Original Article

The role of wedge resection and lymph node examination in stage IA lung carcinoid tumors

Muyu Li^, Qingpeng Zeng, Yuxing Chen, Jun Zhao

Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Contributions: (I) Conception and design: M Li, Q Zeng; (II) Administrative support: J Zhao; (III) Provision of study materials or patients: M Li, Y Chen; (IV) Collection and assembly of data: M Li; (V) Data analysis and interpretation: M Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jun Zhao, MD. Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Panjiayuan Nanli, Panjiayuan Street, Chaoyang District, Beijing 100021, China. Email: drzhaojun2023@163.com.

Background: Current guidelines recommend anatomical resection and mediastinal lymph node resection for stage I to IIIA pulmonary carcinoids (PCs). The role of wedge resection in stage IA PCs remains controversial, previous studies focused on typical carcinoids (TCs) while differentiating histological subtypes preoperatively is not easy. We aimed to study the effect of wedge resection and lymph node examination (LNE) in patients with stage IA PCs.

Methods: Patients who underwent anatomical and wedge resection for stage T1N0M0 lung carcinoid tumors between 2004 and 2019 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. Patients were also divided into a non-LNE group and an LNE group. Kaplan-Meier analysis and the log-rank test were used to calculate and compare overall survival (OS). Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were used to balance the variables between groups. Univariate and multivariate Cox proportional hazard models were developed to determine prognostic factors.

Results: A total of 2,029 patients with bronchopulmonary carcinoid tumors were included in this study, 1,450 underwent lobectomy, 147 underwent segmentectomy and 432 underwent wedge resection. Initially, 5-year survival differed marginally between wedge and anatomical resection (91% *vs.* 95%, P=0.051), but lost significance after adjustment. LNE improved 5-year survival (95% *vs.* 89%, P=0.003), and this remained significant after adjustment. In multivariate cox analysis, LNE remained a significant variable while extent of resection was not. This result also remained consistent after adjustment. OS was comparable between wedge resection and anatomical resection when at least 1 lymph node was examined.

Conclusions: For early-stage PC, wedge resection was not inferior to anatomical resection in terms of OS, while LNE significantly increased the survival in both multivariate and matched studies. The relationship between surgical extent and survival in the unadjusted study may be attributed to the lower rate of LNE in wedge resection. Our findings support wedge resection with emphasis on LNE in early-stage PCs.

Keywords: Bronchopulmonary carcinoid; lymph node examination (LNE); wedge resection; anatomical resection; SEER program

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^ ORCID: 0009-0001-4667-6853.

Introduction

Pulmonary carcinoids (PCs) represent a relatively rare malignancies that comprise 20–30% of all lung neuroendocrine tumors, and 1–2% of all pulmonary neoplasms (1,2). An increase in prevalence has been observed over the last 3 decades (1), probably due to an increased awareness of early lesions. PCs are further divided into typical carcinoids (TCs) with less than 2 mitoses/2 mm^2 without necrosis, and atypical carcinoids (ACs) with 2 to 10 mitoses/2 mm^2 with or without foci of necrosis, both TC and AC carry a favorable prognosis (2,3).

Surgical resection remains the cornerstone of treatment for stage IA PC. Previous studies have indicated that sub-lobar resection (including segmentectomy and wedge resection) yields similar oncological effect with lobar resection (4-9). Current guidelines from the European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines recommend anatomical resection (lobectomy and segmentectomy) with mediastinal lymph node dissection in stage I–IIIA PC (2,10). Studies focusing on the effect of wedge resection primarily center on TCs, which are considered indolent, low-grade tumors, and the results are controversial (8,11-15). For more aggressive intermediate-grade ACs, anatomical resection is believed to be necessary (2,11,13). However, the diagnostic criteria on the basis of mitotic count make it difficult to differentiate TC and AC via biopsy or cytology preoperatively as well as on frozen sections intraoperatively (16-24). Consequently, deciding whether to proceed with lobectomy in patients initially treated with wedge resection and later confirmed to have ACs presents a clinical dilemma. Close follow-up is often recommended in these cases (11). To support the use of wedge resection before or during surgery, it is important to conduct a comprehensive study that treats PC as a single disease entity, rather than distinguishing between its subtypes. For these reasons, in the present study, we compared the outcomes of stage IA PC patients who underwent wedge resection with those who underwent anatomical resection in the Surveillance Epidemiology End Results (SEER) database. Additionally, the role of lymph node examination (LNE) in this surgical series was investigated. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-745/rc).

Highlight box

Key findings

- Wedge resection with emphasis on lymph node assessment can achieve comparable outcome to anatomical resection in early-stage pulmonary carcinoids (PCs).

What is known and what is new?

- Wedge resection offers similar effect to anatomical resection on typical PC while it is difficult to differentiate typical carcinoid from atypical carcinoid preoperatively.
- PC was studied as a combined disease (typical and atypical) in our study; the significance of lymph node examination (LNE) in wedge resection was studied. We employed inverse probability of treatment weighting to balance the baseline variables which ensured a more sufficient sample size compared to the propensity scored matching used in previous studies.

What is the implication, and what should change now?

