Univariable and multivariable logistic regression analyses of the factors correlated to the 4–6-month postoperative mortality of patients after pneumonectomy

Variables	Univariable logistic regression		Multivariable logistic regression	
	OR (95% CI)	P value	OR (95% CI)	P value
Gender (male *vs.* female)	1.310 (0.976–1.758)	0.07*	1.330 (0.973–1.818)	0.07
Age (>60 *vs.* ≤60 years)	1.492 (1.129–1.971)	0.005*	1.441 (1.074–1.934)	0.01
Race (other *vs.* White)	1.024 (0.704–1.490)	0.90		
Marriage (other *vs.* married)	0.968 (0.737–1.270)	0.81		
Laterality (right *vs.* left)	1.318 (1.152–1.507)	<0.001*	1.292 (1.122–1.488)	<0.001
Grade		0.10		
II *vs.* I	1.236 (0.585–2.609)	0.57		
III/IV *vs.* I	1.631 (0.786–3.386)	0.18		
Histology		0.01*		0.07
SCC *vs.* ADC	0.825 (0.616–1.106)	0.19	0.848 (0.620–1.158)	0.29
NEC *vs.* ADC	0.717 (0.257–2.003)	0.52	0.778 (0.274–2.209)	0.63
Other *vs.* ADC	1.491 (1.025–2.169)	0.03	1.396 (0.941–2.071)	0.09
Tumor size (cm)		0.06*		0.52
3< T ≤ 5 *vs.* T ≤3	1.030 (0.721–1.471)	0.87	1.029 (0.714–1.481)	0.87
5< T ≤7 *vs.* T ≤3	1.061 (0.704–1.599)	0.77	0.979 (0.642–1.492)	0.92
T >7 *vs.* T ≤3	1.578 (1.069–2.329)	0.02	1.290 (0.858–1.939)	0.22
N stage		0.009*		0.01
N1 *vs.* N0	0.899 (0.653–1.238)	0.51	1.038 (0.746–1.444)	0.82
N2 *vs.* N0	1.506 (1.097–2.067)	0.01	1.698 (1.192–2.418)	0.003
N3 *vs.* N0	2.086 (0.721–6.034)	0.17	2.290 (0.756–6.932)	0.14
Surgery type		0.07*		0.10
Radical Pneu *vs.* Pneu	0.885 (0.667–1.176)	0.40	0.934 (0.694–1.257)	0.65
Extended Pneu *vs.* Pneu	1.664 (0.930–2.979)	0.08	1.734 (0.948–3.172)	0.07
Chemotherapy (no *vs.* yes)	1.336 (1.027–1.740)	0.03*	1.766 (1.273–2.449)	0.001
Radiotherapy (no *vs.* yes)	0.711 (0.530–0.954)	0.02*	0.599 (0.417–0.862)	0.006

*, these factors with P value less than 0.1 were defined as parameters significantly associated with postoperative mortality in univariable analysis. OR, odds ratio; CI, confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma; NEC, neuroendocrine carcinoma; Pneu, pneumonectomy.

patients, with rates of 5% and 11% for left- and right-sided pneumonectomies, respectively. The corresponding 90-day mortality rates were 12% for the entire cohort, 9% for left-sided pneumonectomies, and 20% for right-sided pneumonectomies (16). Pricopi *et al.* found that among NSCLC patients who underwent right-sided pneumonectomies, the 30- and 90-day mortality rates were

9.4% and 11.2%, respectively. The corresponding rates for left-sided pneumonectomies were significantly lower at 3.1% and 4.7%, respectively (9). These trends were similar to those observed in the present study.

