Original Article

Surgical management of stage IE/IIE primary pulmonary lymphomas: a propensity score matching study

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Background: Primary pulmonary lymphomas (PPLs) are rare malignancies that are frequently misdiagnosed due to their non-specific symptoms and ambiguous imaging findings. Although chemotherapy and radiation are typically the main treatment options, the role of surgery in managing PPLs remains uncertain. This study aimed to evaluate the impact of surgery on survival outcomes in patients with stage IE/IIE PPLs.

Methods: We analyzed 2,693 patients with stage IE/IIE PPLs using Cox regression and Kaplan-Meier analyses to assess overall survival (OS) and cancer-specific survival (CSS). Subgroup analyses were performed based on histological subtypes, including mucosa-associated lymphoid tissue (MALT) lymphoma, diffuse large B-cell lymphoma (DLBCL), other non-Hodgkin's lymphoma (NHL), and Hodgkin's lymphoma (HL). Additionally, we analyzed tumor stage and patient characteristics. Propensity score matching (PSM) was applied to reduce potential biases.

Results: Among the patients, 1,013 underwent surgery, while 1,680 did not. After PSM, surgery was associated with significantly improved OS [hazard ratio (HR) =0.75, 95% confidence interval (CI): 0.66–0.86, P<0.001] and CSS (HR =0.66, 95% CI: 0.54–0.81, P<0.001). Notably, surgery significantly improved OS and CSS in patients with stage IE (OS: HR =0.62, 95% CI: 0.46–0.84, P=0.002; CSS: HR =0.57, 95% CI: 0.39–0.84, P=0.005) and stage IIE (OS: HR =0.64, 95% CI: 0.41–0.99, P=0.046; CSS: HR =0.47, 95% CI: 0.27–0.85, P=0.01) DLBCL. However, surgery did not significantly affect OS (P=0.24) or CSS (P=0.83) in patients with HL, stage IE/IIE MALT lymphoma (stage IE: OS, P=0.11; CSS, P=0.34; stage IIE: OS, P=0.40; CSS, P=0.75), or stage IE/IIE other NHL (stage IE: OS, P=0.050; CSS, P=0.46; stage IIE: OS, P=0.22; CSS, P=0.11). Additionally, sublobectomy demonstrated outcomes comparable to lobectomy/pneumonectomy in terms of OS and CSS for both stage IE (OS: HR =0.81, 95% CI: 0.63–1.06, P=0.13; CSS: HR =0.91, 95% CI: 0.58–1.43, P=0.70) and stage IIE (OS: HR =0.66, 95% CI: 0.40–1.09, P=0.10; CSS: HR =0.58, 95% CI: 0.26–1.29, P=0.18) PPLs.

Conclusions: Surgery improves oncological outcomes for patients with stage IE/IIE DLBCL but does not provide survival benefits for MALT lymphoma, other NHL, or HL. Sublobectomy may be a viable surgical option when complete resection is achieved.

Keywords: Surgery; stage IE/IIE; primary pulmonary lymphomas (PPLs); survival

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Introduction

Primary pulmonary lymphomas (PPLs) are defined as malignancies originating from lymphatic tissue in the lungs, accounting for 3–4% of extranodal lymphomas and 0.5–1% of all primary pulmonary malignancies (1). PPLs include both Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), with mucosa-associated lymphoid tissue (MALT) lymphoma being the most common histological subtype, followed by diffuse large B-cell lymphoma (DLBCL) (2,3). Approximately 50% of PPL patients are asymptomatic, while the remaining patients typically present with non-specific symptoms, such as fever, cough, and dyspnea (4). Additionally, the imaging characteristics of PPLs are often non-specific, leading to frequent misdiagnoses as other diseases before pathological examination, such as pneumonia, lung cancer, and tuberculosis (3). The prognosis of PPLs varies depending on the histological type. For example, the estimated 5- and 10-year overall survival (OS) rates of MALT lymphoma are 90% and 72%, respectively (5). In contrast, pulmonary DLBCL has a poorer prognosis, with a median survival of 3 to 5 years (6).

Due to the low incidence of this disease, there is no consensus on the optimal treatment approach. Chemotherapy and radiation are the two mainstream treatments for lymphomas (7), leaving thoracic surgeons with limited opportunities to diagnose and treat PPLs. As a result, the role of surgery in the management of PPLs remains unclear. This study aims to investigate whether surgery can improve survival outcomes for PPL patients. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1524/rc).

Highlight box

Key findings

- Surgery improves overall survival (OS) and cancer-specific survival (CSS) in stage IE/IIE diffuse large B-cell lymphoma (DLBCL) but not in mucosa-associated lymphoid tissue (MALT) lymphoma, other non-Hodgkin's lymphoma (NHL), or Hodgkin's lymphoma (HL).
- Sublobectomy provided equivalent OS and CSS compared to lobectomy or pneumonectomy in stage IE/IIE primary pulmonary lymphomas (PPLs), suggesting that it may be a viable alternative when complete resection is achieved.

What is known and what is new?

- The role of surgery in the management of PPLs was unclear, especially in terms of survival benefits. Previous research often highlighted chemotherapy and radiation as the primary treatments for PPLs.
- This study provides clear evidence that surgery benefits patients with stage IE/IIE DLBCL in terms of OS and CSS but does not offer survival advantages for patients with stage IE/IIE MALT lymphoma, other NHL, or HL. Additionally, sublobectomy shows comparable outcomes to lobectomy/pneumonectomy in early-stage PPLs.

What is the implication, and what should change now?

- Surgical intervention should be considered as part of the treatment strategy for stage IE/IIE DLBCL, potentially improving survival outcomes. For other subtypes like MALT lymphoma and other NHL, surgery does not offer significant survival benefits, suggesting a shift toward non-surgical treatments in these cases.
- Clinical guidelines may need to be updated to recommend surgery, especially sublobectomy, for stage IE/IIE DLBCL patients while reconsidering its necessity for MALT lymphoma and other NHL cases. A more tailored, subtype-specific approach to the surgical treatment of PPLs should be adopted.

Methods

Database and patient selection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Data for this study were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database, specifically from the SEER-18, SEER-13, and SEER-9 registries, based on the November 2020 submission. Our request for access to the SEER Research Database was approved, and data were analyzed using SEER*Stat software version 8.4.0.1 (https://seer.cancer.gov/seerstat/software/). As this study utilized deidentified secondary data, it did not qualify as research involving human participants, and therefore institutional review board approval was not required.

This study included patients aged 18 years and older diagnosed with Ann Arbor stage IE/IIE PPLs between 1983 and 2015, confirmed by histology using the International Classification of Diseases for Oncology Version 3 histology codes (Table S1). Eligible cases had their primary tumor located in the following lung sites: 'C34.0-Main bronchus', 'C34.1-Upper lobe of lung', 'C34.2-Middle lobe of lung', 'C34.3-Lower lobe of lung', 'C34.8-Overlapping lesion of lung', or 'C34.9-Lung, NOS'. Patients were excluded if they met any of the following criteria: (I) secondary lymphoma; (II) lack of histological confirmation; (III) unknown survival data or survival duration of 0 months; and (IV) missing surgical information.

Statistical analysis

First, we used SEER*Stat software to analyze the age-adjusted incidence rate (AAIR) of PPLs, calculated as new cases per 100,000 and age-adjusted to the 2000 US Standard population. Next, patients were divided into two groups: the surgery group and the non-surgery group. Given the small amount of missing data (≤5% for a given covariate), we classified these values as unknown in our study. Baseline characteristics between the two groups were compared using Chi-squared or Fisher exact tests. Univariate and multivariate Cox regression analyses were performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for potentially clinically relevant factors. OS and cancer-specific survival (CSS) were compared using log-rank tests and Kaplan-Meier (KM) curves. To reduce bias, propensity score matching (PSM) was performed using a 1:1 ratio with nearest neighbor matching logistic regression analysis with a caliper of 0.2. The confounding factors included in the PSM analysis were age, sex, race, marital status, laterality, histology, Ann Arbor stage, and treatment modalities. Subgroup analyses were also performed to assess the impact of surgery on survival based on different histological subtypes for stage IE and stage IIE disease. The PSM analysis was performed separately for each histological subtype, and the numbers of matched pairs differ between subtype analyses due to differences in sample size and matching feasibility within each group. Additionally, we explored the impact of different surgical approaches on survival outcomes. After PSM, adjusted KM survival curves for OS and CSS were generated. All analyses were conducted using SEER*Stat software (version 8.4.0.1), SPSS (version 22.0), and R (version 4.1.0). A two-tailed P value of <0.05 was considered statistically significant.

Results

Incidence and characteristics of PPLs

The AAIR of PPLs showed a relatively increasing trend from 1975 to 2019, with an annual percentage change of 2.11% (Figure S1A). In terms of sex, the AAIRs were similar between males and females (Figure S1B).

