Clinicopathological Characteristics and Survival Outcomes for Pneumonectomy: a Population-Based Study

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Research

Keywords: Pneumonectomy (PN), SEER database, non-small cell lung cancer (NSCLC), Propensity score matching (PSM), forest plots

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Abstract

Background: Prognostic factors in pneumonectomy (PN) are not yet fully defined. This study is to analyze and evaluate long-term survival after PN for non-small cell lung cancer (NSCLC).

Methods: We obtained data from the Surveillance, Epidemiology, and End Results (SEER) database for patients who underwent PN between 2004 and 2015. In order to reduce bias and imbalance, propensity score matching (PSM) analysis was performed. We used Kaplan-Meier curves to estimate overall survival (OS), performed univariate and multivariate Cox proportional hazards regression analyses to identify independent prognostic factors for OS, and applied the Cox proportional hazards model to create a forest plot.

Results: A total of 1557 PN patients from the SEER database were included. The patients were grouped according to the side of PN. Before matching, OS was worse after right PN (hazard ratio [HR]: 1.303; 95% confidence interval [CI] 1.133-1.498; P<0.001), but survival difference between groups was not significant after matching (HR: 1.061; 95% CI 0.912-1.235; P=0.443). Regression analysis revealed that age, grade, N-stage, radiotherapy, and chemotherapy were independent predictors of OS (P<0.05). Chemotherapy was associated with improved OS (HR: 0.709; 95% CI 0.609-0.825; P<0.001), but radiotherapy was associated with increased risk of death in OS (HR: 1.268; 95% CI 1.061-1.561; P=0.009). On the forest plot, patients with primary overlapping lesions had better OS (HR: 0.684; 95% CI 0.497-0.941; P=0.020) in left, *vs* right, PN; patients diagnosis during 2004 to 2007 had lower OS (HR: 0.576; 95% CI 0.346-0.960; P=0.034) for left PN vs right PN.

Conclusions: Laterality was not a significant prognostic factor for long-term survival after PN for NSCLC. Chemotherapy was a significant independent predictor of improved OS, while radiotherapy appeared to be a negative prognostic factor with increased risk of death in OS.

Background

Lung cancer incidence (11.6%) and mortality rates (18.4%) are among the highest of all malignant tumors in China and the world. The most recent estimate predicts 228,820 new cases and 135,720 deaths in 2020, emphasizing the serious worldwide effects of this disease, which has a 5-year survival rate of approximately 19 percent [1]. Radical resection remains the preferred treatment for NSCLC, and current widely-accepted surgical techniques include lobectomy, segmentectomy, pneumonectomy, and pulmonary sleeve with pulmonary artery reconstruction [2–4]. Central lung tumors are relatively common in clinical practice. Some can be treated with lobectomy or pulmonary sleeve resection, but when these methods cannot completely remove the tumor, PN is required, even as the prognostic factors for left and right PN remain under investigation. Depending on the surgeon's experience and the histological and anatomical characteristics of the lung and tumor, it is possible that survival is better for left PN than for right PN [5]. The aim of this study is to analyze and evaluate long-term survival after PN in patients with NSCLC. We used a population-based national registry, the Surveillance, Epidemiology, and End Results

(SEER) database, to analyze clinical characteristics and prognosis for PN and for left and right PN. Based on the results of the survival analysis, we created a forest plot by using the Cox proportional hazards model.

Methods

Data collection

We extracted data from the SEER database (https://seer.cancer.gov/) through SEER*Stat software (v8.3.6, https://seer.cancer.gov/seerstat/) to identify patients with a confirmed diagnosis of NSCLC between 2004 and 2015, and those undergoing PN (SEER Surgery Codes: 55, 56, 65, 66, 70) were included in our study. The inclusion criteria were: (1) diagnosis between 2004 and 2015; (2) diagnosis of NSCLC confirmed microscopically; (3) only one primary tumor; (4) survival for at least 1 month; (5) active follow-up; and (6) available clinical information. The exclusion criteria were: (1) incomplete survival or clinical data, including unknown race, grade, tumor stage, T- or N-stage, extent of lymph node dissection, summary stage, and vital status recode; (2) small cell lung cancer; (3) distant metastasis; (4) diagnosed solely on autopsy or death certificate (Fig. 1).

Variables

This study was based on public data from the SEER database. The covariates included age, sex, race, marital status, year of diagnosis, primary site, summary stage, histopathology, grade, extent of lymph node dissection, tumor stage, T-stage, N-stage, radiotherapy, and chemotherapy. We classified age into five groups: ≤50, 51-60, 61-70, 71-80, and 81 and older. The year of diagnosis was classified into three groups: 2004-2007, 2008-2011, and 2012-2015. The grade was classified as well differentiated, moderately differentiated, poorly differentiated, and undifferentiated. We followed the seventh edition American Joint Committee on Cancer (AJCC) lung cancer staging system, and updated the T-stage (T1, T2, T3 and T4), N-stage (N0, N1, N2-N3), and tumor stage (I, II, III) for all patients in all time periods. Overall survival (OS) was defined as the time from diagnosis to death from any cause.

Propensity score matching

In order to avoid bias between left and right PN groups, we applied 1: 1 propensity score matching (PSM) for age, sex, race, marital status, year of diagnosis, primary site, grade, summary stage, histopathology, lymph node dissection, tumor stage, T-stage, N-stage, radiotherapy, chemotherapy, survival months, and vital status recode.

Statistical analysis

Categorical variables are expressed as percentages and continuous variables are expressed as mean ± standard deviation (SD). Variables were compared using Student’s t test, Chi-square test, and analysis of variance. We used the Kaplan-Meier method to generate survival curves and analyzed differences between curves by the log-rank test. We used the Cox proportional hazards model to examine

independent prognostic factors and calculate the hazard ratio (HR) and the corresponding 95% confidence interval (CI). Specific results are depicted as forest plots. Data were analyzed with Statistical Product and Service Solutions 22.0 software (SPSS, Inc., Chicago, IL, USA). P values <0.05 (two-sided) were considered statistically significant. Survival curves and the forest plot were drawn with GraphPad Prism (Version 8.3.1).

Results

Patient and clinicopathological characteristics.