The National Surgical Quality Improvement Program (NSQIP) database categorizes any death occurring within 30 days of non-cardiothoracic surgery, regardless of the

Table 4 Univariable and multivariable logistic regression analyses of the factors correlated to the 7–9-month postoperative mortality of patients after pneumonectomy

Variables	Univariable logistic regression		Multivariable logistic regression	
	OR (95% CI)	P value	OR (95% CI)	P value
Gender (male *vs.* female)	1.162 (0.852–1.585)	0.34		
Age (>60 *vs.* ≤60 years)	1.170 (0.875–1.566)	0.29		
Race (other *vs.* White)	0.941 (0.621–1.426)	0.77		
Marriage (other *vs.* married)	1.150 (0.862–1.534)	0.34		
Laterality (right *vs.* left)	1.016 (0.882–1.169)	0.82		
Grade		0.40		
II *vs.* I	1.740 (0.747–4.056)	0.19		
III/IV *vs.* I	1.770 (0.767–4.084)	0.18		
Histology		0.94		
SCC *vs.* ADC	0.980 (0.721–1.331)	0.89		
NEC *vs.* ADC	1.089 (0.428–2.770)	0.85		
Other *vs.* ADC	0.870 (0.539–1.405)	0.56		
Tumor size (cm)		<0.001*		<0.001
3< T ≤ 5 *vs.* T ≤3	0.934 (0.629–1.388)	0.73	0.921 (0.619–1.369)	0.68
5< T ≤7 *vs.* T ≤3	0.979 (0.621–1.545)	0.92	0.943 (0.597–1.491)	0.80
T >7 *vs.* T ≤3	2.142 (1.438–3.192)	<0.001	2.038 (1.362–3.052)	0.001
N stage		0.50		
N1 *vs.* N0	0.577 (0.173–1.923)	0.37		
N2 *vs.* N0	0.675 (0.202–2.251)	0.52		
N3 *vs.* N0	0.535 (0.157–1.817)	0.31		
Surgery type		0.054*		0.11
Radical Pneu *vs.* Pneu	0.810 (0.599–1.096)	0.17	0.787 (0.577–1.072)	0.12
Extended Pneu *vs.* Pneu	1.594 (0.858–2.961)	0.14	1.330 (0.705–2.507)	0.37
Chemotherapy (no *vs.* yes)	0.894 (0.675–1.185)	0.43		
Radiotherapy (no *vs.* yes)	0.630 (0.462–0.859)	0.003*	0.665 (0.483–0.916)	0.01

*, these factors with P value less than 0.1 were defined as parameters significantly associated with postoperative mortality in univariable analysis. OR, odds ratio; CI, confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma; NEC, neuroendocrine carcinoma; Pneu, pneumonectomy.

cause, as a surgery-related death. The assessment of 30-day mortality encompasses not only the surgical risk index but also the projected survival benefit and unanticipated postoperative death (17). A 30-day window is typically adequate for documenting all procedure-related deaths following conventional thoracic surgery, including sub-lobar resections and lobectomies. However, recent investigations of the pneumonectomy procedure have demonstrated that the 90-day mortality (3.0–21.0%) can be twice as high as the 30-day mortality (1.5–12.0%) (18). Thus, the surgical risk related to pneumonectomy persists beyond the initial 30-day period or the time of discharge. As a result, pneumonectomy patients require intensive care, comprehensive treatment, and prolonged
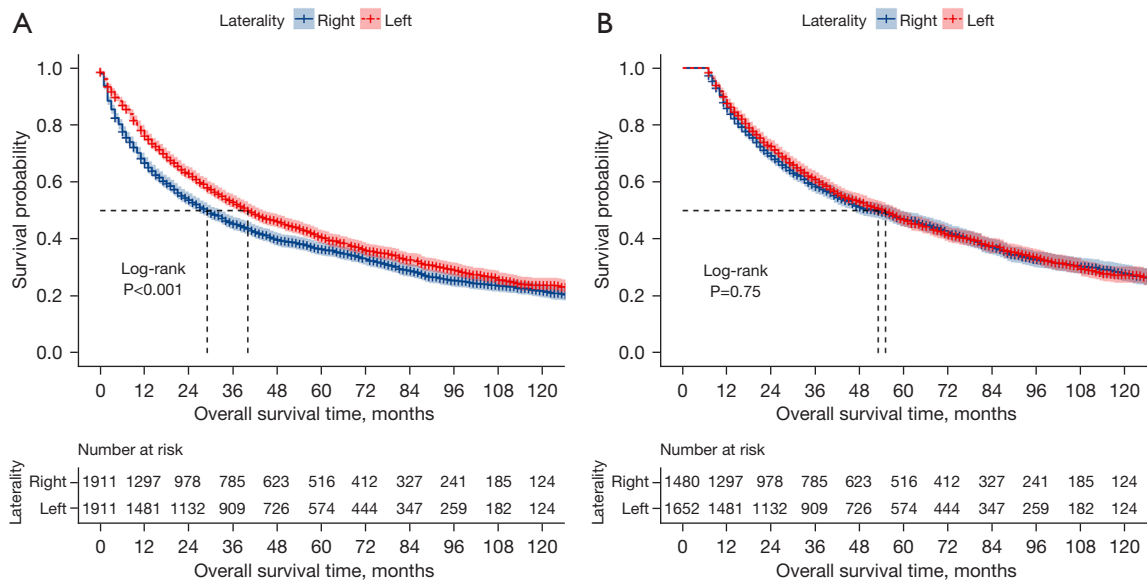
Figure 3 The overall survival Kaplan-Meier curves of the enrolled patients who underwent a pneumonectomy in the total cohort (A) and the subgroup of patients with a follow-up time of more than 6 months (B).