The clinicopathological characteristics of the patients are summarized in *Table 1*. A total of 2,693 eligible PPL patients were reviewed in this study, including 1,013 patients who underwent surgery and 1,680 who did not. Among these cases, surgery was more commonly performed in patients aged less than 70 years (62.2% *vs.* 53.3%, P<0.001), female sex (57.3% *vs.* 50.4%, P=0.001), White race (88.7% *vs.* 85.4%, P=0.048), and married patients (58.8% *vs.* 54.2%, P=0.02). Patients with unilateral PPLs were more likely to undergo surgery (95.2% *vs.* 90.8%, P<0.001). In the surgery group, MALT lymphoma was the predominant histological type (50.1%). In contrast, among patients who did not undergo surgery, the proportion of DLBCL was significantly higher (36.6%) and the proportion of MALT lymphoma was markedly lower (28.2%). Few patients in either group were diagnosed with HL (5.0% *vs.* 7.4%, P<0.001). Patients who did not undergo surgery were more likely to receive radiation (23.0% *vs.* 7.8%, P<0.001) and chemotherapy (59.2% *vs.* 30.8%, P<0.001) compared to those who did. As shown in Figure S2A, the OS of patients with HL was the highest, while the OS for DLBCL was the lowest (P<0.001). Similarly, CSS was most favorable for patients with HL and MALT lymphoma, while patients with DLBCL had the poorest CSS (P<0.001, Figure S2B).

Cox regression analysis

As shown in *Table 2*, the factors associated with worse OS included age ≥70 years (HR =2.786, 95% CI: 2.495–3.111), male sex (HR =1.359, 95% CI: 1.223–1.510), Black race (HR =1.078, 95% CI: 0.890–1.306), being single (HR =1.427, 95% CI: 1.280–1.591), DLBCL histology type (HR =2.099, 95% CI: 1.840–2.395), and other NHL histology type (HR =1.669, 95% CI: 1.461–1.907). In contrast, undergoing surgery was associated with better OS (HR =0.738, 95% CI: 0.661–0.823). Regarding CSS, factors associated with worse outcomes included age ≥70 years (HR =2.021, 95% CI: 1.726–2.365), male sex (HR =1.514, 95% CI: 1.297–1.766), being single (HR =1.786, 95% CI: 1.529–2.086), bilateral PPLs (HR =1.432, 95% CI: 1.059–1.936), DLBCL histology type (HR =4.098, 95% CI: 3.248–5.169), other NHL histology type (HR =2.707, 95% CI: 2.153–3.405), HL histology type (HR =1.438, 95% CI: 0.934–2.214), stage IIE disease (HR =1.062, 95% CI: 0.901–1.251), and patients receiving chemotherapy (HR =1.015, 95% CI: 0.853–1.208). On the other hand, receiving surgery was associated with better CSS (HR =0.692, 95% CI: 0.583–0.822).

Surgical outcome analysis

Among all PPL patients, those who underwent surgery had significantly better OS (HR =0.64, 95% CI: 0.58–0.71, P<0.001, Figure S3A) and CSS (HR =0.53, 95% CI: 0.45–0.62, P<0.001, Figure S3B) compared to those who did

Table 1 Clinicopathological characteristics of all primary pulmonary lymphomas before and after propensity score matching

Variables	All patients (n=2,693)	Before PSM			After PSM		
		Surgery (n=1,013)	Non-surgery (n=1,680)	P	Surgery (n=806)	Non-surgery (n=806)	P
Age (years)				<0.001			0.29
<70	1,525 (56.6)	630 (62.2)	895 (53.3)		483 (59.9)	462 (57.3)	
≥70	1,168 (43.4)	383 (37.8)	785 (46.7)		323 (40.1)	344 (42.7)	
Sex				0.001			0.19
Female	1,427 (53.0)	580 (57.3)	847 (50.4)		469 (58.2)	443 (55.0)	
Male	1,266 (47.0)	433 (42.7)	833 (49.6)		337 (41.8)	363 (45.0)	
Race				0.048			0.39
White	2,334 (86.7)	899 (88.7)	1,435 (85.4)		700 (86.8)	718 (89.1)	
Black	218 (8.1)	69 (6.8)	149 (8.9)		63 (7.8)	53 (6.6)	
Other	141 (5.2)	45 (4.4)	96 (5.7)		43 (5.3)	35 (4.3)	
Marital status				0.02			0.45
Married	1,506 (55.9)	596 (58.8)	910 (54.2)		440 (54.6)	464 (57.6)	
Single	1,065 (39.5)	381 (37.6)	684 (40.7)		331 (41.1)	312 (38.7)	
Unknown	122 (4.5)	36 (3.6)	86 (5.1)		35 (4.3)	30 (3.7)	
Laterality				<0.001			0.97
Unilateral	2,490 (92.5)	964 (95.2)	1,526 (90.8)		757 (93.9)	759 (94.2)	
Bilateral	134 (5.0)	36 (3.6)	98 (5.8)		36 (4.5)	34 (4.2)	
Unknown	69 (2.6)	13 (1.3)	56 (3.3)		13 (1.6)	13 (1.6)	
Histology				<0.001			0.83
MALT	981 (36.4)	508 (50.1)	473 (28.2)		324 (40.2)	312 (38.7)	
DLBCL	832 (30.9)	217 (21.4)	615 (36.6)		196 (24.3)	212 (26.3)	
Other NHL	705 (26.2)	237 (23.4)	468 (27.9)		236 (29.3)	234 (29.0)	
HL	175 (6.5)	51 (5.0)	124 (7.4)		50 (6.2)	48 (6.0)	
Stage				<0.001			0.66
Stage IE	1,828 (67.9)	790 (78.0)	1,038 (61.8)		589 (73.1)	581 (72.1)	
Stage IIE	865 (32.1)	223 (22.0)	642 (38.2)		217 (26.9)	225 (27.9)	
Radiation				<0.001			>0.99
No	2,227 (82.7)	934 (92.2)	1,293 (77.0)		727 (90.2)	727 (90.2)	
Yes	466 (17.3)	79 (7.8)	387 (23.0)		79 (9.8)	79 (9.8)	
Chemotherapy				<0.001			0.31
No	1,387 (51.5)	701 (69.2)	686 (40.8)		505 (62.7)	485 (60.2)	
Yes	1,306 (48.5)	312 (30.8)	994 (59.2)		301 (37.3)	321 (39.8)	

Data are presented as n (%). PSM, propensity score matching; MALT, mucosa-associated lymphoid tissue; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma.

Table 2 Univariate and multivariate Cox regression analyses of OS and CSS in all primary pulmonary lymphomas

Variables	OS				CSS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age (years)								
<70	–	–	–	–	–	–	–	–
≥70	2.864	2.577–3.183	2.786	2.495–3.111	1.940	1.669–2.255	2.021	1.726–2.365
Sex								
Female	–	–	–	–	–	–	–	–
Male	1.216	1.100–1.345	1.359	1.223–1.510	1.368	1.180–1.586	1.514	1.297–1.766
Race								
White	–	–	–	–	–	–	–	–
Black	0.924	0.767–1.114	1.078	0.890–1.306	1.005	0.769–1.313	–	–
Other	0.729	0.563–0.945	0.835	0.644–1.083	0.798	0.553–1.151	–	–
Marital status								
Married	–	–	–	–	–	–	–	–
Single	1.509	1.361–1.673	1.427	1.280–1.591	1.793	1.543–2.083	1.786	1.529–2.086
Unknown	1.098	0.846–1.425	0.905	0.696–1.176	0.754	0.475–1.198	0.682	0.429–1.085
Laterality								
Unilateral	–	–	–	–	–	–	–	–
Bilateral	0.940	0.737–1.199	0.983	0.770–1.254	1.361	1.009–1.836	1.432	1.059–1.936
Unknown	1.467	1.087–1.981	1.460	1.079–1.975	1.351	0.865–2.109	1.247	0.797–1.950
Histology								
MALT	–	–	–	–	–	–	–	–
DLBCL	2.163	1.901–2.461	2.099	1.840–2.395	4.527	3.656–5.604	4.098	3.248–5.169
Other NHL	1.843	1.615–2.103	1.669	1.461–1.907	3.067	2.447–3.846	2.707	2.153–3.405
HL	0.556	0.412–0.751	0.743	0.546–1.010	1.323	0.879–1.990	1.438	0.934–2.214
Stage								
Stage IE	–	–	–	–	–	–	–	–
Stage IIE	1.061	0.953–1.182			1.258	1.079–1.468	1.062	0.901–1.251
Surgery								
No	–	–	–	–	–	–	–	–
Yes	0.642	0.577–0.714	0.738	0.661–0.823	0.532	0.451–0.626	0.692	0.583–0.822
Radiation								
No	–	–	–	–	–	–	–	–
Yes	0.909	0.793–1.042	–	–	0.951	0.781–1.159	–	–
Chemotherapy								
No	–	–	–	–	–	–	–	–
Yes	1.103	0.997–1.220	–	–	1.531	1.318–1.778	1.015	0.853–1.208

OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; MALT, mucosa-associated lymphoid tissue; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma.

