Original Article

Implications of surgical intervention in patients with metastatic pulmonary carcinoid tumors: a SEER-based population study and propensity score matching comparative analysis

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Background: Currently, there are few studies on the significance of surgery for patients with metastatic pulmonary carcinoid tumors (PC). This study aims to explore the value of surgery for the long-term survival of patients with metastatic PC using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: Details on PC patients diagnosed between 2000 and 2020 were obtained from the SEER database (version 8.4.3) and assessed according to the presence or absence of surgical treatment. Propensity score matching (PSM) was used to ensure a balance in clinicopathological factors between the two groups. Kaplan-Meier (K-M) survival curves and log-rank test were used to confirm the surgical benefit in patients with metastatic PC, and the Cox proportional hazards model was used to reveal the prognostic factors.

Results: From the SEER database, 472 patients were found to meet the criteria for inclusion, with 118 of them having received surgery and 354 not having undergone any surgical treatment. After conducting a 1:1 PSM, there were 82 patients in each of the surgical and non-surgical groups. The patient cohort showed that surgery independently affected the prognosis of overall survival (OS). Furthermore, patients who received surgery exhibited notably better OS and cancer-specific survival (CSS) rates than those receiving no surgery, as indicated by the K-M survival curves (P=0.02, P=0.02).

Conclusions: The prognostic value of surgical treatment for individuals with metastatic PC was clarified through the PSM analysis utilizing SEER data. Surgical treatment at the primary site has been shown to significantly enhance the OS and CSS in this population. Therefore, primary-site surgical treatment should be actively employed for patients with metastatic PC. However, more prospective experiments are needed to verify this conclusion.

Keywords: Pulmonary carcinoid tumor (PC); surgery; survival; Surveillance, Epidemiology, and End Results (SEER)

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Introduction

Lung neuroendocrine tumors encompass large-cell neuroendocrine carcinoma (LCNEC), small-cell lung cancer (SCLC), and pulmonary carcinoid tumors (PC) (1,2). The development of PC is linked to neuroendocrine cells in the bronchial mucosa. Individuals diagnosed with carcinoid tumors are generally younger, have a more positive prognosis, and are less associated with smoking, unlike those with SCLC and LCNEC (3). Mitotic activity and necrosis are used to differentiate between typical carcinoid

(TC) and atypical carcinoid (AC) tumors in PC (4-6). While TC has a low rate of cell division (<2 mitoses per high-power field) and no necrosis, AC has a higher mitotic rate, regardless of the presence of necrosis (7). Approximately 20–25% of neuroendocrine tumors and 1–2% of lung tumors are identified as PC (4-6,8-10). Advancements in diagnostic methods and enhancements in preventive healthcare are leading to a rise in their detection rate (8-11). It is estimated that roughly half of individuals with carcinoid tumors are without symptoms at initial diagnosis (12). Patients with symptoms often show signs like difficulty breathing, coughing up blood, coughing, and pneumonia that blocks airways. Carcinoid tumors are commonly linked to paraneoplastic syndromes such as carcinoid syndrome and Cushing's syndrome (13). The main signs of carcinoid syndrome are redness of the skin and diarrhea (14). Carcinoid syndrome was present in 229 (7.6%) of the 3,002 patients with PC in a large-scale study (15).

Surgical removal is the primary method of treatment for carcinoid tumors, as shown in past research (16). The prognosis for TC patients is generally good, with few fatalities directly attributed to the tumor. The preferred course of action for central tumors is usually lobectomy. Segmental lung resection is a possible consideration for tumors found in the outer regions of the lungs. TC patients have excellent survival rates even with lymph node metastases (17). The 5-year survival rate is notably lower for individuals with AC, ranging from 61% to 88%, in comparison to those with TC (18-20).

Despite being labeled as low and moderately malignant neuroendocrine tumors, TC and AC can still metastasize to regional lymph nodes and distant sites (21). TC exhibits a lower prevalence of lymph node metastases, with rates varying from 4% to 14%, while AC has a much higher range of 35% to 64%. Stage IV TC has a 10-year overall survival (OS) rate of 47%, while AC only has 18% (21,22). Since PC is relatively resistant to chemotherapy and radiotherapy, surgery may be a treatment for metastatic conditions (23). However, the current literature is unclear about the efficacy of surgical treatment for metastatic PC. The available treatment options are limited, primarily based on reviewing past data, trials with only one group, and analyzing subsets of phase II/III trials for metastatic neuroendocrine tumors, and inferences drawn from the data obtained during the Gastroenteropancreatic Neuroendocrine Tumors Phase III Trial. Therefore, this study explored the implications of patients with metastatic PC receiving surgical treatment using the Surveillance, Epidemiology, and End Results (SEER) database. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2024-1935/rc).