A total of 1557 patients who underwent PN between 2004 and 2015 were selected from the SEER database. Of these, 904 (57.7%) had left PN and 653 (42.3%) had right PN. The patient characteristics are shown in Table 1. The two groups were similar in age, sex, marital status, race, year of diagnosis, grade, lymph node dissection, tumor stage, T-stage, N-stage, radiotherapy, and chemotherapy, while the primary tumor site and histopathology had a significant difference between sides (P<0.05).

Survival analysis

Among all 1557 patients, the mean follow-up was 61.57 ± 10.83 months (61.75 ± 10.62 months, left PN and 61.31 ± 11.12 months, right PN, P=0.432). Median OS was 52 months for left PN *vs* 33 months for right PN (HR: 0.635; 95% CI 0.552-0.729). One-, 3-, and 5-year overall survival rates for all patients, left PN, and right PN were 76.7%, 53.5%, and 44.7%; 81.4%, 57.5%, and 47.7%; and 70.1%, 48.1% and 40.2%, and OS was significantly worse for right PN (HR: 1.303; 95% CI 1.133-1.498; P<0.001) compared with left PN(Fig. 2a).

We used univariate analysis to identify possible prognostic factors in PN for NSCLC and found statistically significant (P<0.05) correlations between OS and age, sex, summary stage, grade, tumor stage, T-stage, N-stage, radiotherapy, and chemotherapy (Table 2). Chemotherapy was associated with a better prognosis (Fig. 3a) and radiotherapy was associated with a worse prognosis (Fig. 4a). Race, marital status, year of diagnosis, histopathology, primary site, and lymph node dissection were not significant prognostic factors in our univariate analysis (P>0.05). Compared with right PN, left PN had: age ≤50 years (P=0.036), 61-70 years (P=0.001); female (P=0.031), male (P=0.002); white (P<0.001); married (P<0.001); year of diagnosis 2008-2011 (P=0.004), 2012-2015 (P<0.001); single lobe (P=0.035) and overlapping lesion (P=0.001); squamous cell carcinoma (P<0.001); moderately differentiated (P=0.007) and poorly differentiated (P=0.014); regional (P<0.001); number of regional lymph nodes dissected ≥4 (P<0.001); tumor stage II (P=0.001) and III (P=0.026); T2 (P=0.010) and T3 (P=0.004); N0 (P=0.036) and N1 (P<0.001); no radiotherapy (P<0.001) and no/unknown chemotherapy (P<0.001).

Multivariate analysis performed with the Cox regression model included age, sex, summary stage, grade, lymph node dissection, tumor stage, T-stage, N-stage, radiotherapy, and chemotherapy. The results showed that age, sex, grade, lymph node dissection, N-stage, radiotherapy, and chemotherapy were independent predictors of survival time in OS (P<0.05) (Table 2), with radiotherapy appearing as a

negative prognostic factor with increased risk of death for OS (HR: 1.264; 95% CI 1.049-1.523; P=0.014) and chemotherapy appearing as an independent predictor of improved for OS (HR: 0.564; 95% CI 0.480-0.661; P<0.001).

Propensity score matching survival analysis

All variables were well balanced between the two groups after 1:1 PSM. The propensity scores before matching were 0.407 ± 0.081 for left PN and 0.436 ± 0.086 for right PN (P<0.001). After matching, the propensity score for both was 0.428 ± 0.082 (P=0.755). Finally, a total of 1230 patients (615 left PN and 615 right PN) were included in our study. We found there were no significant differences in baseline characteristics between matched groups except year of diagnosis (Table 3) (P=0.05). The mean follow-up time was 61.16 ± 10.92 months (61.43 ± 10.89 months, left PN and 61.49 ± 10.95 months, right PN, P=0.927). Median OS was 40 months, left PN, *vs* 35 months, right PN (HR: 0.875; 95% CI 0.752-1.018). One-, 3-, and 5-year OS rates for all patients were 75.4%**,** 50.7%, and 41.0%, and between-group OS was not significantly different after matching (HR: 1.061; 95% CI 0.912-1.235; P=0.443) (Fig. 2b).

Subgroup analysis in matched groups

Univariate analysis to identify possible prognostic factors after matching found statistically significant correlations between OS and age, sex, histopathology, summary stage, grade, tumor stage, T-stage, N-stage, radiotherapy, and chemotherapy (P<0.05) (Table 4). The subsequent multivariate Cox regression model showed that age ≥61 (P≤0.002), higher tumor grade (P<0.001), and higher N-stage (P<0.05) were significant independent negative prognostic factors. The multivariate analysis also revealed that chemotherapy was an independent predictor of improved OS (HR: 0.522; 95% CI 0.439-0.621; P<0.001), while radiotherapy remained as a worse prognostic factor with increased risk of death for OS (HR: 1.304; 95% CI 1.063-1.600; P=0.011). The forest plot shows that for all time intervals other than the 2004-2007 period, patients with primary overlapping lung lesions had better OS for left PN *vs* right PN (HR: 0.684; 95% CI 0.497-0.941; P=0.020). During the 2004-2007 interval, OS for left PN was lower (HR: 0.576; 95% CI 0.346-0.960 P=0.034) (Fig. 5).

Discussion

Anatomic surgical resection is currently the preferred method of treating lung cancer. Central tumors may be amenable to lobectomy or bronchial sleeve lobectomy [6-7], but in patients with large tumors, tumor invasion of the left or right main bronchus, and tumors crossing lung fissures, anatomic resection cannot be completed, and PN is required in order to achieve a clinical effect [8-9]. Nonetheless, PN has relatively high morbidity and mortality (5.0% to 10.0%) in the treatment of lung cancer [10]. The operation is traumatic and the risk of postoperative complications including cardiac arrhythmias, cardiac failure, pulmonary infection, bronchopleural fistula, and acute respiratory distress syndrome (ARDS) is high [11-12]. Martin et al. [13] had a total mortality rate of 3.8% after PN (18/470), with an overall incidence of PN of 38.1% (179/470). Ludwig et al. [14] reported that the 5-year overall survival rate after PN was 27%, while Wang et al. [15] reported a post-PN 5-year survival rate of 46.3% in patients with pIII-N2 NSCLC. In

this study, 1-, 3-, and 5-year OS rates after PN were 76.7%, 53.5%, and 44.7% before PSM, and OS was worse after right PN *vs* left PN (HR: 1.303; 95% CI 1.133-1.498; P<0.001). However, after matching, 1-, 3-, and 5-year OS rates were 75.4%, 50.7%, and 41.0% and there was no significant difference between sides (P>0.05). The results of Yang et al. [16] were similar, but they did not find significant difference in 5-year survival rate between left and right PN before or after matching.