follow-up to minimize operative mortality and postoperative complications management (19).

Patients undergoing right-sided pneumonectomies were found to be at a greater risk of perioperative mortality compared to those undergoing left-sided pneumonectomies. This difference was primarily a result of postoperative complications rather than the procedure itself and may be related to several potential factors (20). First, the right lung contributes to a greater share of overall lung ventilation; therefore, a right-sided pneumonectomy can disproportionately affect lung function. The asymmetrical mediastinal shift, with the heart shifted to the left side, also provides relief on the left side after pneumonectomy. The absence of counteracting resistance on the right side can trigger a mediastinal shift, leading to detrimental structural alterations in the hilum that affect pulmonary ventilation and cardiac hemodynamic stability, posing a potentially life-threatening risk. Moreover, right-sided surgery is associated with a greater risk of serious complications, such as acute respiratory distress syndrome (ARDS) and bronchopleural fistula (BPF), resulting in greater morbidity and mortality. The greater loss of pulmonary function following right total lung surgery, with a considerably reduced pulmonary vascular bed area, leads to higher pulmonary artery pressure and increased right ventricular afterload. This, in turn, increases the risk of general complications, including postoperative ARDS and arrhythmias (21).

Following pneumonectomy, the right bronchus becomes wider than the left bronchus, which increases the tension and leads to a greater risk of BPF. The left stump is covered by the aortic arch, while the right bronchial stump lacks protection from the surrounding mediastinal tissue, making it more susceptible to inflammation and rupture. The risk of perioperative mortality is higher in the presence of respiratory complications, particularly ARDS, because of the significant reduction in lung function following pneumonectomy. A retrospective study has reported a significant association between ARDS and pulmonary edema caused by increased pulmonary blood flow after unilateral total lung resection (22). The incidence of ARDS among pneumonectomy patients ranges from approximately 0.9% to 46.0%, with perioperative morbidity and mortality rates ranging from 33.3% to 59.8% (23). Blanc *et al.* investigated 543 cases of total lung resection and conducted a systematic analysis to assess the occurrence, management, and prognosis of perioperative ARDS after pneumonectomy. Their multifactorial analysis revealed that right-sided pneumonectomy and a high Charlson Comorbidity Index (CCI) were independent risk factors for ARDS. This may be because of the greater perfusion and ventilation of the right lung, along with a higher gradient of elevated pulmonary artery pressure after right-sided pneumonectomy (24).