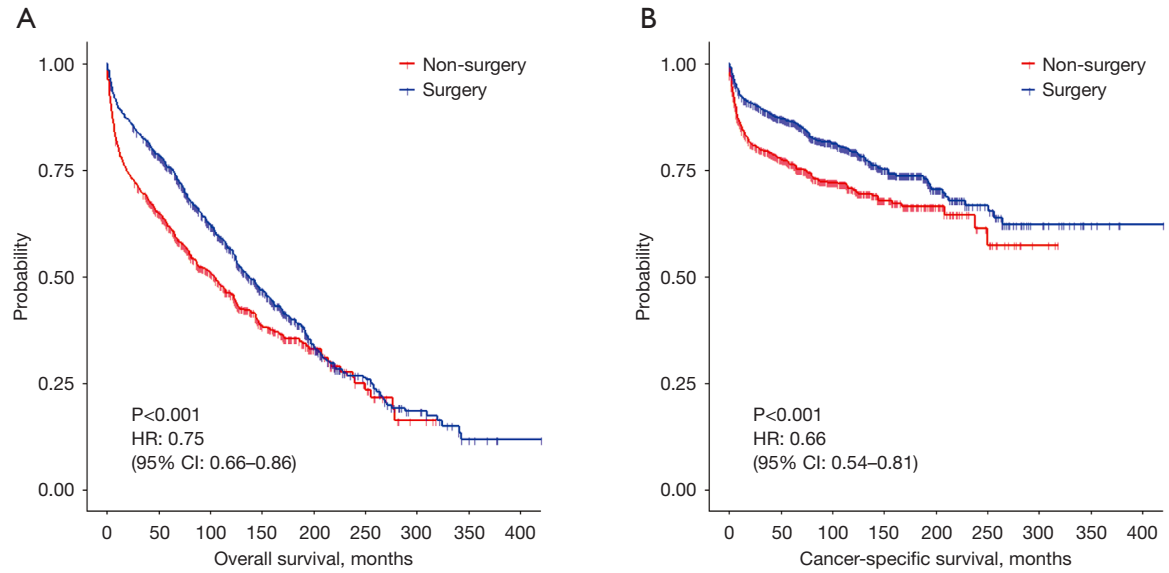

Figure 1 Kaplan-Meier survival curves of all PPLs after PSM. (A) OS for patients receiving surgery *vs.* non-surgery; (B) CSS for patients receiving surgery *vs.* non-surgery. HR, hazard ratio; CI, confidence interval; PPLs, primary pulmonary lymphomas; PSM, propensity score matching; OS, overall survival; CSS, cancer-specific survival.

not. After PSM, 806 patients remained in both the surgery and non-surgery groups. The clinical characteristics of these matched patients are summarized in *Table 1*. Similar to the results before PSM, surgery was still associated with significantly better OS (HR =0.75, 95% CI: 0.66–0.86, P<0.001, *Figure 1A*) and CSS (HR =0.66, 95% CI: 0.54–0.81, P<0.001, *Figure 1B*) after PSM.

For patients with MALT lymphoma, surgery was associated with better OS (HR =0.68, 95% CI: 0.55–0.82, P<0.001, Figure S4A) and CSS (HR =0.58, 95% CI: 0.40–0.84, P=0.004, Figure S4B) compared to non-surgery. However, after PSM, with 612 patients remaining (Table S2), the survival advantage of surgery disappeared, and no significant differences in OS (HR =0.86, 95% CI: 0.67–1.11, P=0.25, *Figure 2A*) or CSS (HR =0.88, 95% CI: 0.53–1.46, P=0.62, *Figure 2B*) were observed between the surgery and non-surgery groups.

For patients with DLBCL, surgery significantly improved both OS (HR =0.74, 95% CI: 0.61–0.90, P=0.002, Figure S5A) and CSS (HR =0.72, 95% CI: 0.56–0.93, P=0.01, Figure S5B). After PSM, 412 patients remained (Table S3), and KM curves confirmed that surgery markedly improved OS (HR =0.70, 95% CI: 0.55–0.88, P=0.003, *Figure 3A*) and CSS (HR =0.63, 95% CI: 0.47–0.86, P=0.003, *Figure 3B*).

For patients with other NHL, surgery significantly improved both OS (HR =0.63, 95% CI: 0.53–0.76, P<0.001, Figure S6A) and CSS (HR =0.55, 95% CI: 0.41–0.73, P<0.001, Figure S6B). After PSM, 400 patients remained (Table S4), and KM curves showed that surgery significantly improved OS (HR =0.70, 95% CI: 0.55–0.88, P=0.003, *Figure 4A*). However, CSS was comparable between the two groups (HR =0.70, 95% CI: 0.48–1.01, P=0.056, *Figure 4B*).

For patients with HL, KM curves did not show a significant difference in OS (HR =1.24, 95% CI: 0.68–2.25, P=0.49, Figure S7A) or CSS (HR =1.58, 95% CI: 0.75–3.32, P=0.23, Figure S7B) between those treated with surgery and those who were not. After PSM, only 90 patients remained (Table S5), and the survival differences remained non-significant in both OS (HR =1.69, 95% CI: 0.71–4.02, P=0.24, *Figure 5A*) and CSS (HR =1.11, 95% CI: 0.43–2.89, P=0.83, *Figure 5B*).

Subgroup analysis in MALT lymphoma according to stage

Before PSM, KM curves indicated that surgery improved both OS (HR =0.64, 95% CI: 0.52–0.80, P<0.001, Figure S8A) and CSS (HR =0.60, 95% CI: 0.39–0.92, P=0.02, Figure S8B) in stage IE MALT lymphoma. However, no significant differences in OS (HR =0.88, 95% CI: 0.55–1.39, P=0.57, Figure S8C) and CSS (HR =0.58, 95% CI: 0.25–1.33, P=0.20, Figure S8D) were observed

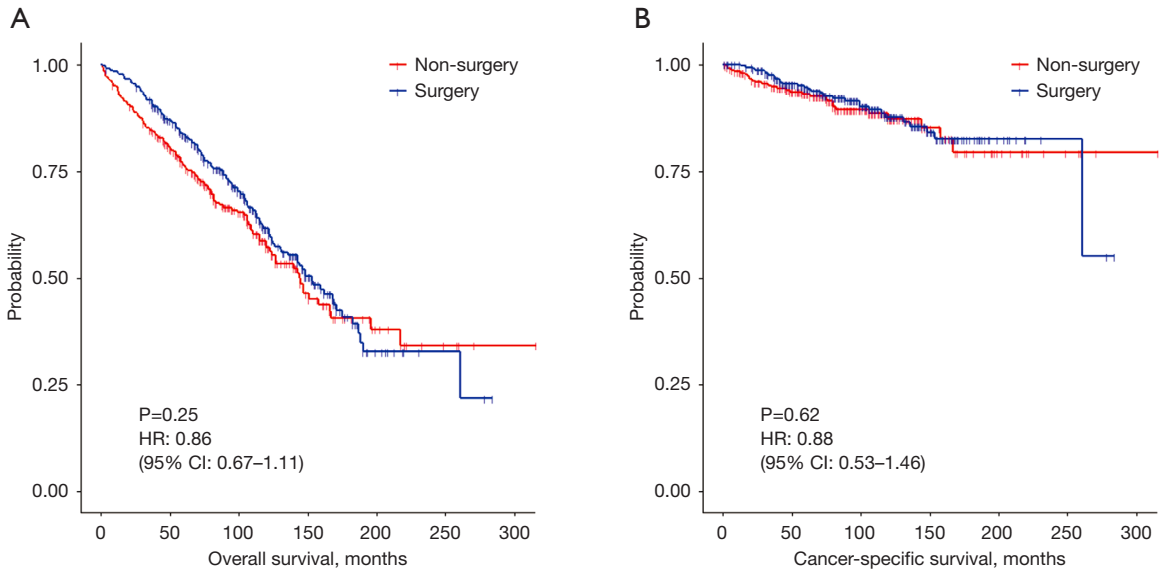

Figure 2 Kaplan-Meier survival curves of MALT lymphoma after PSM. (A) OS for patients receiving surgery *vs.* non-surgery; (B) CSS for patients receiving surgery *vs.* non-surgery. HR, hazard ratio; CI, confidence interval; MALT, mucosa-associated lymphoid tissue; PSM, propensity score matching; OS, overall survival; CSS, cancer-specific survival.