Of note, the multivariate Cox proportional hazards regression analysis found that PN patients receiving chemotherapy had significantly prolonged survival, both before and after matching (P<0.001). However, radiotherapy was a worse prognostic factor, showing increased risk of death in OS before and after matching (P<0.05). This might be because the substantial changes in lung function after PN decrease the tolerance to radiotherapy and increase the potential risk of adverse events that can shorten survival. Yamaguchi et al. [17] found that there was no significant difference in 5-year survival between lobectomy and PN in patients with advanced tumors who received chemoradiotherapy before surgery and recommended that patients needing PN be treated with caution, and Brunelli et al. [18] have observed that neoadjuvant chemotherapy is not associated with an increased perioperative risk in PN patients. Therefore, while the current clinical research indicates that both neoadjuvant and adjuvant chemotherapy can be recommended for patients undergoing PN [19], adjuvant radiotherapy remains controversial and may require further research.

Similar to a previous study [20], our subgroup analysis showed that OS is not significantly different between left and right PN (P=0.443). Age ≥61 (P≤0.002), higher tumor grade (P<0.001), and higher N-stage (P<0.05) were significant independent negative prognostic factors. Chemotherapy was an independent predictor of improved OS (HR: 0.709; 95% CI 0.609-0.825; P<0.001) (Fig. 3b). Notably, our finding that radiotherapy was a worse prognostic factor associated with increased risk of death for OS (HR: 1.268; 95% CI 1.061-1.561; P=0.009) (Fig. 4b), has not been frequently reported.

Patients undergoing right PN lose more lung capacity than those undergoing left PN because the right lung accounts for 55-60% of the total lung volume. Therefore, preoperative optimization of cardiopulmonary function before right PN is particularly important. However, Deslauriers et al. [21] have reported that expiratory lung function decreases by approximately 30% following PN regardless of operation side, indicating that even though the proportion of lung volume loss is greater after right PN, long-term postoperative adjustments in pulmonary function may allow patients to adapt and lead near-normal lives. Ilonen et al. [22] have also reported that there was no significant difference in pulmonary function after right *vs* left PN. Nonetheless, the relationship between lung function and survival prognosis after PN remains controversial, and there may be a poorer prognosis after right PN *vs* left PN. In this study, we did not compare the difference in lung function in relation to long-term survival after PN because of shortcomings of the database itself.

Because our data were collected from the SEER database, biases and errors may exist even though we used the PSM analysis. Several limitations were identified in this study. First, the study lacks detailed information regarding chemotherapy, radiotherapy, targeting, and even immunotherapy, whether pre- or

postoperative. Second, we grouped the no or unknown variables into one group, leading to data bias. Third, we used the 7th AJCC staging system, which replaced the 6th edition in 2010. Because the data we collected from the SEER database were from 2004-2015, there are inconsistencies in the data transformation process. Last, but not least, the SEER database lacks information on imaging, smoking history, tumor markers, etc., and our study did not address the impact of these factors on the prognosis in PN patients, even though they may play a significant role.

Conclusion

There was no significant difference in long-term survival between patients with NSCLC undergoing left *vs* right PN. Laterality was not a prognostic factor for survival after PN. Both neoadjuvant and adjuvant chemotherapy can prolong postoperative survival and either can be recommended. However, radiotherapy appeared to be a negative prognostic factor associated with increased risk of death in overall survival. Additional long-term survival and outcomes analyses should be conducted in larger numbers of patients.

Abbreviations

PN, pneumonectomy; NSCLC, non-small cell lung cancer; SEER, Surveillance, Epidemiology, and End Results; PSM, propensity score matching; OS, overall survival; HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; ARDS, acute respiratory distress syndrome.

Declarations

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Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Authors' Contributions

LLW and LHG drafted the manuscript. The data acquisition was performed by LLW and LHG. YYL and LLW designed the analysis. YR and LLW participated in the conception and design. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Shenyang Chest Hospital and Tenth People's Hospital. The SEER database was used by permission.

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Tables

Table 1
Baseline patient characteristics before matching

Characteristic	Patient characteristics			
	Total N = 1557	Left side N = 904	Right side N = 653	P^b value
Age (mean ± SD)	61.57 ± 10.83	61.75 ± 10.62	61.31 ± 11.12	0.432
Sex (%)				0.468
Female	567 (36.4%)	336 (37.2%)	231 (35.4%)	
Male	990 (63.6%)	568 (62.8%)	422 (64.6%)	
Race (%)				0.501
White	1339 (86.0%)	771 (85.3%)	568 (87.0%)	0.341
Black	127 (8.2%)	75 (8.3%)	52 (8.0%)	0.813
Other	91 (5.8%)	58 (6.4%)	33 (5.0%)	0.258
Marriage (%)				0.557
No[a]	607 (39.0%)	358 (39.6%)	546 (60.4%)	
Yes	950 (61.0%)	249 (38.1%)	404 (61.9%)	
Year of diagnosis (%)				0.659
2004–2007	129 (8.3%)	70 (7.7%)	59 (9.0%)	0.361
2008–2011	575 (36.9%)	336 (37.2%)	239 (36.6%)	0.819
2012–2015	853 (54.8%)	498 (55.1%)	355 (54.4%) %)	0.777
Primary Site (%)				0.001
Main bronchus	148 (9.5%)	92 (10.2%)	56 (8.6%)	0.288
Lobe	1199 (77.0%)	717 (79.3%)	482 (73.8%)	0.011
Overlapping lesion of lung	137 (8.8%)	61 (6.7%)	76 (11.6%)	0.001
Lung NOS	73 (4.7%)	34 (3.8%)	39 (6.0%)	0.042
Histopathology				< 0.001

[a]Includes separated, single (never married), divorced, unmarried or domestic partners, and widowed.

[b]*P* value between left and right PN was calculated by chi-square test, respectively.