- Wedge resection could be offered to early-stage PCs even without specific knowledge of the histological subtype, but LNE should be emphasized in wedge resection.

Methods

Data source

The SEER database is a cancer database that covers approximately 35% of the US population; and collects enormous information on cancer patients. Using Seer*Stat (version 8.4.2), the SEER database was quired for all histologically confirmed PC patients aged over 18 with a single primary cancer that diagnosed from 2004 to 2019. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patient selection

Among the enrolled population, patients with tumor size ≤30 mm who were treated with wedge resection or anatomical resection were included in our study. The exclusion criteria were as follows: (I) patients with no staging, tumor size and LNE information; (II) patients with distant metastasis, lymph nodes metastasis or local infiltration; (III) patients with tumor size <8 mm, we did not enroll the patients with a tumor size smaller than 8 mm because the NCCN guideline recommends further evaluation for solid tumors ≥8 mm (6,25).

Data elements

The demographic and socioeconomic variables included age, sex, year of diagnosis, race (White/Black/unknown or other), marital status, income (low: income lower

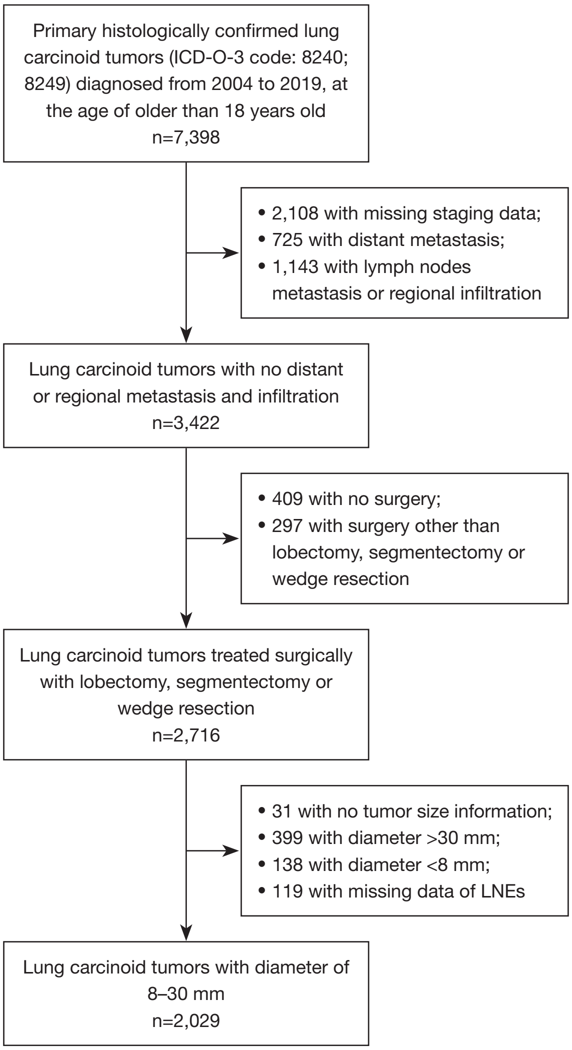

Figure 1 Diagram detailing selection of patient cohort. ICD-O, International Classification of Disease for Oncology; LNEs, lymph node examinations.

than $70,000/high: income higher than $70,000) and area (metropolitan area/nonmetropolitan area) and clinicopathological variables of laterality (right/left), site (upper lobe/middle lobe/lower lobe/unknown or other), LNEs (none/at least 1), tumor size (mm) and surgery type (lobectomy/segmentectomy/wedge resection) were included in our study. Overall survival (OS) was calculated from the time of diagnosis to the time of death from any cause.

Statistical analysis

Patients were categorized into wedge resection and anatomical resection groups, and also non-LNE group and LNE group. Patients in the LNE group were further divided into three groups based on the exact number of LNEs (1–3; 4–6; ≥7). Categorical variables were presented as counts (percentages), numerical variables were reported as the mean (standard deviation) or median [interquartile range (IQR)]. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were employed to balance baseline characteristics between groups. PSM involved 1:1 nearest neighbor PSM (caliper =0.025), propensity scores were calculated through a logistic regression model that included age, sex, race, year of diagnosis, marital status, income, living area, primary site, laterality, histology, tumor size and LNE. In the IPTW method, the predicted probabilities from the propensity-score model were used to generate stabilized inverse-probability-weighting weights, which were subsequently used to weight the characteristics. For clarity and ease of understanding, the total sample size after IPTW weighting has been approximated to the nearest integer. The effects of PSM and IPTW were assessed via standard mean difference (SMD) graphs. Variables were compared using Pearson's chi-squared (χ^2) test for categorical variables and Student's *t*-test or the Wilcoxon rank-sum test for contentious variables. Kaplan-Meier curve and log-rank tests were used to estimate and compare OS between groups. Univariate and multivariate Cox proportional hazard models were used to identify predictors for OS. A significant level of $P<0.05$ was adopted. Statistical analysis was performed using R version 4.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). The statistical power was calculated using PASS 2021 software (version 21.0.3, NCSS LLC, Kaysville, UT, USA).