Highlight box

Key findings

- Surgery at the primary site of the tumor can improve the prognosis of patients with metastatic lung carcinoids.

What is known and what is new?

- Despite being labeled as low and moderately malignant neuroendocrine tumors, pulmonary carcinoid tumor (PC) can still metastasize to regional lymph nodes and distant sites. However, the current literature is unclear about the efficacy of surgical treatment for metastatic PC.
- The prognostic importance of surgical intervention in metastatic PC patients was clarified through the propensity score matching study using Surveillance, Epidemiology, and End Results (SEER) database data.

What is the implication, and what should change now?

- Surgical resection at the primary site has been shown to significantly enhance the overall survival and cancer-specific survival in metastatic PC. Therefore, aggressive surgical management should be considered for individuals with metastatic PC.

Methods

Database

The study was performed using the SEER public database, which includes 18 SEER registries and is currently updated to the SEER*Stat 8.4.3 dataset.

Study population

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. SEER*Stat software (version 8.4.3) was utilized to obtain all details regarding patients with metastatic PC from the SEER database. Inclusion criteria: (I) patients with a primary cancer diagnosis of PC in the SEER database from 2000 to 2020 (International Classification of Diseases code 8240 for TC and 8249 for AC); (II) those with definitive pathological confirmation of PC; (III) those with distant metastasis; (IV) those with detailed surgical data. Exclusion criteria: (I) no complete survival data (including year of diagnosis, cause of death, survival time, and current survival status); (II) unknown Tumor-Node-Metastasis (TNM) staging; (III) pathologic confirmation by autopsy/

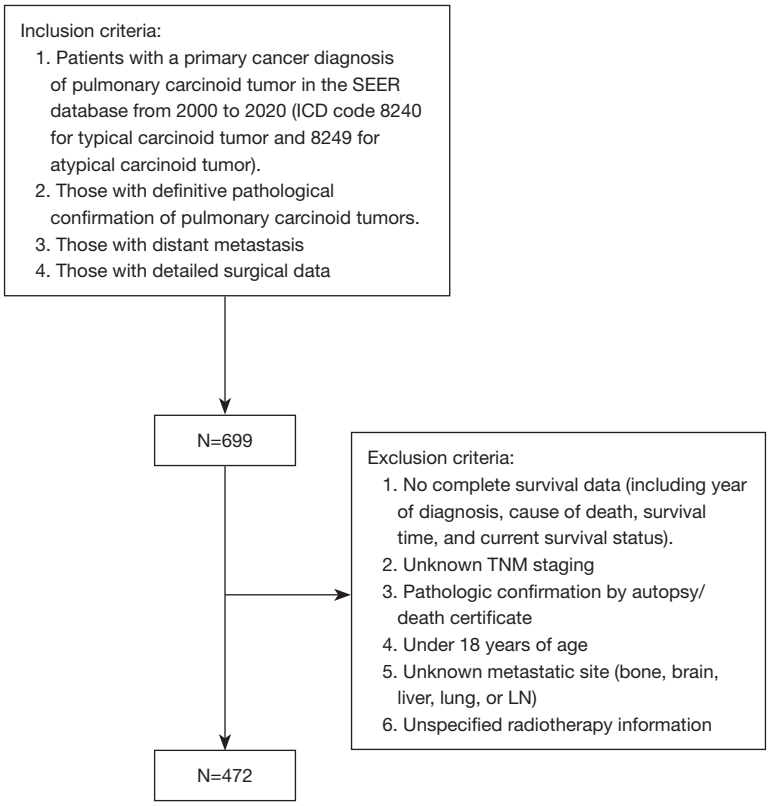

Figure 1 Flowchart of the study cohort screening process. LN, lymph node; SEER, Surveillance, Epidemiology, and End Results.

death certificate; (IV) under 18 years of age; (V) unknown metastatic site (bone, brain, liver, lung, or lymph node); (VI) unspecified radiotherapy information. Information on individuals who fit the specific criteria was gathered, such as age, ethnicity, sex, marital status, year of diagnosis, location of the main tumor, histological grade, TNM staging, treatment modalities, where distant metastases occurred, and OS duration in months. Ultimately, the study included a total of 472 suitable participants (refer to *Figure 1* for a flowchart illustrating the study cohort selection process).

Data preprocessing

For further statistical analysis, we classified age groups as follows: <60, 60–79, and ≥80 years; tumor size groups: <3 and ≥3 cm. The restaging of all subjects was conducted in accordance with the updated criteria provided in the TNM Staging Manual (9th Edition) (24).