Characteristic		Patient	characteristics	
	Total N = 1557	Left side N = 904	Right side N = 653	P^b value
Squamous cell carcinoma	792 (50.9%)	501 (55.4%)	291 (44.6%)	< 0.001
Adenocarcinoma	550 (35.3%)	290 (32.1%)	260 (39.8%)	0.002
Others	215 (13.8%)	113 (12.5%)	102 (15.6%)	0.078
Summary stage				0.618
Localized	264 (17.0%)	149 (16.5%)	115 (17.6%)	0.558
Regional	1166 (74.9%)	685 (75.8%)	481 (73.7%)	0.342
Distant	127 (8.2%)	70 (7.7%)	57 (8.7%)	0.483
Grade (%)				0.621
Well differentiated	128 (8.2%)	78 (8.6%)	50 (7.7%)	0.491
Moderately differentiated	587 (37.7%)	346 (38.3%)	241 (36.9%)	0.583
Poorly differentiated Poorly differentiated	793 (50.9%)	455 (50.3%)	338 (51.8%)	0.578
Undifferentiated	49 (3.1%)	25 (2.8%)	24 (3.7%)	0.310
Lymph node dissection (%)				0.113
1–3 removed	54 (3.5%)	26 (2.9%)	28 (4.3%)	0.038
≥ 4 removed	1446 (92.9%)	850 (94.0%)	596 (91.3%)	0.037
None/unknown	57 (3.7%)	28 (3.1%)	29 (4.4%)	0.164
Tumor Stage (%)				0.466
I	218 (13.0%)	131 (14.5%)	87 (13.3%)	0.512
II	571 (36.7%)	339 (37.5%)	232 (35.5%)	0.426
III	768 (49.3%)	434 (48.0%)	334 (51.1%)	0.221
T-stage (%)				0.443
T1	136 (8.7%)	78 (8.6%)	58 (8.9%)	0.861

[a]Includes separated, single (never married), divorced, unmarried or domestic partners, and widowed.

[b]*P* value between left and right PN was calculated by chi-square test, respectively.

Characteristic		Patient	characteristics	
	Total N = 1557	Left side N = 904	Right side N = 653	P^b value
T2	636 (40.8%)	383 (42.4%)	253 (38.7%)	0.151
T3	528 (33.9%)	293 (32.4%)	235 (36.0%)	0.141
T4	257 (16.5%)	150 (16.6%)	107 (16.4%)	
N-stage (%)				0.438
N0	577 (37.1%)	332 (36.7%)	245 (37.5%)	0.914
N1	615 (39.5%)	371 (41.0%)	244 (37.4%)	0.143
N2-N3	365 (23.4%)	201 (22.2%)	164 (25.1%)	0.186
Radiotherapy (%)				0.883
No	1245 (80.0%)	724 (80.1%)	521 (79.8%)	
Yes	312 (20.0%)	180 (19.9%)	132 (20.2%)	
Chemotherapy (%)				0.418
No/Unknown	699 (44.9%)	398 (44.0%)	301 (46.1%) (39850.6%)	
Yes	858 (55.1%)	506 (56.0%)	352 (53.9%)	

[a]Includes separated, single (never married), divorced, unmarried or domestic partners, and widowed.

[b]*P* value between left and right PN was calculated by chi-square test, respectively.

Table 2

Univariate and Multivariate analysis of OS[a] before matching

Characteristic	Univariate analysis		Multivariate analysis	
	HR[b] (95% CI[c])	*P* value	HR (95% CI)	*P* value
Laterality		< 0.001		< 0.001
Left	Reference	—	Reference	—
Right	1.303 (1.133–1.498)	< 0.001	1.298 (1.127–1.494)	< 0.001
Age (yr)		< 0.001		< 0.001
≤ 50	Reference	—	Reference	—
51–60	1.272 (0.997–1.624)	0.053	1.246 (0.972–1.598)	0.082
61–70	1.526 (1.205–1.934)	< 0.001	1.402 (1.101–1.786)	0.006
71–80	1.966 (1.552–2.539)	< 0.001	1.754 (1.346–2.285)	< 0.001
≥81	3.641 (2.442–5.427) +------)	< 0.001	3.084 (2.039–4.663) +------)	< 0.001
Sex		0.001		0.004
Female	Reference	—	Reference	—
Male	1.291 (1.112–1.498) .438) +------)	0.001	1.248 (1.074–1.451)	0.004
Race		0.923	—	—
White	Reference	—	—	—
Black	1.049 (0.815–1.350)	0.712	—	—
Other	0.980 (0.720–1.334)	0.900	—	—
Marriage		0.213	—	—
No	Reference	—	—	—
Yes	0.914 (0.794–1.053)	0.213	—	—
Year of diagnosis		0.084	—	—
2004–2007	Reference	—	—	—

[a]OS, overall survival; [b]HR, hazard ratio; [c]CI, confidence interval.

Characteristic	Univariate analysis		Multivariate analysis	
	HR[b] (95% CI[c])	*P* value	HR (95% CI)	*P* value
2008–2011	1.003 (0.791–1.273)	0.977	—	—
2012–2015	0.851 (0.669–1.084)	0.192	—	—
Primary Site		0.292	—	—
Main bronchus			—	—
Lobe	1.105 (0.854–1.430)	0.447	—	—
Overlapping lesion of lung	1.238 (0.866–1.731)	0.211	—	—
Lung NOS	1.401 (0.946–2.073)	0.092	—	—
Histopathology		0.080	—	—
Squamous cell carcinoma	Reference	—	—	—
Adenocarcinoma	0.845 (0.724–0.986)	0.033	—	—
Others	1.008 (0.819–1.241)	0.941	—	—
Summary stage		< 0.001		0.412
Localized	Reference	—	Reference	—
Regional	1.458 (1.187–1.791)	< 0.001	1.068 (0.800-1.427)	0.654
Distant	2.003 (1.493–2.687)	< 0.001	1.292 (0.856–2.142)	0.223
Grade		< 0.001		< 0.001
Well differentiated	Reference	—	Reference	—
Moderately differentiated	1.922 (1.365–2.707)	< 0.001	1.659 (1.159–2.376)	0.006
Poorly differentiated	2.416 (1.728–3.380)	< 0.001	2.034 (1.430–2.893)	< 0.001
Undifferentiated	2.529 (1.540–4.154)	< 0.001	2.381 (1.429–3.967)	0.001
Lymph node dissection		0.007		0.011
1–3 removed	1.834 (1.146–2.937)	0.012	1.787 (1.111–2.875)	0.017
≥ 4 removed	1.103 (0.774–1.572)	0.587	1.087 (0.760–1.555)	0.647
None/unknown	Reference	—	Reference	—
Tumor stage (AJCC 7th ed.)		< 0.001		0.416
I	Reference	—	Reference	—

[a]OS, overall survival; [b]HR, hazard ratio; [c]CI, confidence interval.