Results

Baseline characteristics

According to the inclusion and exclusion criteria, 2,029 patients were ultimately included in our study (*Figure 1*). Wedge resection was performed in 432 patients, while anatomical resection was conducted in 1,597 patients (lobectomy, n=1,450; segmentectomy, n=147). The baseline characteristics stratified by surgical extent are presented in *Table 1*. Wedge resection was more common among older patients, females, those with smaller tumors and unmarried individuals. No significant differences were observed in surgery type between TC and AC. PSM and IPTW effectively balanced baseline characteristics (*Figure 2A*),

Table 1 Baseline patient demographics and clinical characteristics of surgical groups

Variables	Unadjusted cohort			PSM adjusted cohort			IPTW adjusted cohort		
	Wedge (N=432)	Anatomical (N=1,597)	P	Wedge (N=258)	Anatomical (N=258)	P	Wedge (N=1,983)	Anatomical (N=2,061)	P
Age (years), mean (SD)	63.57 (10.57)	58.59 (13.71)	<0.001	63.74 (10.69)	63.06 (12.39)	0.50	60.81 (11.39)	60.26 (13.85)	0.61
Male, n (%)	96 (22.2)	486 (30.4)	0.001	59 (22.9)	57 (22.1)	0.92	527.7 (26.6)	584.5 (28.4)	0.66
Race, n (%)			0.93			0.75			0.91
White	390 (90.3)	1,442 (90.3)		235 (91.1)	237 (91.9)		1,776.6 (89.6)	1,868.4 (90.7)	
Black	26 (6.0)	91 (5.7)		13 (5.0)	14 (5.4)		124.8 (6.3)	111.9 (5.4)	
Other	16 (3.7)	64 (4.0)		10 (3.9)	7 (2.7)		81.5 (4.1)	80.6 (3.9)	
Year, median [IQR]	2015 [2013, 2017]	2016 [2013, 2018]	0.03	2016 [2013, 2018]	2016 [2013, 2018]	0.72	2016 [2013, 2018]	2016 [2013, 2018]	0.55
Marital: unmarried, n (%)	183 (42.4)	585 (36.6)	0.03	103 (39.9)	102 (39.5)	>0.99	719.8 (36.3)	795.5 (38.6)	0.54
Income: high, n (%)	189 (43.8)	691 (43.3)	0.90	113 (43.8)	127 (49.2)	0.25	850.2 (42.9)	912.5 (44.3)	0.72
Area: Nonmetro, n (%)	55 (12.7)	174 (10.9)	0.33	30 (11.6)	33 (12.8)	0.79	240.8 (12.1)	226.8 (11.0)	0.65
Site, n (%)			0.31			0.98			0.56
Lower	195 (45.1)	686 (43.0)		114 (44.2)	119 (46.1)		884.3 (44.6)	899.3 (43.6)	
Middle	91 (21.1)	340 (21.3)		59 (22.9)	56 (21.7)		494.6 (24.9)	438.1 (21.3)	
Upper	136 (31.5)	504 (31.6)		77 (29.8)	75 (29.1)		542.4 (27.4)	641.5 (31.1)	
Other	10 (2.3)	67 (4.2)		8 (3.1)	8 (3.1)		61.7 (3.1)	82.0 (4.0)	
Laterality: right, n (%)	245 (56.7)	957 (59.9)	0.25	157 (60.9)	146 (56.6)	0.37	1,233.1 (62.2)	1,217.2 (59.1)	0.41
Histology: TC, n (%)	381 (88.2)	1,430 (89.5)	0.47	223 (86.4)	227 (88.0)	0.69	1,722.8 (86.9)	1,825.3 (88.5)	0.54
Size (mm), mean (SD)	15.47 (5.30)	18.30 (5.82)	<0.001	15.87 (5.34)	16.62 (5.76)	0.13	18.05 (6.14)	17.64 (5.83)	0.46
LN: no LNE, n (%)	240 (55.6)	78 (4.9)	<0.001	67 (26.0)	69 (26.7)	0.92	319.6 (16.1)	351.2 (17.0)	0.70

SD, standard deviation; IQR, interquartile range; TC, typical carcinoid; LN, lymph node; LNE, lymph node examination; PSM, propensity score matching; IPTW, inverse probability of treatment weighting.

Figure 2 SMD plot showing effect of PSM and IPTW. (A) Cohorts of patients receiving wedge resection versus anatomical resection for T1N0 bronchopulmonary carcinoid tumors. (B) Cohorts of patients receiving LNE versus no LNE during surgery. With the vertical red bar representing a SMD of 10%. LNE, lymph node examination; PSM, propensity score matching; IPTW, inverse probability of treatment weighting; SMD, standardized mean difference.