Research results

The results of this research involved OS and cancer-specific survival (CSS), with OS being determined from the time of diagnosis to the time of death for any reason. From the moment of diagnosis to the time of death due to PC, CSS was assessed, regardless of the direct or indirect cause.

Statistical analysis

The baseline characteristics and clinical features of patients in the surgical and non-surgical groups were compared through the use of a Pearson Chi-squared test and Student's *t*-test. The effectiveness of surgery in patients with advanced PC was assessed using the Kaplan-Meier (K-M) method and log-rank test. A 1:1 propensity score matching (PSM) was conducted using the "MatchIt" R package to ensure balance in the variables between the surgical and non-surgical cohorts. The logistical model incorporated variables such as patient race, gender, tumor site, age group, year of diagnosis, histological grade, T stage, N stage, tumor size, radiotherapy, lymph node dissection, and site of metastasis to calculate propensity scores, using a caliper of 0.01. In R software (version 4.1.2), statistical tests were conducted with a significance level of $P<0.05$.

Table 1 Baseline characteristics of patients with metastatic pulmonary carcinoid tumors treated with *vs.* without surgery

Characteristics	No (n=354)	Yes (n=118)	P
Race			
Black	39 (11.0)	16 (13.6)	0.47
Other	14 (4.0)	7 (5.9)	
White	301 (85.0)	95 (80.5)	
Sex			
Female	234 (66.1)	93 (78.8)	0.01
Male	120 (33.9)	25 (21.2)	
Site			
Lower lobe	136 (38.4)	42 (35.6)	0.03
Main bronchus	17 (4.8)	6 (5.1)	
Middle lobe	38 (10.7)	20 (16.9)	
Overlapping lesion of lung	1 (0.3)	4 (3.4)	
Unknown	62 (17.5)	17 (14.4)	
Upper lobe	100 (28.2)	29 (24.6)	
Age, years			
<60	85 (24.0)	59 (50.0)	<0.001
60–79	212 (59.9)	57 (48.3)	
80+	57 (16.1)	2 (1.7)	
Year			
2010–2014	113 (31.9)	61 (51.7)	<0.001
2015–2020	241 (68.1)	57 (48.3)	
Grade			
I/II	137 (38.7)	65 (55.1)	0.004
III/IV	14 (4.0)	1 (0.8)	
Unknown	203 (57.3)	52 (44.1)	
T stage			
T1	74 (20.9)	23 (19.5)	0.03
T2	66 (18.6)	24 (20.3)	
T3	75 (21.2)	39 (33.1)	
T4	139 (39.3)	32 (27.1)	
N stage			
N0	166 (46.9)	83 (70.3)	<0.001
N1	27 (7.6)	11 (9.3)	
N2	119 (33.6)	22 (18.6)	
N3	42 (11.9)	2 (1.7)	
Size			
<3 cm	151 (42.7)	80 (67.8)	<0.001
≥3 cm	159 (44.9)	34 (28.8)	
Unknown	44 (12.4)	4 (3.4)	
Radiation			
None/unknown	262 (74.0)	110 (93.2)	<0.001
Yes	92 (26.0)	8 (6.8)	
Chemotherapy			
No/unknown	211 (59.6)	97 (82.2)	<0.001
Yes	143 (40.4)	21 (17.8)	
DLN			
No	319 (90.1)	116 (98.3)	0.008
Yes	35 (9.9)	2 (1.7)	
Brain			
No	302 (85.3)	117 (99.2)	<0.001
Yes	52 (14.7)	1 (0.8)	
Bone			
No	238 (67.2)	103 (87.3)	<0.001
Yes	116 (32.8)	15 (12.7)	
Liver			
No	225 (63.6)	92 (78.0)	0.006
Yes	129 (36.4)	26 (22.0)	
Lung			
No	219 (61.9)	71 (60.2)	0.82
Yes	135 (38.1)	47 (39.8)	
Survival, months	28.44 (28.86)	57.01 (37.33)	<0.001

Categorical variables are presented as n (%) and continuous variables are presented as mean ± standard deviation. DLN, distance lymph node.