Characteristic	Univariate analysis		Multivariate analysis	
	HR[b] (95% CI[c])	*P* value	HR (95% CI)	*P* value
II	1.262 (0.983–1.621)	0.068	1.141 (0.817–1.593)	0.439
III	2.023 (1.597–2.563)	< 0.001	1.345 (0.844–2.142)	0.213
T-stage		< 0.001		0.090
T1	Reference	—	Reference	—
T2	0.901 (0.688–1.181)	0.451	0.838 (0.628–1.117)	0.228
T3	1.339 (1.024–1.750)	0.033	1.079 (0.774–1.504) .50)	0.654
T4	1.484 (1.109–1.987)	0.008	1.087 (0.721–1.637)	0.691
N-stage		< 0.001		0.013
N0	Reference	—	Reference	—
N1	1.320 (1.117–1.559)	0.001	1.226 (0.959–1.568)	0.104
N2-N3	1.729 (1.444–2.070)	< 0.001	1.613 (1.157–2.248)	0.005
Radiotherapy		0.001		0.014
No	Reference	—	Reference	—
Yes	1.321 (1.122–1.555)	0.001	1.264 (1.049–1.523)	0.014
Chemotherapy		< 0.001		< 0.001
No/Unknown	Reference	—	Reference	—
Yes	0.761 (0.662–0.875)	< 0.001	0.564 (0.480–0.661)	< 0.001

[a]OS, overall survival; [b]HR, hazard ratio; [c]CI, confidence interval.

Table 3
Baseline patient characteristics after matching

Characteristic	Patient characteristics			
	Total N = 1230	Left side N = 615	Right side N = 615	*P* value
Age (mean ± SD)	61.46 ± 10.92	61.43 ± 10.89	61.49 ± 10.95	0.927
Sex (%)				0.812
Female	444 (36.1%)	224 (36.4%)	220 (35.8%)	
Male	786 (63.9%)	391 (63.6%)	395 (64.2%)	
Race (%)				0.086
White	1056 (85.9%)	523 (85.0%)	533 (86.7%)	0.413
Black	96 (7.8%)	44 (7.2%)	52 (8.5%)	0.395
Other	78 (6.3%)	48 (7.8%)	30 (4.9%)	0.035
Marriage (%)				0.953
No	473 (38.5%)	236 (38.4%)	237 (38.5%)	
Yes	757 (61.5%)	379 (61.6%)	378 (61.5%)	
Year of diagnosis (%)				0.008
2004–2007	87 (7.1%)	30 (4.9%)	57 (9.3%)	0.003
2008–2011	476 (38.7%)	250 (40.7%)	226 (36.7%)	0.160
2012–2015	667 (54.2%)	335 (54.5%)	332 (54.0%) %)	0.864
Primary Site (%)				0.327
Main bronchus	95 (7.7%)	40 (6.5%)	55 (8.9%)	0.109
Lobe	954 (77.6%)	488 (79.3%)	466 (75.8%)	0.133
Overlapping lesion of lung	114 (9.3%)	53 (8.6%)	61 (9.9%)	0.285
Lung NOS	67 (5.4%)	34 (5.5%)	33 (5.4%)	0.432
Histopathology				0.352
Squamous cell carcinoma	577 (46.9%)	292 (47.5%)	285 (46.3%)	0.689
Adenocarcinoma	469 (38.1%)	224 (36.4%)	245 (39.8%)	0.218

Characteristic		Patient	characteristics	
	Total N = 1230	Left side N = 615	Right side N = 615	*P* value
Others	184 (15.0%)	99 (16.1%)	85 (13.8%)	0.263
Summary stage				0.374
Localized	202 (16.4%)	92 (15.0%)	110 (17.9%)	0.166
Regional	920 (74.8%)	467 (75.9%)	453 (73.7%)	0.358
Distant	108 (8.8%)	56 (9.1%)	52 (8.5%)	0.687
Grade (%)				0.740
Well differentiated	100 (7.1%)	54 (8.8%)	46 (7.5%)	0.404
Moderately differentiated	456 (37.1%)	222 (36.1%)	234 (38.0%)	0.479
Poorly differentiated Poorly differentiated	633 (51.5%)	320 (52.0%)	313 (50.9%)	0.690
Undifferentiated	41 (3.3%)	19 (3.1%)	22 (3.6%)	0.634
Lymph node dissection (%)				0.450
1–3 removed	48 (3.9%)	21 (3.4%)	27 (4.4%)	0.377
≥ 4 removed	1132 (92.0%)	572 (93.0%)	560 (91.1%)	0.206
None/unknown	50 (4.1%)	22 (3.6%)	28 (4.6%)	0.386
Stage (%)				0.618
I	157 (12.8%)	73 (11.9%)	84 (13.7%)	0.347
II	444 (36.1%)	222 (36.1%)	222 (36.1%)	1.000
III	629 (51.1%)	320 (52.0%)	309 (50.2%)	0.530
T-stage (%)				0.652
T1	100 (8.1%)	45 (7.3%)	55 (8.9%)	0.297
T2	482 (39.2%)	239 (38.9%)	243 (39.5%)	0.815
T3	439 (35.7%)	221 (35.9%)	218 (35.4%)	0.858
T4	209 (17.0%)	110 (17.9%)	99 (16.1%)	0.404
N-stage (%)				0.641
N0	455 (37.0%)	222 (36.1%)	233 (37.9%)	0.516

Characteristic		Patient	characteristics	
	Total N = 1230	Left side N = 615	Right side N = 615	*P* value
N1	474 (38.5%)	245 (39.8%)	229 (37.2%)	0.349
N2-N3	301 (24.5%)	148 (24.1%)	153 (24.9%)	0.740
Radiotherapy (%)				0.777
No	980 (79.7%)	488 (79.3%)	492 (80.0%)	
Yes	250 (20.3%)	127 (20.7%)	123 (20.0%)	
Chemotherapy (%)				0.731
No/Unknown	558 (45.4%)	276 (44.9%)	282 (45.9%)	
Yes	672 (54.6%)	339 (55.1%)	333 (54.1%)	