Table 2 Baseline patient demographics and clinical characteristics of LNE groups

Variables	Unadjusted cohort			PSM adjusted cohort			IPTW adjusted cohort		
	No LNE (N=318)	≥1 LNE (N=1,711)	P	No LNE (N=238)	≥1 LNE (N=238)	P	No LNE (N=2,201)	≥1 LNE (N=2,019)	P
Age (years), mean (SD)	62.23 (11.66)	59.17 (13.48)	<0.001	62.74 (11.72)	62.51 (11.45)	0.83	58.62 (14.13)	59.73 (13.24)	0.53
Male, n (%)	82 (25.8)	500 (29.2)	0.24	60 (25.2)	59 (24.8)	>0.99	578.9 (26.3)	571.1 (28.3)	0.71
Race, n (%)			0.90			0.53			0.76
White	285 (89.6)	1547 (90.4)		219 (92.0)	216 (90.8)		2,008.0 (91.2)	1,827.5 (90.5)	
Black	20 (6.3)	97 (5.7)		10 (4.2)	15 (6.3)		139.7 (6.3)	113.5 (5.6)	
Other	13 (4.1)	67 (3.9)		9 (3.8)	7 (2.9)		53.5 (2.4)	77.6 (3.8)	
Year, median [IQR]	2015 [2012, 2017]	2016 [2013, 2018]	<0.001	2015 [2013, 2018]	2016 [2013, 2018]	0.88	2016 [2013, 2018]	2016 [2013, 2018]	0.29
Marital: unmarried, n (%)	134 (42.1)	634 (37.1)	0.10	95 (39.9)	95 (39.9)	>0.99	860.8 (39.1)	764.2 (37.8)	0.83
Income: high, n (%)	128 (40.3)	752 (44.0)	0.25	103 (43.3)	107 (45.0)	0.78	865.0 (39.3)	879.6 (43.6)	0.48
Area: Nonmetro, n (%)	41 (12.9)	188 (11.0)	0.37	28 (11.8)	25 (10.5)	0.77	303.8 (13.8)	230.3 (11.4)	0.54
Site, n (%)			0.25			0.62			0.38
Lower lobe	133 (41.8)	748 (43.7)		104 (43.7)	108 (45.4)		1,036.6 (47.1)	881.7 (43.7)	
Middle lobe	67 (21.1)	364 (21.3)		47 (19.7)	55 (23.1)		494.6 (22.5)	435.4 (21.5)	
Upper lobe	111 (34.9)	529 (30.9)		81 (34.0)	71 (29.8)		509.7 (23.2)	624.1 (30.9)	
Other	7 (2.2)	70 (4.1)		6 (2.5)	4 (1.7)		160.3 (7.3)	77.4 (3.8)	
Laterality: right, n (%)	167 (52.5)	1,035 (60.5)	0.009	132 (55.5)	132 (55.5)	>0.99	1,329.2 (60.4)	1,204.3 (59.6)	0.90
Histology: TC, n (%)	291 (91.5)	1,520 (88.8)	0.19	214 (89.9)	213 (89.5)	>0.99	1,891.4 (85.9)	1,799.6 (89.2)	0.48
Size (mm), mean (SD)	15.80 (5.59)	18.05 (5.81)	<0.001	16.44 (5.82)	16.17 (5.33)	0.61	18.46 (6.23)	17.74 (5.78)	0.33
Surgery, n (%)			<0.001			0.99			0.84
Wedge resection	240 (75.5)	192 (11.2)		160 (67.2)	159 (66.8)		428 (19.4)	421 (20.9)	
Lobectomy	49 (15.4)	1,401 (81.9)		49 (20.6)	50 (21.0)		1,616 (73.4)	1,450 (71.8)	
Segmentectomy	29 (9.1)	118 (6.9)		29 (12.2)	29 (12.2)		158 (7.2)	147 (7.3)	

LNE, lymph node examination; SD, standard deviation; IQR, interquartile range; TC, typical carcinoid; PSM, propensity score matching; IPTW, inverse probability of treatment weighting.

with no significant differences detected between groups in adjusted cohorts (*Table 1*).

LNE

Of the enrolled patients, 1,711 underwent LNE during surgery, while 318 had no lymph nodes examined. LNE rates differed significantly among surgical approaches (P<0.001), with higher rates observed during lobectomy (96.6%), followed by segmentectomy (80.3%), and wedge resection (44.4%). Older patients, those diagnosed earlier, with smaller tumors and left-sided tumors were more likely to miss LNE (*Table 2*). After applying IPTW and PSM, the balance between the two groups also improved (*Figure 2B*).

Survival analysis

During a median follow-up time of 44 months, 113 patients experienced all-cause mortality. In the unadjusted surgical cohort, patients underwent wedge resection exhibited a 5-year OS of 91% [95% confidence interval (CI): 88–95%] and a 10-year OS of 81% (95% CI: 74–89%), slightly lower