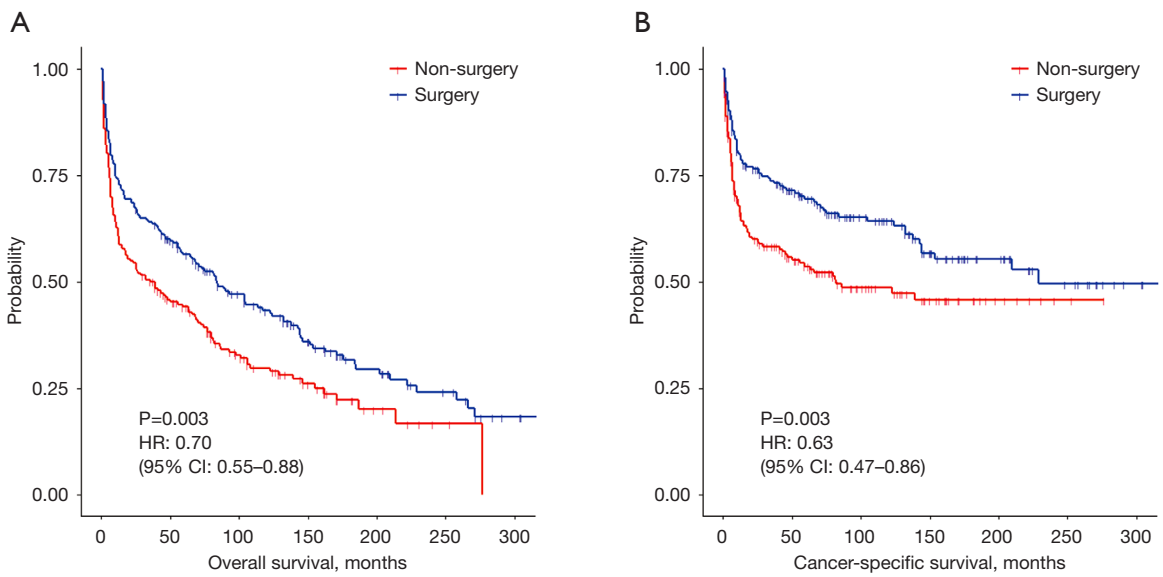

Figure 3 Kaplan-Meier survival curves of DLBCL after PSM. (A) OS for patients receiving surgery *vs.* non-surgery; (B) CSS for patients receiving surgery *vs.* non-surgery. HR, hazard ratio; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; PSM, propensity score matching; OS, overall survival; CSS, cancer-specific survival.

between surgery and non-surgery patients for stage IIE disease. After PSM, surgery did not result in significant improvements in OS or CSS for either stage IE (OS: HR =0.80, 95% CI: 0.60–1.05, P=0.11, *Figure 6A*; CSS: HR =0.76, 95% CI: 0.43–1.34, P=0.34, *Figure 6B*) or stage IIE (OS: HR =1.30, 95% CI: 0.70–2.42, P=0.40, *Figure 6C*; CSS: HR =1.19, 95% CI: 0.41–3.42, P=0.75, *Figure 6D*) MALT lymphoma patients.

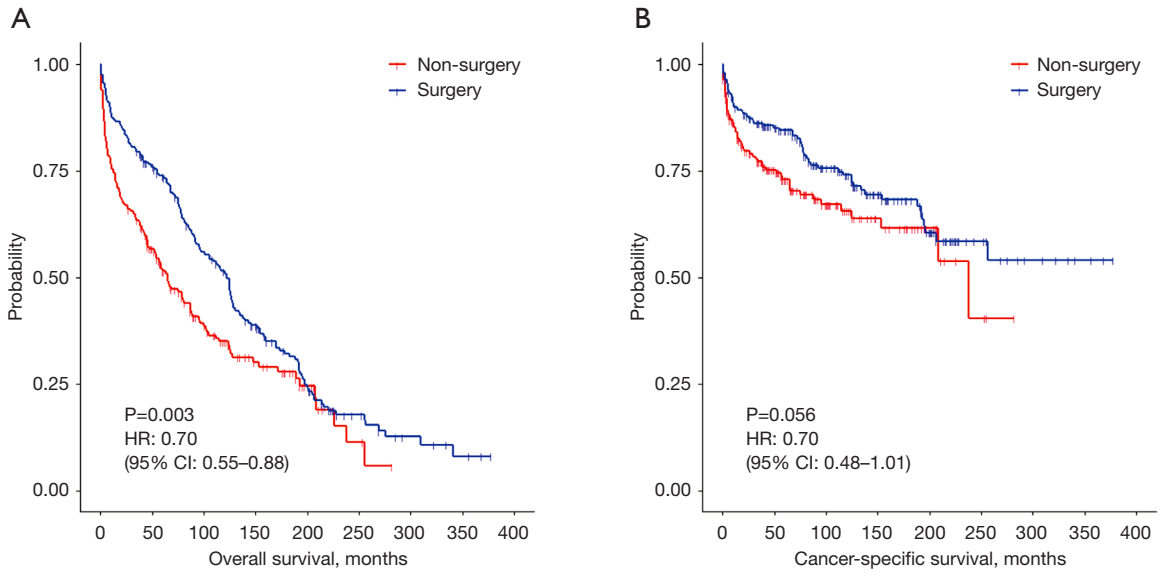

Figure 4 Kaplan-Meier survival curves of other NHL after PSM. (A) OS for patients receiving surgery *vs.* non-surgery; (B) CSS for patients receiving surgery *vs.* non-surgery. HR, hazard ratio; CI, confidence interval; NHL, non-Hodgkin's lymphoma; PSM, propensity score matching; OS, overall survival; CSS, cancer-specific survival.

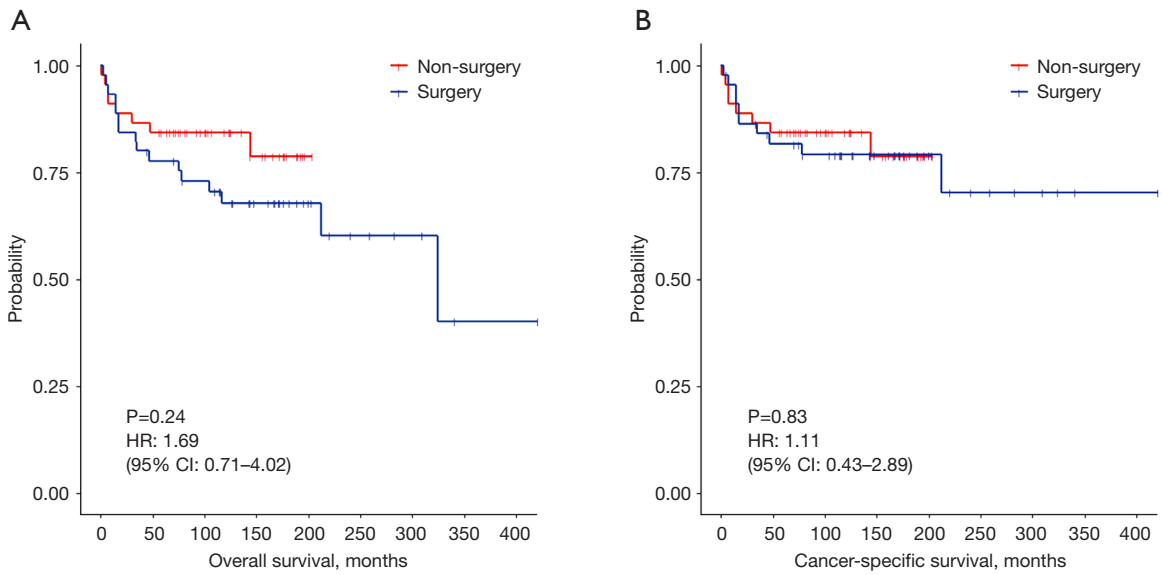

Figure 5 Kaplan-Meier survival curves of HL after PSM. (A) OS for patients receiving surgery *vs.* non-surgery; (B) CSS for patients receiving surgery *vs.* non-surgery. HR, hazard ratio; CI, confidence interval; HL, Hodgkin lymphoma; PSM, propensity score matching; OS, overall survival; CSS, cancer-specific survival.