Table 4

Univariate and Multivariate analysis of OS[a] after matching

Characteristic	Univariate analysis		Multivariate analysis	
	HR[b] (95% CI[c])	*P* value	HR (95% CI)	*P* value
Laterality		0.443	—	—
Left	Reference	—	—	—
Right	1.061 (0.912–1.235)	0.443	—	—
Age (yr)		< 0.001		< 0.001
≤ 50	Reference	—	Reference	—
51–60	1.352 (1.037–1.763)	0.026	1.300 (0.993-1.700)	0.056
61–70	1.699 (1.316–2.195)	< 0.001	1.501 (1.156–1.948)	0.002
71–80	2.170 (1.642–2.866)	< 0.001	1.946 (1.462–2.589)	< 0.001
≥81	3.863 (2.545–5.863) +------)	< 0.001	3.310 (2.151–5.093) +------)	< 0.001
Sex		0.006		0.103
Female	Reference	—	Reference	—
Male	1.256 (1.068–1.477) .438) +------)	0.006	1.152 (0.972–1.366)	0.103
Race		0.687	—	—
White	Reference	—	—	—
Black	1.128 (0.859–1.481)	0.386	—	—
Others	1.010 (0.733–1.392)	0.952	—	—
Marriage		0.274	—	—
No	Reference	—	—	—
Yes	0.917 (0.786–1.071)	0.274	—	—
Year of diagnosis		0.431	—	—
2004–2007	Reference	—	—	—

[a]OS, overall survival; [b]HR, hazard ratio; [c]CI, confidence interval

Characteristic	Univariate analysis		Multivariate analysis	
	HR[b] (95% CI[c])	*P* value	HR (95% CI)	*P* value
2008–2011	1.097 (0.827–1.454)	0.521	—	—
2012–2015	0.988 (0.742–1.317)	0.937	—	—
Primary Site		0.901	—	—
Main bronchus			—	—
Lobe	0.941 (0.700-1.265)	0.688	—	—
Overlapping lesion of lung	0.998 (0.685–1.452)	0.990	—	—
Lung NOS	1.038 (0.673–1.599)	0.867	—	—
Histopathology		0.038		0.303
Squamous cell carcinoma	Reference	—	Reference	—
Adenocarcinoma	0.805 (0.681–0.951)	0.011	0.886 (0.742–1.057)	0.178
Others	0.897 (0.716–1.122)	0.341	0.868 (0.684–1.102)	0.246
Summary stage		< 0.001		0.482
Localized	Reference	—	Reference	—
Regional	1.515 (1.207–1.902)	< 0.001	1.121 (0.823–1.527)	0.469
Distant	1.972 (1.435–2.711)	< 0.001	1.316 (0.841–2.061)	0.230
Grade		< 0.001		< 0.001
Well differentiated	Reference	—	Reference	—
Moderately differentiated	2.144 (1.459–3.151)	< 0.001	1.760 (1.174–2.639)	0.006
Poorly differentiated	2.541 (1.741–3.709)	< 0.001	2.118 (1.423–3.153)	< 0.001
Undifferentiated	2.776 (1.626–4.740)	< 0.001	2.760 (1.570–4.852)	< 0.001
Lymph node dissection		0.075	—	—
1–3 removed	1.715 (1.041–2.827)	0.034	—	—
≥ 4 removed	1.193 (0.822–1.733)	0.353	—	—
None/unknown	Reference	—	—	—
Tumor stage (AJCC 7th ed.)		< 0.001		0.951
I	Reference	—	Reference	—

[a]OS, overall survival; [b]HR, hazard ratio; [c]CI, confidence interval

Characteristic	Univariate analysis		Multivariate analysis	
	HR[b] (95% CI[c])	*P* value	HR (95% CI)	*P* value
II	1.351 (1.019–1.792)	0.036	1.061 (0.734–1.534)	0.751
III	1.954 (1.494–2.555)	< 0.001	1.068 (0.641–1.781)	0.800
T-stage		< 0.001		0.210
T1	Reference	—	Reference	—
T2	1.019 (0.747–1.389)	0.906	0.940 (0.677–1.306)	0.713
T3	1.358 (0.998–1.848)	0.052	1.183 (0.812–1.724) .50)	0.381
T4	1.540 (1.104–2.147)	0.011	1.295 (0.814–2.060)	0.274
N-stage		< 0.001		0.004
N0	Reference	—	Reference	—
N1	1.440 (1.200-1.728)	< 0.001	1.388 (1.060–1.818)	0.017
N2-N3	1.691 (1.389–2.060)	< 0.001	1.840 (1.279–2.647)	0.001
Radiotherapy		0.009		0.011
No	Reference	—	Reference	—
Yes	1.268 (1.061–1.561)	0.009	1.304 (1.063-1.600)	0.011
Chemotherapy		< 0.001		< 0.001
No/Unknown	Reference	—	Reference	—
Yes	0.709 (0.609–0.825)	< 0.001	0.522 (0.439–0.621)	< 0.001