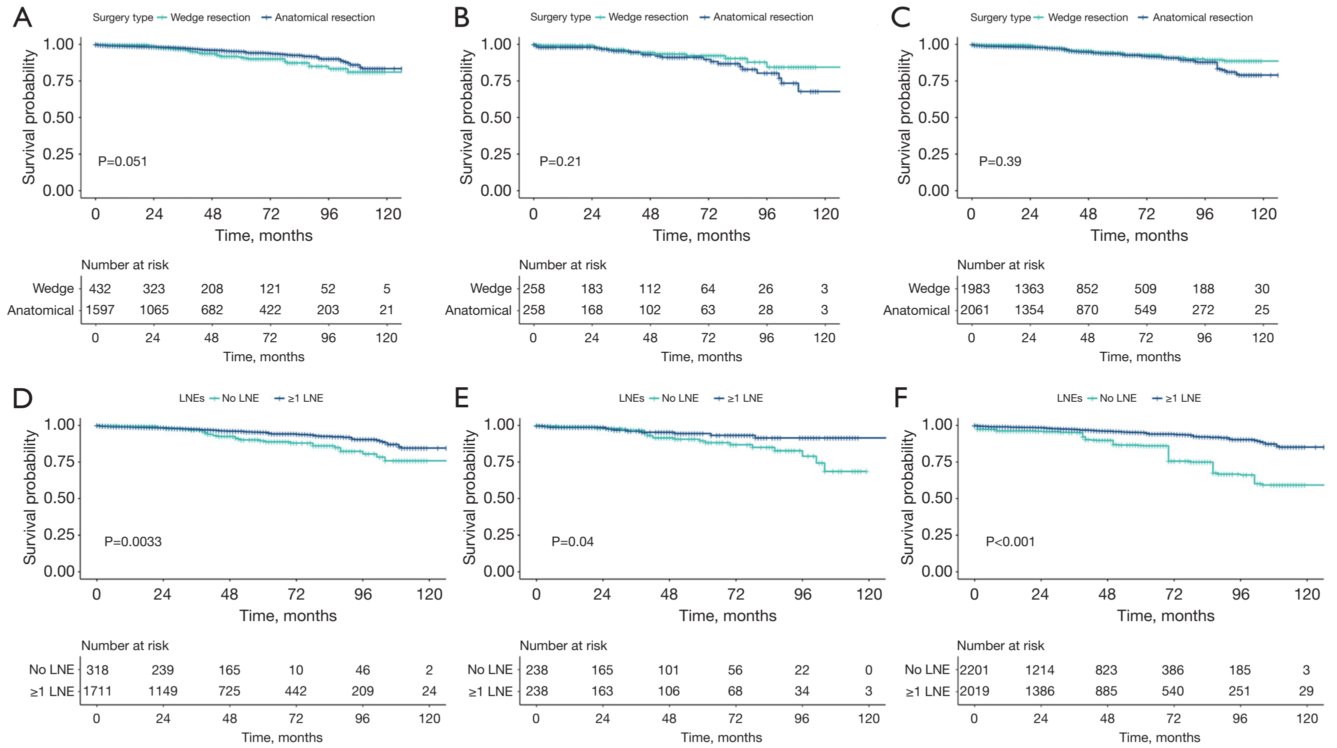

Figure 3 Kaplan-Meier survival curve depicting PCs outcomes treated with wedge resection and anatomical resection, and whether lymph nodes were dissected. (A) Unadjusted surgical cohort; (B) PSM surgical cohort; (C) IPTW surgical cohort; (D) unadjusted LNE cohort; (E) PSM LNE cohort; (F) IPTW LNE cohort. LNE, lymph node examination; PCs, pulmonary carcinoids; PSM, propensity score matching; IPTW, inverse probability of treatment weighting.

than those underwent anatomical with a 5-year OS of 95% (95% CI: 94–96%) and a 10-year OS of 83% (95% CI: 79–88%). However, these differences were only marginally significant (P=0.051, *Figure 3A*). Among 258 matched surgical pairs, no significant difference in OS was observed (P=0.21. *Figure 3B*), with 5-year and 10-year survival rates of 93% (95% CI: 90–97%) and 84% (95% CI: 75–95%) in the wedge group, and 91% (95% CI: 86–96%) and 68% (95% CI: 54–85%) in the anatomical group. In the IPTW set, the 5-year and 10-year survival were 94% (95% CI: 91–98%) and 89% (95% CI: 83–94%), respectively, in the wedge group; and 94% (95% CI: 91–96%) and 79% (95% CI: 71–88%), respectively, in the anatomical group (P=0.39, *Figure 3C*).

Subgroup analysis revealed no significant differences in OS between wedge resection and anatomical resection in unadjusted TC and AC subgroup (P=0.21 and 0.12, respectively, Figure S1A,S1B). The same results were reproduced in matched subgroup studies (P=0.11 and 0.88, respectively, Figure S1C,S1D). When compared with TC, AC has a significant worse OS (before adjustment, P<0.001; after PSM adjustment, P=0.002), this difference persisted regardless of whether anatomical resection (before adjustment, P<0.001; after PSM adjustment, P=0.03) or wedge resection (before adjustment, P=0.002; after PSM adjustment, P=0.04) is performed (Figure S2). Furthermore, within the anatomical resection group, segmentectomy appeared to confer better OS, though not statistically significant (Figure S3).

Patients underwent LNE demonstrated significantly better 5-year OS compared to those without LNE [95% (95% CI: 94–97%) *vs.* 89% (95% CI: 85–94%), P=0.003, *Figure 3D*]. Similar results were observed in cohorts balanced with either PSM [94% (95% CI: 91–98%) *vs.* 89% (95% CI: 84–94%), P=0.04, *Figure 3E*] or IPTW [95% (95% CI: 94–97%) *vs.* 86% (95% CI: 78–96%), P<0.001, *Figure 3F*].