Subgroup analysis in DLBCL according to stage

For stage IE DLBCL, surgery significantly improved OS (HR =0.71, 95% CI: 0.56–0.89, P=0.004, Figure S9A) but did not significantly affect CSS (HR =0.77, 95% CI: 0.56–1.05, P=0.09, Figure S9B). In contrast, for stage IIE DLBCL, surgery did not significantly improved OS (HR =0.73, 95% CI: 0.51–1.04, P=0.08, Figure S9C) but significantly improved CSS (HR =0.59, 95% CI: 0.36–0.97,

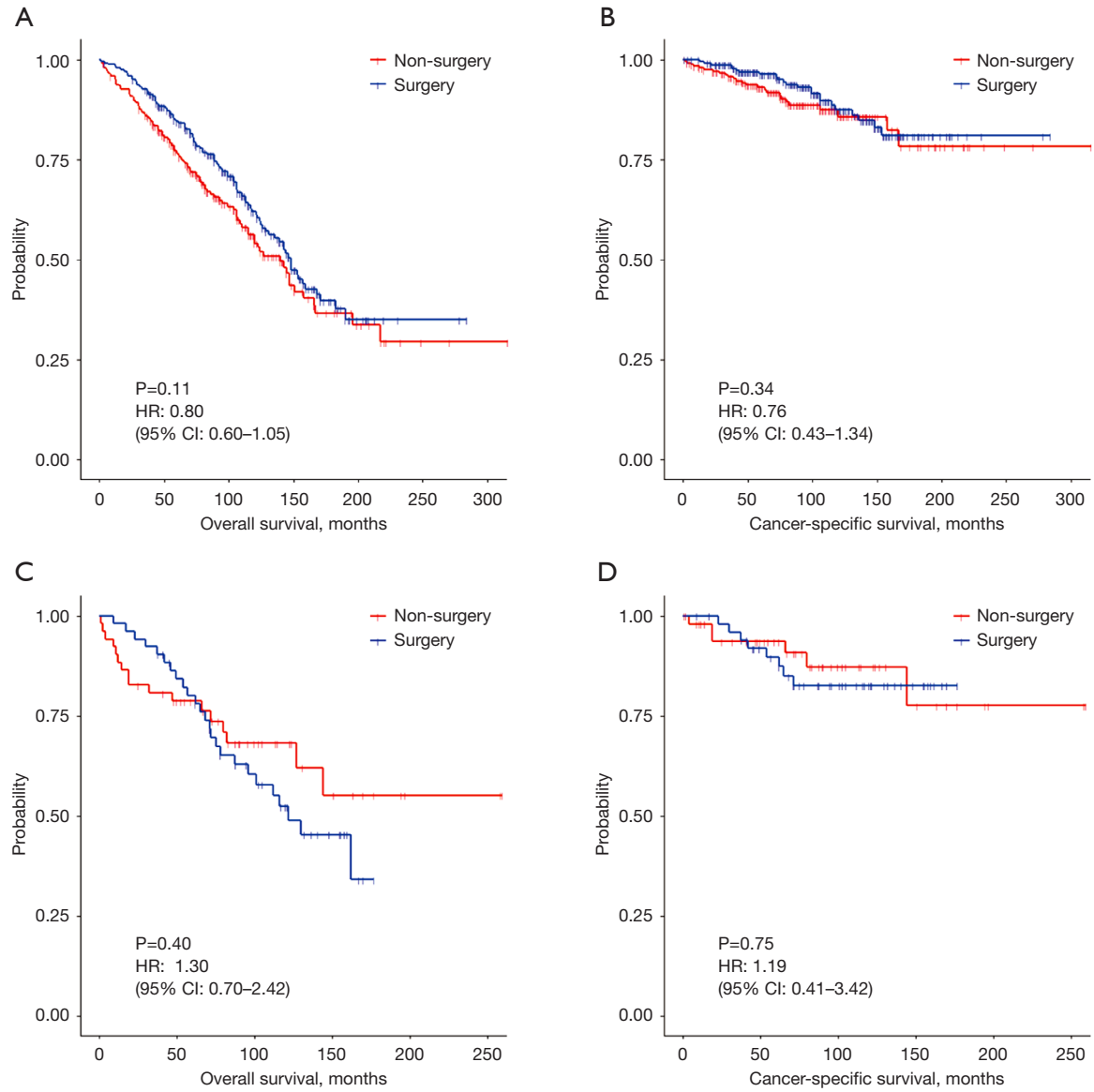

Figure 6 Kaplan-Meier survival curves of stage IE/IIE MALT lymphoma after PSM. (A) OS for patients receiving surgery *vs.* non-surgery in stage IE MALT lymphoma; (B) CSS for patients receiving surgery *vs.* non-surgery in stage IE MALT lymphoma; (C) OS for patients receiving surgery *vs.* non-surgery in stage IIE MALT lymphoma; (D) CSS for patients receiving surgery *vs.* non-surgery in stage IIE MALT lymphoma. HR, hazard ratio; CI, confidence interval; MALT, mucosa-associated lymphoid tissue; PSM, propensity score matching; OS, overall survival; CSS, cancer-specific survival.

P=0.04, Figure S9D). After PSM, KM curves showed that surgery improved both OS and CSS in stage IE (OS: HR =0.62, 95% CI: 0.46–0.84, P=0.002, *Figure 7A*; CSS: HR =0.57, 95% CI: 0.39–0.84, P=0.005, *Figure 7B*) and stage IIE (OS: HR =0.64, 95% CI: 0.41–0.99, P=0.046, *Figure 7C*; CSS: HR =0.47, 95% CI: 0.27–0.85, P=0.01, *Figure 7D*) DLBCL patients.

Subgroup analysis in other NHL according to stage

In stage IE other NHL, surgery improved both OS (HR =0.58, 95% CI: 0.47–0.73, P<0.001, Figure S10A) and CSS (HR =0.51, 95% CI: 0.36–0.73, P<0.001, Figure S10B). However, in stage IIE other NHL, there were no significant differences in OS (HR =0.76, 95% CI: 0.54–1.07, P=0.11,

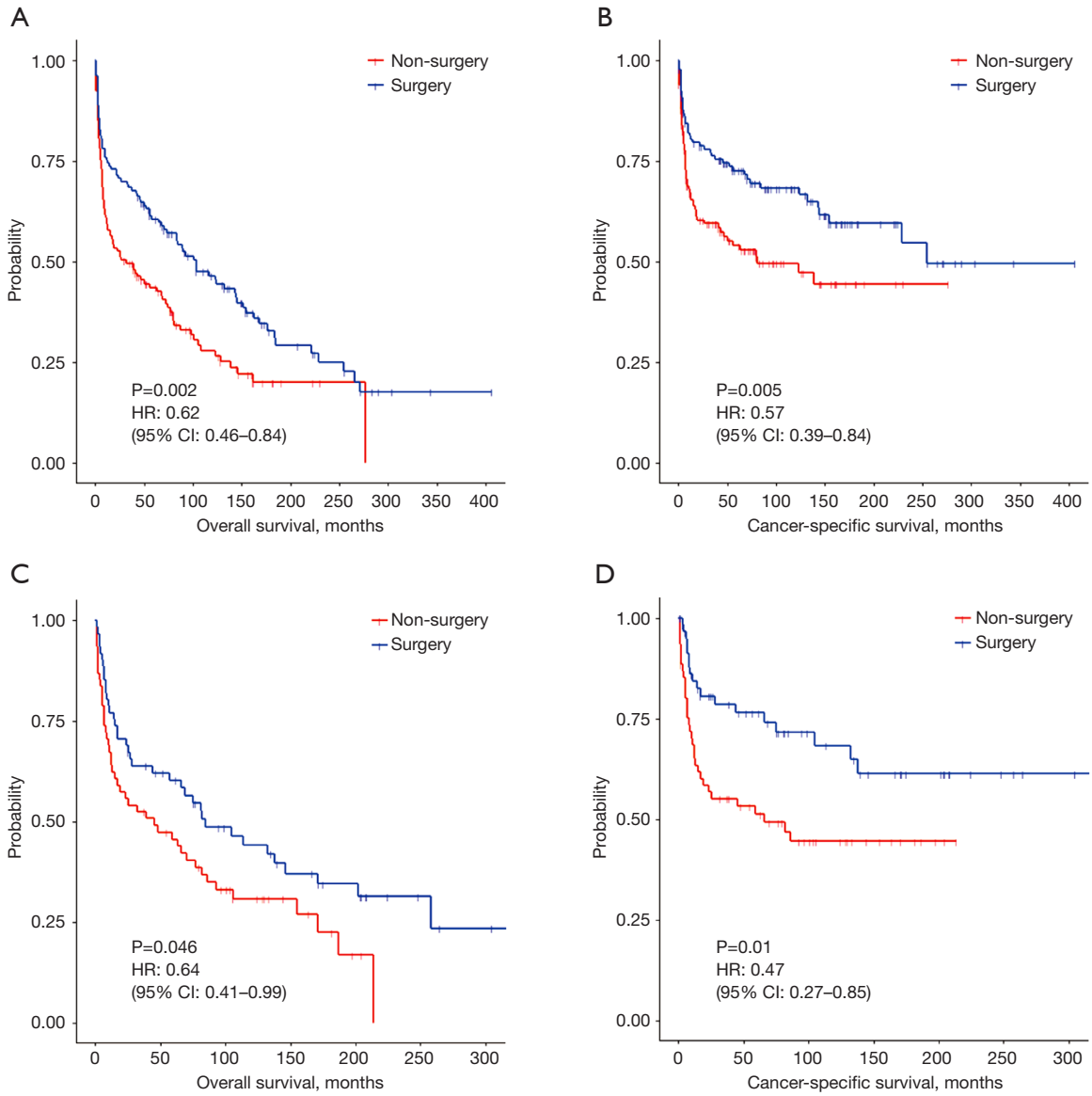

Figure 7 Kaplan-Meier survival curves of stage IE/IIE DLBCL after PSM. (A) OS for patients receiving surgery *vs.* non-surgery in stage IE DLBCL; (B) CSS for patients receiving surgery *vs.* non-surgery in stage IE DLBCL; (C) OS for patients receiving surgery *vs.* non-surgery in stage IIE DLBCL; (D) CSS for patients receiving surgery *vs.* non-surgery in stage IIE DLBCL. HR, hazard ratio; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; PSM, propensity score matching; OS, overall survival; CSS, cancer-specific survival.