[a]OS, overall survival; [b]HR, hazard ratio; [c]CI, confidence interval

Figures

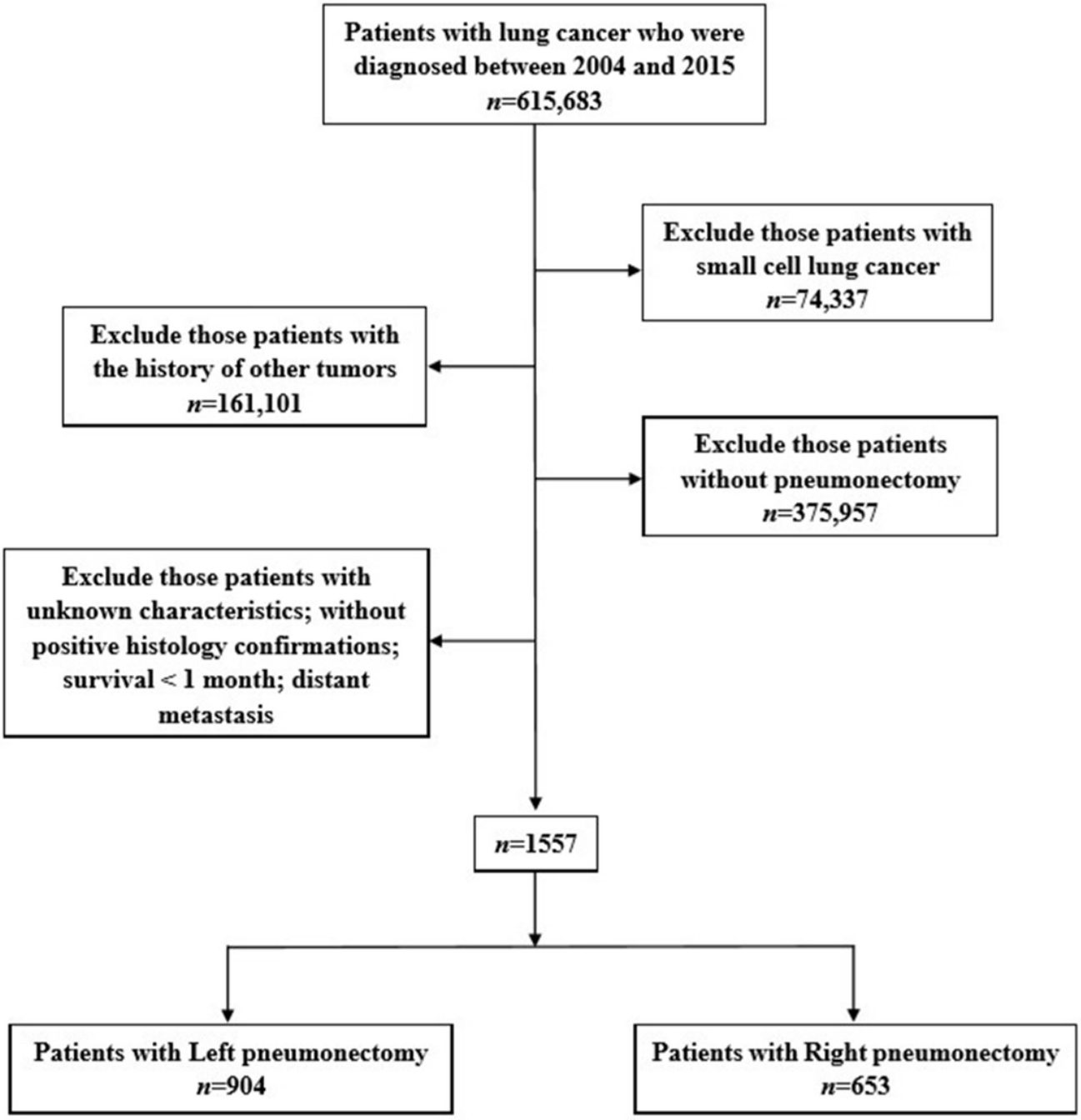

Figure 1

Patient selection flow chart

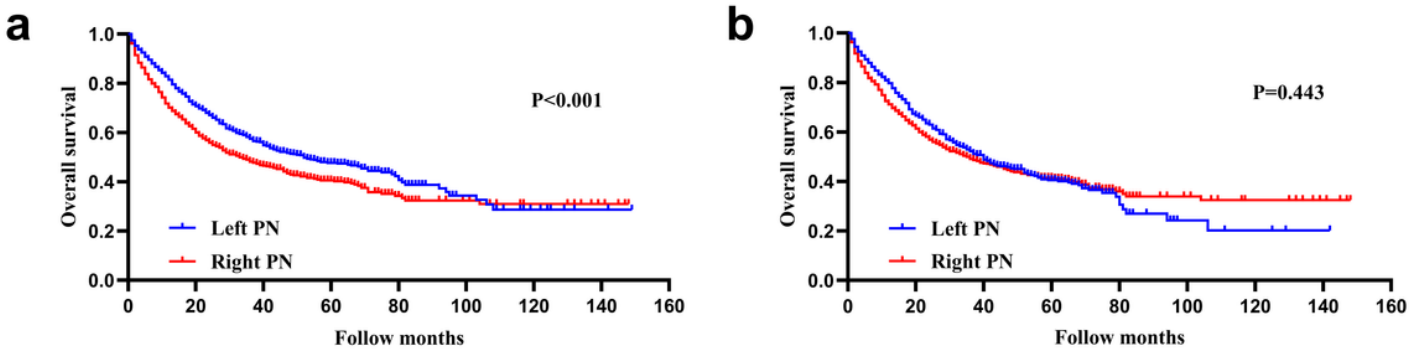

Figure 2

a: Kaplan-Meier survival curves for overall survival in left and right pneumonectomy (PN) before propensity score matching. (Overall survival, HR: 1.303; 95% CI 1.133-1.498; P<0.001). b: Kaplan-Meier survival curves for overall survival in left and right PN after propensity score matching. (Overall survival, HR: 1.061; 95% CI 0.912-1.235; P=0.443)

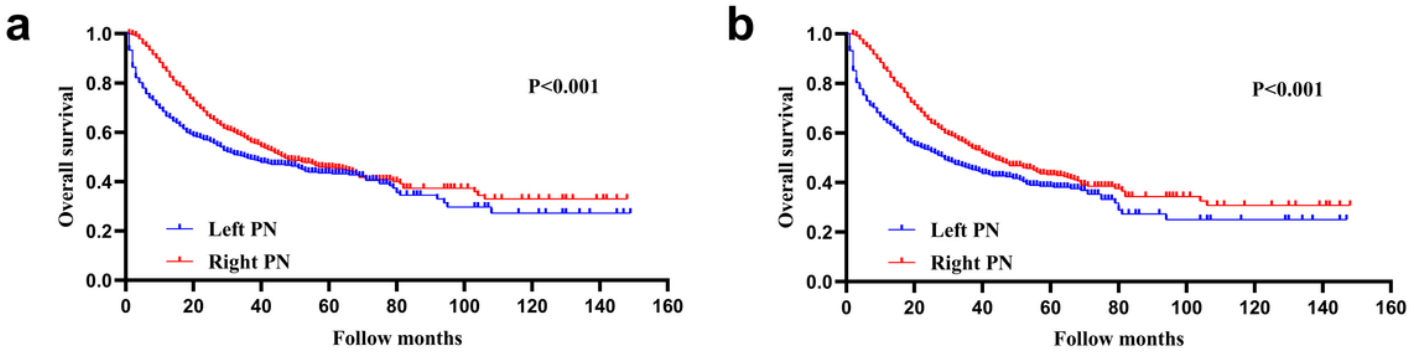

Figure 3

Chemotherapy and overall survival after pneumonectomy (PN) in non-small cell lung cancer. Chemotherapy was associated with significantly improved overall survival time in PN patients in both a: unmatched groups (Overall survival, HR: 0.761; 95% CI 0.662-0.875; P<0.001), and b: matched groups (Overall survival, HR: 0.709; 95% CI 0.609-0.825; P<0.001).