Previous studies have reported that pneumonia occurs in

2–10% of patients after pneumonectomy, mostly because of poor postoperative pain control, limited mobility, or prolonged mechanical ventilation. Pneumonectomy patients who develop pneumonia have a poorer survival prognosis than those without pneumonia (25). It has been reported that supraventricular arrhythmia, such as atrial fibrillation (AF), is the most common type of arrhythmia after pneumonectomy. Postoperative AF occurs in approximately 4–25% of pneumonectomy patients (22). The mechanism underlying postoperative AF is complex and not yet fully understood. Right-sided pneumonectomy is a known risk factor for AF. Pulmonary hypertension and right-sided cardiac insufficiency after pneumonectomy are caused by increased pulmonary blood flow on the healthy side. Severe pulmonary hypertension increases the afterload on the right ventricle, resulting in right-sided cardiac insufficiency as the heart fails to compensate (26).

The prevailing consensus in the medical community is that right-sided pneumonectomy is associated with higher perioperative mortality rates than left-sided pneumonectomy (6). Research conducted by Fernandez *et al.* indicates that there is a significant difference in the mortality rates at 30 and 90 days, with rates of 8% and 16% for right-sided pneumonectomies, and 4% and 9% for left-sided pneumonectomies, respectively (10). Yang *et al.* identified right-sided pneumonectomy as an independent risk factor for 90-day perioperative mortality (hazard ratio: 2.23, $P<0.01$) (27). The incidence of at least one complication in pneumonectomy patients during the perioperative period varied significantly, ranging from 21.4% to 56.7% (28). Pneumonectomy patients also had significantly higher rates of major complications than lobectomy patients.

The laterality of pneumonectomy may be related to short-term morbidity; however, the laterality of pneumonectomy did not affect the long-term survival outcomes of patients. Pneumonectomy patients undergo a sequence of anatomical alterations postoperatively. Fluid gradually accumulates in the empty chest cavity, forming a radiologically visible hydropneumothorax sign. In addition, there may be an upward shift in the diaphragm on the side of the surgery, thorax deformation, and gradual mediastinal displacement (29). The perioperative mortality risk was significantly higher in patients who underwent right-sided pneumonectomies, and this elevated risk persisted for approximately 6 months. However, beyond this period, there was no significant prognostic difference in the OS of the pneumonectomy patients regardless of laterality (30).

Riquet investigated post-pneumonectomy patients who achieved long-term survival, and found no evidence to suggest that laterality had any effect on the prognosis of pneumonectomy patients (6). This accords with the results of the present study, which found that right-sided pneumonectomy patients had a higher risk of early postoperative mortality, but that laterality had no significant effect on survival after 6 months. An analysis of the survival curves for OS in pneumonectomy patients by Fernandez *et al.* revealed a widening survival gap between the two patient groups during the early stages, but a convergent trend after 2 years (10). Consistent with the findings of previous studies, the present study demonstrated that right-sided pneumonectomy patients had an increased risk of early postoperative death, but laterality did not play a significant role in survival after the initial period of 6 months.

Limitations

The authors conducted a comprehensive analysis of the differences in short- and long-term survival between patients who underwent left- and right-sided pneumonectomies. The study also investigated the timeframe for the effect of laterality on post-pneumonectomy outcomes. However, this study was not without certain limitations. First, given its retrospective nature, this study faced inherent natural deviations. The research data were derived from the national cancer registration database. Due to data constraints, some of the variables, such as the specific causes of death, perioperative complications, (neo-)adjuvant treatment strategies, detailed pulmonary function, and surgical approaches (open or minimally invasive) could not be comprehensively analyzed. Additionally, surgical techniques/ intensive care unit management would have changed over the study period. Even if PSM was used to balance the variables of two sets, there was still a certain degree of difference in the characteristics between the two groups of patients. Further, the SEER database includes survival data in months rather than days, which precluded a more precise assessment of short-term prognosis in this study. However, several previous studies have also analyzed perioperative survival in months. Despite these limitations, this study had a large sample size and yielded compelling evidence regarding both early and late mortality in pneumonectomy patients, specifying the exact period for the effect of laterality.

Conclusions

In conclusion, the risk of early mortality was greater after

right-sided pneumonectomy, and this risk persisted for the initial 6 months. However, after this period, there was no significant difference in the survival of the pneumonectomy patients based on laterality. Thus, the long-term survival of patients does not appear to be affected by the laterality of the procedure.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-700/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-700/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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