Figure S10C) or CSS (HR =0.62, 95% CI: 0.36–1.06, P=0.08, Figure S10D) between the surgery and non-surgery groups. After PSM, surgery did not significantly improve OS or CSS in stage IE (OS: HR =0.74, 95% CI: 0.55–1.00, P=0.050, *Figure 8A*; CSS: HR =0.84, 95% CI: 0.52–1.35, P=0.46, *Figure 8B*) or stage IIE (OS: HR =0.77, 95% CI: 0.50–1.17, P=0.22, *Figure 8C*; CSS: HR =0.59, 95% CI: 0.31–1.13, P=0.11, *Figure 8D*) other NHL patients.

Subgroup analysis in all PPLs according to surgical procedure

PPL patients who underwent surgery were categorized into sublobectomy and lobectomy/pneumectomy groups, with 581 and 392 patients, respectively. Before PSM, sublobectomy provided comparable OS and CSS to lobectomy/pneumectomy for stage IE (OS: HR =0.93, 95%

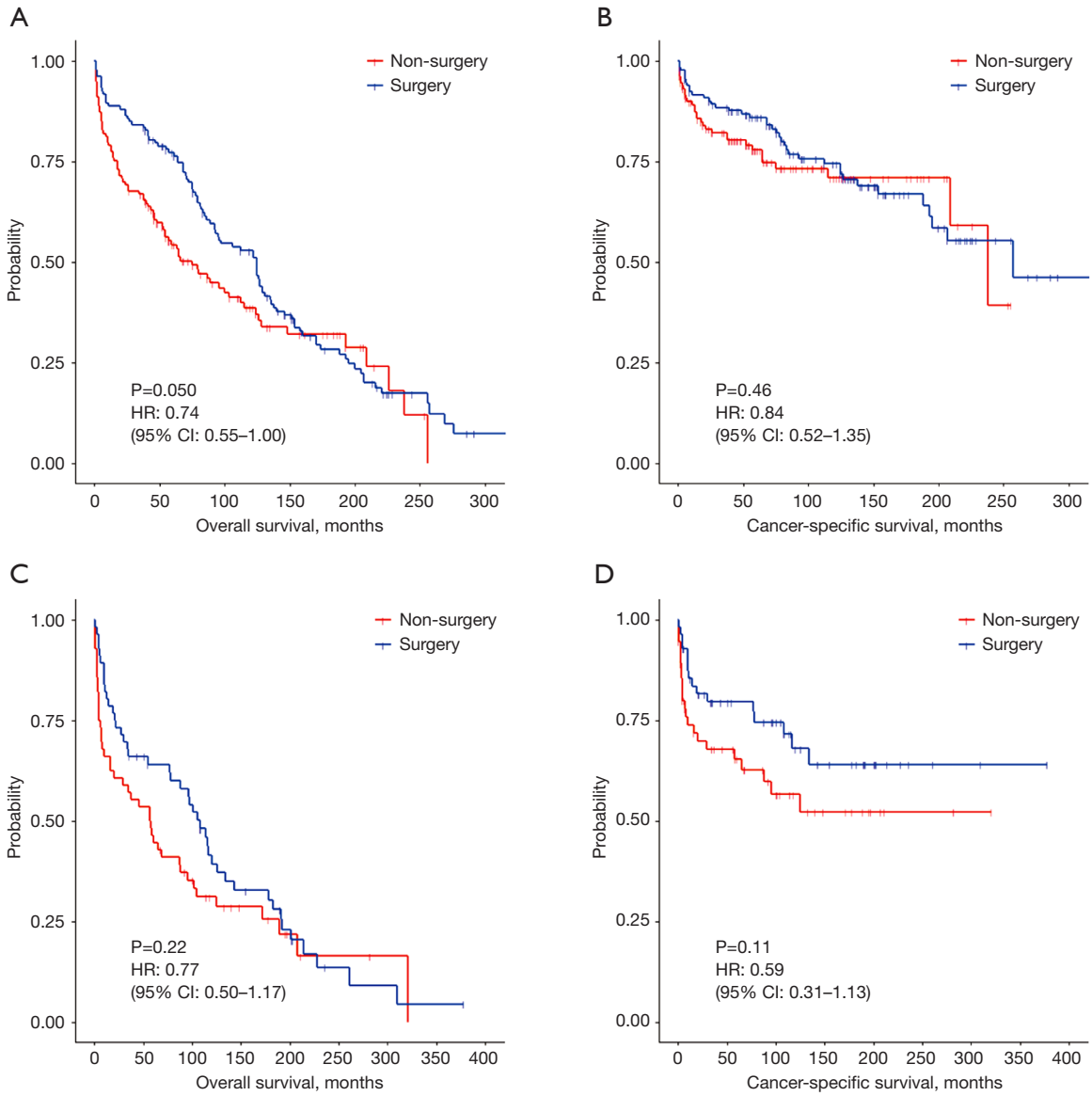

Figure 8 Kaplan-Meier survival curves of stage IE/IIE other NHL after PSM. (A) OS for patients receiving surgery *vs.* non-surgery in stage IE other NHL; (B) CSS for patients receiving surgery *vs.* non-surgery in stage IE other NHL; (C) OS for patients receiving surgery *vs.* non-surgery in stage IIE other NHL; (D) CSS for patients receiving surgery *vs.* non-surgery in stage IIE other NHL. HR, hazard ratio; CI, confidence interval; NHL, non-Hodgkin's lymphoma; PSM, propensity score matching; OS, overall survival; CSS, cancer-specific survival.

CI: 0.76–1.14, P=0.47, Figure S11A; CSS: HR =0.99, 95% CI: 0.71–1.38, P=0.96, Figure S11B) and stage IIE (OS: HR =0.73, 95% CI: 0.50–1.06, P=0.10, Figure S11C; CSS: HR =0.85, 95% CI: 0.47–1.54, P=0.59, Figure S11D) disease. After PSM, sublobectomy continued to show similar OS and CSS to lobectomy/pneumectomy for both stage IE (OS: HR =0.81, 95% CI: 0.63–1.06, P=0.13, *Figure 9A*; CSS: HR =0.91, 95% CI: 0.58–1.43, P=0.70, *Figure 9B*) and stage IIE (OS: HR =0.66. 95% CI: 0.40–1.09, P=0.10, *Figure 9C*; CSS: HR =0.58, 95% CI: 0.26–1.29, P=0.18, *Figure 9D*) disease.