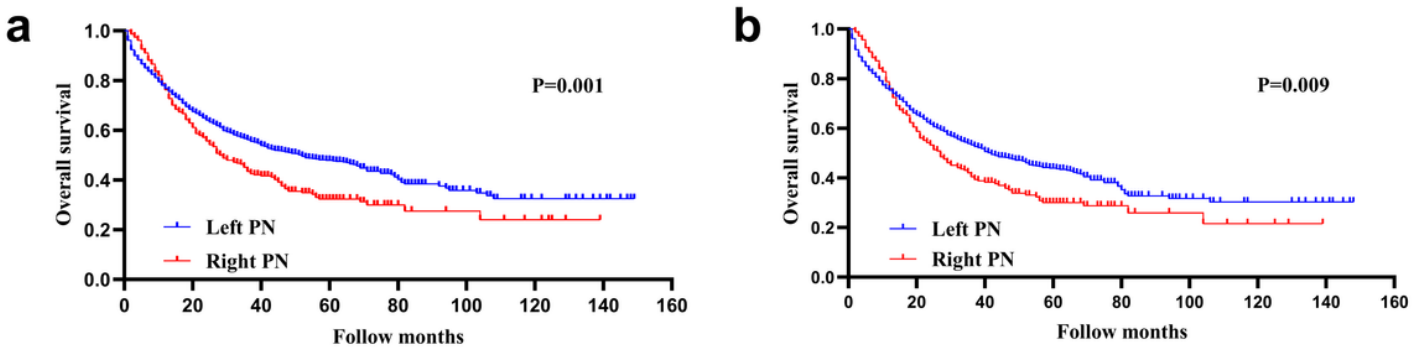

Figure 4

Radiotherapy and overall survival after pneumonectomy (PN) in non-small cell lung cancer. Radiotherapy was a worse prognostic factor in PN patients, showing increased risk of death in overall survival time (P<0.05) in both a: unmatched groups (Overall survival, HR: 1.321; 95% CI 1.122-1.555; P=0.001), and b: matched groups (Overall survival, HR: 1.268; 95% CI 1.061-1.561; P=0.009).

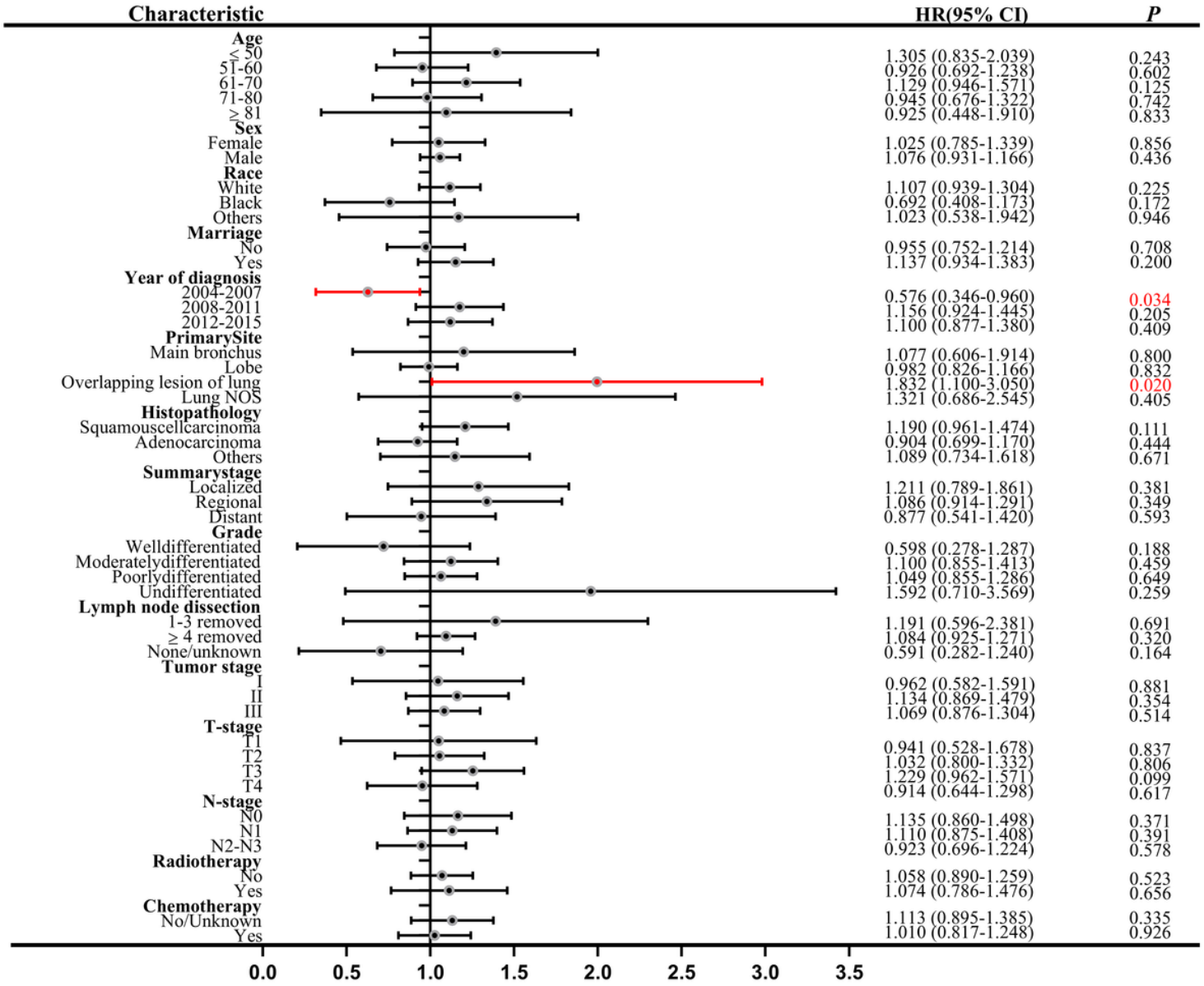

Figure 5

Forest plot of individual hazard ratios for overall survival in left vs right pneumonectomy.