Notably, in patients with at least 1 lymph node examined, no differences in OS were noted between wedge resection and anatomical resection in the unadjusted study (P=0.37,

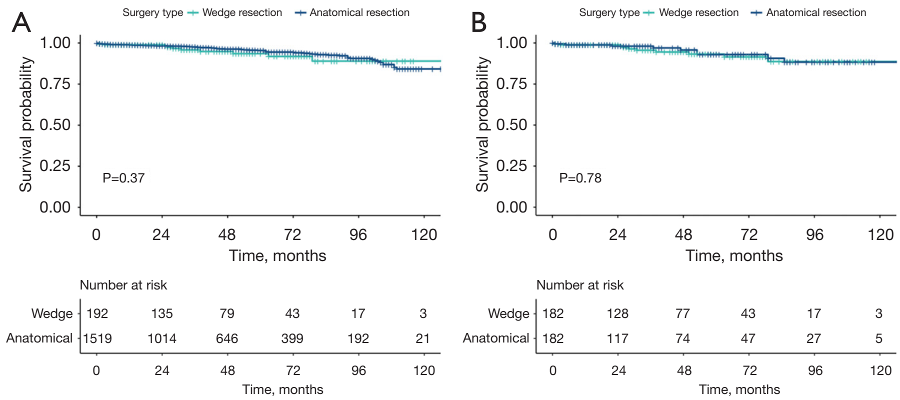

Figure 4 Kaplan-Meier survival curve of pulmonary carcinoids treated with different surgery type in patients with at least 1 lymph nodes examination. (A) Unadjusted cohort; (B) PSM cohort. PSM, propensity score matching.

Figure 4A), and the result was consistent in the PSM adjusted analysis (P=0.78, *Figure 4B*). Moreover, within the LNE group, no survival difference was observed among subgroups with different numbers of LNEs (Figure S4).

Surgical extension, LNEs and histology were identified as predictors for OS in univariate Cox regression (*Table 3*). However, in multivariate model, surgical extent no longer retained its predictive value, while LNEs [no LNE *vs.* LNE, hazard ratio (HR) =2.11, 95% CI: 1.20–3.73, P=0.01] and histology (TC *vs.* AC, HR =0.39, 95% CI: 0.25–0.62, P<0.001) remained significant factors. Consistent findings were observed in the surgical cohorts balanced with PSM (no LNE *vs.* LNE, HR =2.11, 95% CI: 1.02–4.36, P=0.04), (TC *vs.* AC, HR =0.25, 95% CI: 0.12–0.53, P<0.001) or IPTW (no LNE *vs.* LNE, HR =3.28, 95% CI: 1.73–6.22, P<0.001), (TC *vs.* AC, HR =0.23, 95% CI: 0.09–0.59, P=0.002).

Discussion

Surgical resection is recognized as the standard treatment for stage I to IIIA PCs and is often curative especially for localized early-stage PC. The choice of surgical extent depends on various factors including tumor size, histology and location. For centrally located tumors, bronchoplastic procedures with thorough lymph node assessment are favored over pneumonectomy in suitable patients to ensure an oncological resection and preserve more of the lung parenchyma (2). However, the optimal surgical extent for peripherally located tumors remains controversial among studies. Studies on the effect of sublobar resection have demonstrated a similar outcome to those of lobar resection (4-7,9). The ESMO and NCCN guidelines advocate for anatomic pulmonary resection alongside lymph node resection for peripheral PC (2,10). Wedge resection, however, is thought to be associated with an increased risk of recurrence in certain cases (2). The existing evidence mostly comes from small retrospective cohorts (26,27); nonetheless, it is impossible to design a prospective trial due to the rarity of PC.

Recently, the results of a randomized trial (CALGB/ALLIANCE140503) suggested noninferiority in terms of recurrence-free survival and similarity in OS between sublobar resection (in which wedge resections made up 59% of the cases) and lobar resection in stage IA non-small cell lung cancer (NSCLC) (28). It also demonstrated a lower 30- and 90-day mortality rate in sublobar resection than in lobar resection, and a lower rate of grade 3/4/5 adverse events in wedge resection than in lobectomy and segmentectomy (29). Wedge resection is also believed to be more effective in terms of pulmonary function preservation than segmentectomy (30). Conflicting results have arisen from previous studies regarding the impact of wedge resection on PC outcomes. For instance, Filosso *et al.* (12) requested data from the European Society of Thoracic Surgeons, Neuroendocrine Tumors of the Lung Working Group (ESTS NETs-WG) database, and concluded that wedge resection was associated with reduced survival in TC, however, important cofounding factors such as LNEs were not included in that study. Conversely, some authors have used the SEER database and suggested that wedge resection is non-inferior to anatomical resection for the treatment of PC (8,11), nonetheless, both of these studies included patients with more advanced-stage disease, which may introduce bias. Bachman and colleagues (13) reached