Subgroup analysis in DLBCL according to different characteristics

Subgroup analysis was conducted to determine which

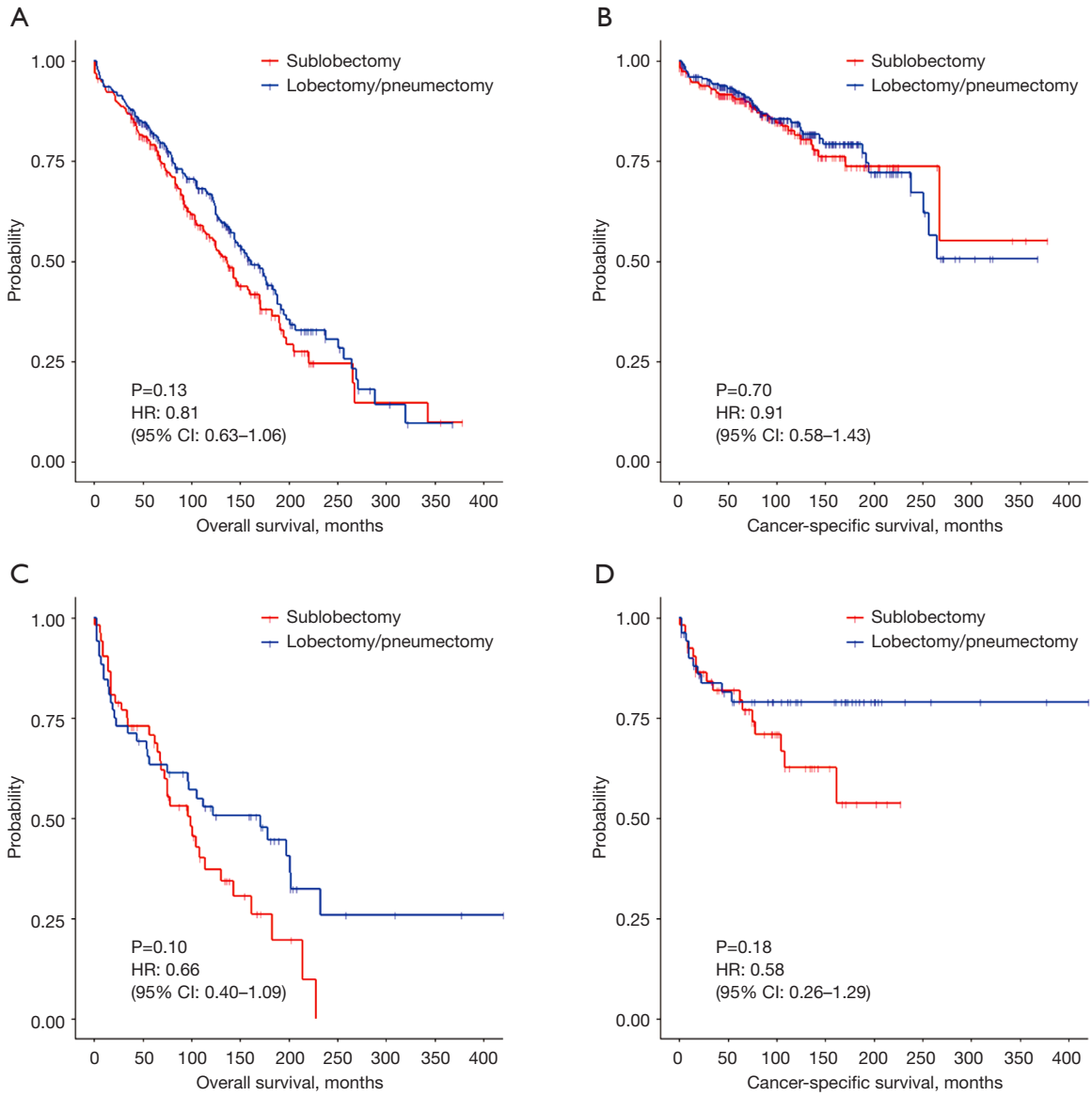

Figure 9 Kaplan-Meier survival curves of stage IE/IIE PPLs receiving surgery after PSM. (A) OS for patients receiving sublobectomy *vs.* lobectomy/pneumectomy in stage IE PPLs; (B) CSS for patients receiving sublobectomy *vs.* lobectomy/pneumectomy in stage IE PPLs; (C) OS for patients receiving sublobectomy *vs.* lobectomy/pneumectomy in stage IIE PPLs; (D) CSS for patients receiving sublobectomy *vs.* lobectomy/pneumectomy in stage IIE PPLs. HR, hazard ratio; CI, confidence interval; PPLs, primary pulmonary lymphomas; PSM, propensity score matching; OS, overall survival; CSS, cancer-specific survival.

DLBCL patients benefit from surgery. In terms of OS (Figure S12A), surgery was beneficial for patients aged 70 years and older (HR =0.60, 95% CI: 0.45–0.81, P=0.001), male sex (HR =0.71, 95% CI: 0.55–0.92, P=0.01), White race (HR =0.71, 95% CI: 0.57–0.87, P=0.001), married patients (HR =0.57, 95% CI: 0.43–0.76, P<0.001), patients with unilateral tumor (HR =0.75, 95% CI: 0.62–0.92, P=0.005), patients not receiving radiation (HR =0.69, 95% CI: 0.56–0.85, P<0.001), and those not receiving chemotherapy (HR =0.55, 95% CI: 0.40–0.76, P<0.001). For CSS (Figure S12B), surgery was favorable for patients aged 70 years and older (HR =0.45, 95% CI: 0.29–0.71, P<0.001), female sex (HR =0.64, 95% CI: 0.42–0.97, P=0.04), White race (HR =0.66, 95% CI: 0.50–0.87,

P=0.003), married patients (HR =0.55, 95% CI: 0.37–0.82, P=0.003), patients with unilateral tumor (HR =0.74, 95% CI: 0.57–0.97, P=0.03), patients not receiving radiation (HR =0.65, 95% CI: 0.50–0.86, P=0.002), and those not receiving chemotherapy (HR =0.48, 95% CI: 0.32–0.74, P=0.001).

Discussion

With advancements in diagnostic techniques, the incidence of PPLs has increased over the past two decades. According to literature reports (8), stage IE PPLs are defined as lesions confined to the lung (which can be bilateral), while stage IIE involves tumor metastasis to sentinel hilar or mediastinal lymph nodes or invasion of adjacent structures such as the chest wall or diaphragm. It is widely accepted that surgery is recommended for localized or regional pulmonary malignancies, such as non-small cell lung cancer (NSCLC) (9). However, the role of surgery in the management of stage IE/IIE PPLs has been debated. Previous studies have focused on surgery's diagnostic value, while its impact on survival remains unclear (8,10,11). To clarify the role of surgery on survival outcomes, large national cancer databases like SEER are crucial for providing reliable clinical evidence.

In the present study, we identified 2,693 PPL patients, including 981 with MALT lymphoma, 832 with DLBCL, 705 with other NHL, and 175 with HL. Both before and after PSM, surgery was associated with improved OS and CSS among all PPL patients. These findings suggested that surgery should be considered for patients with localized or regional diseases. In a study from China involving 90 patients, those who did not undergo surgery had worse survival outcomes (HR =2.179, 95% CI: 1.015–4.679) (12). Additionally, a retrospective study noted that patients who underwent surgical resection had longer survival, regardless of chemotherapy status (10). Due to the rarity of PPLs, a previous single-center study has been limited by small sample sizes, hindering the ability to examine the role of surgery in different histological subtypes (13). Our study addressed this by categorizing patients into four groups (MALT lymphoma, DLBCL, other NHL, and HL), allowing for a more detailed analysis. Before PSM, surgery significantly improved OS and CSS for patients with MALT lymphoma, DLBCL, and other NHL, but not for HL. After PSM, the benefits of surgery were evident only for DLBCL (OS and CSS) and other NHL (OS).

While the lack of efficacy of surgery in patients with MALT lymphoma and HL is an important finding, further consideration is needed as to why surgery was not effective, given that chemotherapy and radiotherapy are the standard of care in HL. Pathologically, both MALT lymphoma and HL differ significantly from other PPLs in ways that influence treatment response. Pulmonary MALT lymphoma is generally indolent and has a good prognosis (14). Compared with gastrointestinal MALT lymphoma, pulmonary MALT lymphoma is more likely to be multifocal within the lungs and often remains localized to the lung (15). Consequently, surgery does not typically offer additional survival benefits beyond localized therapies. In contrast, chemotherapy or combination chemotherapy plus low-dose involved-field radiotherapy (LD-IFRT) is the standard treatment option for HL (16). Surgical intervention is not standard for HL, as the disease is generally systemic, and surgery does not address the need for systemic disease control. Given these considerations, surgery should primarily be reserved for diagnostic purposes or in cases where local complications, such as airway obstruction or bleeding, necessitate surgical intervention. In both MALT lymphoma and HL, integrating surgery as a treatment modality should be approached cautiously and typically considered only when standard treatments are contraindicated or fail. Our findings underscore the importance of positioning surgery as a secondary or supportive measure rather than a primary treatment modality for these lymphoma subtypes.

The tumor stage is a critical factor influencing treatment outcomes. We further explored the effect of surgery on different stages and subtypes of PPLs. For MALT lymphoma, although surgery improved OS and CSS in stage IE before PSM, no significant differences were observed in either OS or CSS for stage IE and IIE patients after PSM. Similarly, surgery did not significantly improve OS or CSS for stage IE/IIE other NHL. These findings align with existing literature on extranodal NHL, where surgical resection is generally not favored over chemotherapy and/or radiation therapy, and treatment has shifted towards organ preservation (17). Some guidelines, such as those from Italy, recommend a "watch and wait" approach for asymptomatic localized MALT PPLs (18). However, a key finding from our study is that surgery may improve both OS and CSS in patients with stage IE/IIE DLBCL. This is consistent with results from a clinical trial on intestinal DLBCL, where surgery plus chemotherapy yielded higher complete response rates (85.3%) and lower relapse rates (15.3%) compared to chemotherapy alone (complete response rate

64.4%, relapse rate 36.8%) (19). Based on our findings, surgery should be recommended for stage IE/IIE DLBCL, but not for stage IE/IIE MALT lymphoma, other NHL, or HL.