Results

Baseline characteristics

This study involved 472 patients from the SEER cohort in the U.S. who met the specified criteria, including 118 patients who received surgical treatment before PSM and 354 patients who did not receive surgical treatment. The baseline characteristics are provided in *Table 1*. The surgical group had a greater proportion of patients under the age of 60 (50.0% *vs.* 24.0%, P<0.001); their histological grading was mostly grade I/II (55.1% *vs.* 38.7%, P=0.004); a greater proportion of patients had a tumor size of less than 3 cm (67.8% *vs.* 42.7%, P<0.001). Those with metastatic PC who did not undergo surgery had a median survival of 28.44 months, whereas those receiving surgery had a median survival of 57.01 months. A 1:1 PSM was conducted on the patient cohort, considering the substantial

Table 2 Baseline characteristics of patients with metastatic pulmonary carcinoid tumors treated with *vs.* without surgery after PSM

Characteristics	No (n=82)	Yes (n=82)	P
Race			
Black	5 (6.1)	7 (8.5)	0.71
Other	7 (8.5)	5 (6.1)	
White	70 (85.4)	70 (85.4)	
Sex			
Female	64 (78.0)	64 (78.0)	>0.99
Male	18 (22.0)	18 (22.0)	
Site			
Lower lobe	30 (36.6)	31 (37.8)	0.95
Main bronchus	2 (2.4)	4 (4.9)	
Middle lobe	15 (18.3)	12 (14.6)	
Overlapping lesion of lung	1 (1.2)	1 (1.2)	
Unknown	14 (17.1)	15 (18.3)	
Upper lobe	20 (24.4)	19 (23.2)	
Age, years			
<60	34 (41.5)	32 (39.0)	0.95
60–79	46 (56.1)	48 (58.5)	
80+	2 (2.4)	2 (2.4)	
Year			
2010–2014	42 (51.2)	37 (45.1)	0.53
2015–2020	40 (48.8)	45 (54.9)	
Grade			
I/II	40 (48.8)	39 (47.6)	0.98
III/IV	1 (1.2)	1 (1.2)	
Unknown	41 (50.0)	42 (51.2)	
T stage			
T1	11 (13.4)	15 (18.3)	0.74
T2	12 (14.6)	14 (17.1)	
T3	31 (37.8)	26 (31.7)	
T4	28 (34.1)	27 (32.9)	
N stage			
N0	59 (72.0)	56 (68.3)	0.75
N1	8 (9.8)	6 (7.3)	
N2	14 (17.1)	18 (22.0)	
N3	1 (1.2)	2 (2.4)	
Size			
<3 cm	48 (58.5)	50 (61.0)	0.94
≥3 cm	30 (36.6)	28 (34.1)	
Unknown	4 (4.9)	4 (4.9)	
Radiation			
None/unknown	70 (85.4)	74 (90.2)	0.47
Yes	12 (14.6)	8 (9.8)	
Chemotherapy			
No/unknown	58 (70.7)	66 (80.5)	0.20
Yes	24 (29.3)	16 (19.5)	
DLN			
No	76 (92.7)	80 (97.6)	0.27
Yes	6 (7.3)	2 (2.4)	
Brain			
No	77 (93.9)	81 (98.8)	0.21
Yes	5 (6.1)	1 (1.2)	
Bone			
No	64 (78.0)	71 (86.6)	0.21
Yes	18 (22.0)	11 (13.4)	
Liver			
No	51 (62.2)	63 (76.8)	0.06
Yes	31 (37.8)	19 (23.2)	
Lung			
No	42 (51.2)	45 (54.9)	0.75
Yes	40 (48.8)	37 (45.1)	
Survival, months	42.46 (36.29)	52.67 (35.31)	0.07

Categorical variables are presented as n (%) and continuous variables are presented as mean ± standard deviation. DLN, distance lymph node; PSM, propensity score matching.

discrepancies in demographics and medical factors between the two groups, including sex, site of primary tumor, year of diagnosis, age, histological grade, T stage, N stage, tumor size, lymph nodes, and metastatic site. There were 82 patients each in the surgical and non-surgical groups after PSM. All covariates had P values above 0.05 post-matching, suggesting that PSM effectively reduced potential selection bias. The baseline data of patients after PSM are shown in *Table 2*.

Analysis of OS and CSS using Cox regression (univariate and multivariate) before PSM in patients

Tables 3,4 illustrate the results of Cox regression analyses (univariate and multivariate) for OS and CSS in patients with metastatic PC before PSM. The multivariate Cox regression model included only variables with P values

Table 3 Univariate and multivariate Cox regression analyses of OS in patients before PSM