Table 3 Cox proportional hazard models of survival

Variables	Unadjusted				PSM adjusted		IPTW adjusted	
	Univariable		Multivariable†		HR (95% CI) (univariable)	P	HR (95% CI) (univariable)	P
	HR (95% CI)	P	HR (95% CI)	P				
Age	1.07 (1.05–1.08)	<0.001	1.07 (1.05–1.09)	<0.001	1.08 (1.04–1.13)	<0.001	1.05 (1.02–1.08)	0.002
Sex (Ref.: female)								
Male	1.60 (1.09–2.33)	0.02	2.27 (1.54–3.36)	<0.001	0.79 (0.34–1.82)	0.58	0.69 (0.31–1.55)	0.37
Race (Ref.: White)								
Black	2.36 (1.35–4.14)	0.003	3.11 (1.74–5.56)	<0.001	1.82 (0.55–6.00)	0.32	0.78 (0.33–1.81)	0.56
Other	0.24 (0.03–1.74)	0.16	0.27 (0.04–1.93)	0.19	0.79 (0.11–5.82)	0.82	0.15 (0.02–1.04)	0.06
Year of diagnosis	0.89 (0.82–0.96)	0.002	0.92 (0.85–1.00)	0.05	0.86 (0.75–0.99)	0.04	0.93 (0.76–1.14)	0.49
Marital status (Ref.: married)								
Unmarried	1.61 (1.11–2.33)	0.01	1.35 (0.91–1.98)	0.13	2.04 (1.02–4.08)	0.04	1.72 (0.70–4.20)	0.24
Income (Ref.: low)								
High	0.69 (0.46–1.03)	0.07	0.82 (0.54–1.25)	0.37	0.69 (0.33–1.46)	0.34	0.58 (0.23–1.43)	0.24
Area (Ref.: Metro)								
Nonmetro	1.60 (0.99–2.60)	0.06	1.27 (0.77–2.10)	0.36	3.12 (1.48–6.57)	0.003	1.36 (0.52–3.58)	0.53
Site (Ref.: lower lobe)								
Middle lobe	0.73 (0.42–1.27)	0.27			0.98 (0.39–2.42)	0.96	0.99 (0.32–3.11)	0.99
Upper lobe	1.28 (0.85–1.92)	0.25			0.95 (0.43–2.10)	0.90	0.97 (0.33–2.79)	0.95
Other	1.22 (0.48–3.07)	0.67			1.11 (0.15–8.50)	0.92	0.39 (0.10–1.56)	0.18
Laterality (Ref.: left)								
Right	0.74 (0.51–1.07)	0.11			0.67 (0.34–1.34)	0.26	1.25 (0.54–2.88)	0.61
Histology (Ref.: AC)								
TC	0.38 (0.25–0.58)	<0.001	0.39 (0.25–0.62)	<0.001	0.25 (0.12–0.53)	<0.001	0.23 (0.09–0.59)	0.002
Size (mm)	1.00 (0.97–1.03)	0.85			1.02 (0.96–1.08)	0.61	1.01 (0.94–1.08)	0.89
Surgery (Ref.: wedge)								
Lobectomy	0.71 (0.47–1.06)	0.09	1.26 (0.73–2.17)	0.40	1.30 (0.61–2.77)	0.49	1.70 (0.89–3.24)	0.11
Segmentectomy	0.30 (0.09–0.99)	0.05	0.41 (0.12–1.37)	0.15	0.20 (0.03–1.48)	0.12	0.36 (0.08–1.56)	0.17
LNE (Ref.: 1+ LNE)								
No LNE	1.83 (1.22–2.76)	0.004	2.11 (1.20–3.73)	0.01	2.11 (1.02–4.36)	0.04	3.28 (1.73–6.22)	<0.001

†, univariate predictors with P<0.1 were included in the multivariable model. AC, atypical carcinoid; TC, typical carcinoid; LNE, lymph node examination; PSM, propensity score matching; IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval.

the similar conclusion using the National Cancer Database (NCDB). Most previous studies have focused on TC, while a more extensive resection is often deemed necessary for AC. However, achieving an accurate and specific histological diagnosis before obtaining the final surgical specimen poses a significant challenge (16-19). Despite efforts to improve diagnostic accuracy, previous studies have reported diagnostic accuracy rates of 60–70% for PC, and only 40–50% for subtype differentiation in bronchoscopy biopsies (24,31). This rate is even lower for percutaneous biopsy (32).