Regarding surgical procedures, sublobectomy, lobectomy, and pneumectomy are commonly performed to remove pulmonary lesions. Previous studies have shown that sublobectomy offers equivalent outcomes to lobectomy for early-stage NSCLC (20,21). Our analysis demonstrated similar findings for PPLs, as sublobectomy provided outcomes comparable to lobectomy/pneumonectomy for both stage IE and IIE PPLs, both before and after PSM. This supports the notion that sublobectomy is a reasonable alternative for early-stage PPLs. This result was consistent with the opinion of Vanden Eynden *et al.* (13) that more extensive resection was based on the possibility of performing a complete resection. Similarly, the practice guideline from Italian emphasized that a wedge resection or segmentectomy is possible. Besides, if limited resection led to positive surgical margins, following chemotherapy could deal with this trouble which may not alter the survival (22). In our opinion, it is even more plausible that the surgical procedure was determined by tumor size in real practice (23). In other words, limited resection was allowed if complete resection was achieved.

As mentioned above, our study confirms that surgery is beneficial for patients with stage IE/IIE DLBCL. To further identify subgroups of patients who benefit from surgery, we conducted a subgroup analysis based on patient characteristics. We found that surgery was particularly beneficial for patients aged 70 years and older, White race, married patients, patients with unilateral lesions, and those who underwent chemotherapy and radiation. We also have further interpreted the significant interactions to explore why surgery shows greater benefits in certain subgroups. First, for patients aged 70 years and older, the greater benefit from surgery may be related to the lower tolerance of older individuals to non-surgical treatments. Older patients often have more comorbidities and may struggle with the side effects of chemotherapy or radiotherapy, making surgery a more viable option for achieving local disease control. Second, the benefits seen in White and married patients may reflect differences in social support and access to healthcare resources, which can positively impact recovery and follow-up care post-surgery. Third, for patients with unilateral lesions, the enhanced benefit from surgery may be due to the increased feasibility of achieving complete resection, as these lesions are typically more localized. Fourth, in patients who received chemotherapy and radiotherapy, surgery may complement systemic treatments by providing local control, potentially leading to synergistic improvements in survival outcomes.

There are several limitations in this study. First, being a retrospective analysis, it is subject to inherent biases, even with PSM adjustments. Second, the SEER database lacks important variables such as tumor size, number of lesions, laboratory data, patient comorbidities, and pulmonary function, which could impact survival outcomes. Patients who did not receive surgery may have been more ill and this may explain why they did not receive surgery and why their OS was worse. Third, detailed information on chemotherapy and radiation regimens was not available, which may have influenced our results. Systemic therapies continued to evolve during the study period, and the introduction of rituximab in particular may have had a significant impact on treatment outcomes for PPL patients. Because our study period spanned the pre- and post-rituximab eras, the differences in survival outcomes may be due in part to the introduction of this drug. Fourth, the SEER database does not provide detailed information on surgical margin status, which limits our ability to fully assess the adequacy of resection in patients undergoing sublobectomy. Without access to margin data, our findings should be interpreted with caution, as they are based on the assumption that sublobectomy was adequately performed with clear margins. Finally, due to the limited number of other NHL cases, further subgroup analyses could not be performed, which may reduce the reliability of findings in this cohort.

Conclusions

In conclusion, surgery improves oncological outcomes for stage IE/IIE DLBCL, but not for stage IE/IIE MALT lymphoma, other NHL, or HL. Additionally, sublobectomy does not significantly compromise long-term survival for patients with stage IE/IIE PPLs. Further randomized controlled studies are needed to validate these findings and determine the optimal surgical approach for early-stage PPLs.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1524/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1524/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). We obtained our data from the publicly accessible SEER database. As the data were de-identified and publicly available, no additional ethical approval or patient consent was required for this research. We have taken measures to ensure data privacy and have adhered to the terms of use and citation guidelines provided by the SEER database for data availability and transparency.

References

1. Peng Y, Qi W, Luo Z, et al. Role of 18F-FDG PET/CT in patients affected by pulmonary primary lymphoma. Front Oncol 2022;12:973109.
2. Zhang XY, Gu DM, Guo JJ, et al. Primary Pulmonary Lymphoma: A Retrospective Analysis of 27 Cases in a Single Tertiary Hospital. Am J Med Sci 2019;357:316-22.
3. Yao D, Zhang L, Wu PL, et al. Clinical and misdiagnosed analysis of primary pulmonary lymphoma: a retrospective study. BMC Cancer 2018;18:281.
4. Wang Y, He Z, Zhu Z, et al. Primary pulmonary extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type: a case report and literature review. Am J Transl Res 2022;14:9072-7.
5. Borie R, Wislez M, Thabut G, et al. Clinical characteristics and prognostic factors of pulmonary MALT lymphoma. Eur Respir J 2009;34:1408-16.
6. Piña-Oviedo S, Weissferdt A, Kalhor N, et al. Primary Pulmonary Lymphomas. Adv Anat Pathol 2015;22:355-75.
7. Sanguedolce F, Zanelli M, Zizzo M, et al. Primary Pulmonary B-Cell Lymphoma: A Review and Update. Cancers (Basel) 2021;13:415.
8. Ferraro P, Trastek VF, Adlakha H, et al. Primary non-Hodgkin's lymphoma of the lung. Ann Thorac Surg 2000;69:993-7.
9. Lang-Lazdunski L. Surgery for nonsmall cell lung cancer. Eur Respir Rev 2013;22:382-404.
10. Hu YH, Hsiao LT, Yang CF, et al. Prognostic factors of Chinese patients with primary pulmonary non-Hodgkin's lymphoma: the single-institute experience in Taiwan. Ann Hematol 2009;88:839-46.
11. Hu M, Gu W, Chen S, et al. Clinical Analysis of 50 Cases of Primary Pulmonary Lymphoma: A Retrospective Study and Literature Review. Technol Cancer Res Treat 2022;21:15330338221075529.
12. He H, Tan F, Xue Q, et al. Clinicopathological characteristics and prognostic factors of primary pulmonary lymphoma. J Thorac Dis 2021;13:1106-17.
13. Vanden Eynden F, Fadel E, de Perrot M, et al. Role of surgery in the treatment of primary pulmonary B-cell lymphoma. Ann Thorac Surg 2007;83:236-40.
14. Kang HS, Lee HY, Kim SJ, et al. An Unusual Presentation of Pulmonary Mucosa-Associated Lymphoid Tissue Lymphoma as Diffuse Pulmonary Infiltrates with Spontaneous Regression. Cancer Res Treat 2015;47:943-8.
15. Maley JH, Dannheim K, Kooistra T, et al. A Man with a Decade of Persistent Pulmonary Opacities. Ann Am Thorac Soc 2018;15:1344-8.
16. Keraliya AR, Tirumani SH, Shinagare AB, et al. Beyond PET/CT in Hodgkin lymphoma: a comprehensive review of the role of imaging at initial presentation, during follow-up and for assessment of treatment-related complications.

Insights Imaging 2015;6:381-92.
17. Wang L, Xia ZJ, Zhang YJ, et al. Radical surgery may be not an optimal treatment approach for pulmonary MALT lymphoma. Tumour Biol 2015;36:6409-16.
18. Zinzani PL, Martelli M, Poletti V, et al. Practice guidelines for the management of extranodal non-Hodgkin's lymphomas of adult non-immunodeficient patients. Part I: primary lung and mediastinal lymphomas. A project of the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation. Haematologica 2008;93:1364-71.
19. Kim SJ, Kang HJ, Kim JS, et al. Comparison of treatment strategies for patients with intestinal diffuse large B-cell lymphoma: surgical resection followed by chemotherapy versus chemotherapy alone. Blood 2011;117:1958-65.
20. Saji H, Okada M, Tsuboi M, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. Lancet 2022;399:1607-17.
21. Altorki NK, Yip R, Hanaoka T, et al. Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. J Thorac Cardiovasc Surg 2014;147:754-62; Discussion 762-4.
22. Parissis H. Forty years literature review of primary lung lymphoma. J Cardiothorac Surg 2011;6:23.
23. Raman V, Jawitz OK, Voigt SL, et al. The Effect of Tumor Size and Histologic Findings on Outcomes After Segmentectomy vs Lobectomy for Clinically Node-Negative Non-Small Cell Lung Cancer. Chest 2021;159:390-400.

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