The current WHO 5th edition of the Classification of Thoracic Tumors discourages the classification of carcinoids in biopsy samples, recommending the diagnosis of "carcinoid tumor not otherwise specified (NOS)" in non-resected specimens (3). In more recent studies, Moonen *et al.* (22) reviewed 330 PCs who underwent preoperative biopsy, revealing that in 57% (n=189) of patients, biopsy specimen diagnosis did not align with the final diagnosis. Notably, a diagnosis of carcinoid NOS were made in 158 patients. Given the challenges in achieving a definitive preoperative diagnosis, our study adopted a pragmatic approach. Rather than categorizing tumors as TC or AC, we combined them under a single diagnosis of PC to simulate a preoperative diagnosis of "carcinoid NOS", which is more reflective of real-world scenarios, and studied the effect of wedge resection in this combined group of diseases. We observed that while wedge resection was initially associated with poorer OS in unadjusted analysis, this difference was no longer evident in multivariate analysis or after adjusting for confounding factors such as age, histology, and lymph node evaluations using PSM and IPTW. This result is similar to the conclusions of some previous studies (8,11,13,15). However, it is important to note that, as retrospective studies, almost every previous research has used PSM to eliminate the impact of confounding factors. In our study, in addition to PSM, we further applied IPTW to balance the baseline data between groups. While PSM can eliminate confounding, it has a significant drawback: a substantial portion of the sample size is lost during the matching process. This loss can lead to insufficient statistical power and potentially inaccurate conclusions, especially when the original sample size is small or the differences between groups are minor. In contrast, IPTW uses a weighting method to create a pseudopopulation, which balances baseline data while preserving the maximum sample size. In our study, PSM yielded 258 matched pairs, with a 5-year loss to follow-up rate of approximately 55%. Based on previous literature (12,14) and our data, the 5-year survival rates after wedge resection and anatomical resection are about 90% and 95%, respectively. Consequently, the statistical power for the log-rank test in the PSM cohort was calculated to be less than 30%. In contrast, after applying IPTW, the pseudopopulation for the wedge resection group and anatomical resection group were 1,983 and 2,061, respectively, with a statistical power for the log-rank test close to 90%. Clearly, the results adjusted by IPTW are more robust and convincing.

Previous studies have demonstrated that clinical lymph node staging for carcinoids is unreliable, and have reported an upstaging rate of 4–13% for cT1N0M0 tumors (33), for which lymph node assessment has been emphasized by surgeons (2,10,15,33). In the present study, LNE was associated with improved survival in surgically managed patients, which is consistent with previous literatures. However, the exact number of LNEs was not significantly associated with survival, likely due to the indolent nature of the disease and the relatively small sample size of our study. Compared with anatomical resection, wedge resection yielded out much fewer lymph nodes, over half of the patients who underwent wedge resection did not have any lymph nodes examined, while almost every patient undergoing anatomical resection had at least 1 LNE. Interestingly, in our study, when at least 1 lymph node was examined during surgery, anatomical resection no longer had a survival advantage over wedge resection. Similar findings have been reported in NSCLC (34). This suggests that, the survival benefit of anatomical resection could be, at least partially, attributed to a more thorough lymph node assessment.

Our study has demonstrated that, when adjusted for potential cofounding factors (especially LNEs), wedge resection offers an equivalent oncological effect to anatomical resection in early-stage peripheral carcinoid tumors. Due to the utilization of IPTW, we have maximized sample size while effectively controlling for confounding variables. To our knowledge, we consider our study to be the most compelling research on this topic to date. This finding may support the selection of wedge resection in early stage, pre- or intraoperatively diagnosed "carcinoid NOS" while specific subtypes are not available, particularly in older patients with underlying comorbidities who are marginal surgical candidates. However, when certain histological features are present in biopsy specimens (e.g., mitoses or punctate necrosis), which suggests AC, anatomical resection or even a lobectomy should be favored, because, similar to previous findings, our study showed that AC has significantly worse prognosis compared to TC, regardless of the surgical extent, even though subgroup analysis in our study revealed no difference between wedge resection and anatomical resection of the AC. Additionally, our study revealed that more than half of the wedge resections performed for PC in the United States did not include lymph node sampling, which contradicts current perspectives. This may be related to the pursuit of minimally invasive surgery, and the inherent difficulty of sampling intrapulmonary lymph nodes during wedge resections. Given this situation, we suggest that lymph node sampling should be further emphasized in wedge resection. However, the specific location and quantity of lymph node sampling still require further discussion.

There are several limitations in this study. Firstly, the retrospective nature of the SEER database may result in potential bias even after adjustment, and several potential confounding factors such as comorbidities and data on disease recurrence were not available. In addition, due to the lack of information about preoperative diagnoses, we simply combined the two separate diagnoses of TC and AC to simulate the preoperative diagnosis of "carcinoid NOS", this may bias the results, Further studies on surgical extension based on pre- and intraoperative diagnosis are warranted. Furthermore, our study considered whether to perform lymph node biopsy as a binary variable, and additional discussion is required regarding the specific number and location of lymph nodes to be dissected.

Conclusions

Wedge resection tends to have much lower LNE rate than anatomical resection. For early-stage PC, wedge resection showed no inferiority in OS to anatomical resection in multivariate studies or matched studies, while LNE showed a prognostic effect in both multivariate studies and matched studies, indicating a stronger association between LNE and OS than between surgical extent and OS. The observed association between surgical extent and OS may be attributed, at least in part, to the lower rate of LNE in wedge resection. Our study provides preliminary evidence suggesting that wedge resection, with an emphasis on LNE, may be comparable to anatomical resection in preoperatively diagnosed PC patients. While our findings indicate this potential equivalence, we acknowledge that further studies are necessary to confirm these results, though designing prospective studies may be impractical due to the rarity of PCs.

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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-24-745/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-24-745/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). Since the data were deidentified, requirement for patient informed consent was waived, and this study was exempted from institutional review by the ethics committee of our hospital.

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