Characteristics	N (%)	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Surgery					
No	354 (75.0)				
Yes	118 (25.0)	0.28 (0.19–0.41)	<0.001	0.54 (0.36–0.82)	0.003
Race					
Black	55 (11.7)				
White	396 (83.9)	1.04 (0.69–1.56)	0.86		
Other	21 (4.4)	0.79 (0.36–1.75)	0.56		
Sex					
Female	327 (69.3)				
Male	145 (30.7)	1.74 (1.32–2.28)	<0.001	1.23 (0.91–1.66)	0.18
Site					
Lower lobe	178 (37.7)				
Main bronchus	23 (4.9)				
Middle lobe	58 (12.3)				
Overlapping lesion of lung	5 (1.1)				
Unknown	79 (16.7)				
Upper lobe	129 (27.3)				
Age, years					
<60	144 (30.5)				
60–79	269 (57.0)	1.40 (1.03–1.91)	0.03	1.42 (1.02–1.97)	0.03
80+	59 (12.5)	2.20 (1.45–3.34)	<0.001	2.90 (1.80–4.66)	<0.001
Year					
2010–2014	174 (36.9)				
2015–2020	298 (63.1)	1.61 (1.20–2.16)	0.002	1.39 (1.01–1.90)	0.045
Grade					
I/II	202 (42.8)				
III/IV	15 (3.2)	3.71 (1.97–6.98)	<0.001	2.14 (1.10–4.16)	0.02
Unknown	255 (54.0)	1.63 (1.24–2.16)	<0.001	1.41 (1.05–1.90)	0.02
Size					
<3 cm	231 (48.9)				
≥3 cm	193 (40.9)	1.95 (1.47–2.57)	<0.001	1.34 (0.98–1.83)	0.06
Unknown	48 (10.2)	1.63 (1.03–2.57)	0.03	1.23 (0.77–1.98)	0.39
T stage					
T1	97 (20.6)				
T2	90 (19.1)	1.35 (0.90–2.00)	0.14		
T3	114 (24.2)	0.83 (0.56–1.22)	0.33		
T4	171 (36.2)	0.92 (0.64–1.32)	0.63		

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	N (%)	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
N stage					
N0	249 (52.8)				
N1	38 (8.1)	2.28 (1.43–3.63)	<0.001	1.64 (1.00–2.70)	0.050
N2	141 (29.9)	3.23 (2.39–4.36)	<0.001	2.14 (1.54–2.97)	<0.001
N3	44 (9.3)	3.34 (2.15–5.17)	<0.001	1.41 (0.87–2.30)	0.16
Radiation					
None/unknown	372 (78.8)				
Yes	100 (21.2)	2.21 (1.66–2.95)	<0.001	1.06 (0.74–1.51)	0.74
Chemotherapy					
No/unknown	308 (65.3)				
Yes	164 (34.7)	2.25 (1.72–2.93)	<0.001	1.29 (0.93–1.78)	0.12
DLN					
No	435 (92.2)				
Yes	37 (7.8)	1.35 (0.83–2.18)	0.22		
Brain					
No	419 (88.8)				
Yes	53 (11.2)	3.41 (2.39–4.88)	<0.001	2.11 (1.37–3.24)	0.001
Bone					
No	341 (72.2)				
Yes	131 (27.8)	2.22 (1.67–2.95)	<0.001	1.50 (1.11–2.04)	0.009
Liver					
No	317 (67.2)				
Yes	155 (32.8)	2.00 (1.53–2.62)	<0.001	1.26 (0.92–1.73)	0.14
Lung					
No	290 (61.4)				
Yes	182 (38.6)	0.65 (0.50–0.86)	0.003	1.03 (0.75–1.42)	0.86

n=472, events =225, likelihood ratio test =167.45 on 18 df (P<0.001). CI, confidence interval; DLN, distance lymph node; HR, hazard ratio; OS, overall survival; PSM, propensity score matching.

below 0.05 in univariate analysis. Surgery was identified as an independent prognostic determinant for OS (P=0.003) and CSS (P=0.007) in metastatic PC patients, as indicated by the results of multivariate Cox regression analysis. In addition, age exceeding 80 years, histologic grade 3 or 4, N2 stage, brain metastasis, and bone metastasis were all identified as independent factors affecting OS and CSS. Being between 60 and 79 years old was identified as a significant predictor of OS (P=0.03) but did not show the same impact on CSS (P=0.09). Tumor sizes ≥3 cm (P=0.02) and N1 (P=0.02) were identified as predictors of CSS but did not show the same impact on OS (P=0.06, P=0.050). Race, sex, primary tumor site, year of diagnosis, T stage, lymph node dissection, and postoperative adjuvant therapy were not associated with patient prognosis.

Survival outcomes and CSS before PSM

The K-M survival curves for OS and CSS in patients before PSM are shown in *Figure 2* and *Figure 3*, respectively, with

Table 4 Univariate and multivariate Cox regression analysis of CSS in patients before PSM

Characteristics	N (%)	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Surgery					
No	354 (75.0)				
Yes	118 (25.0)	0.25 (0.16–0.39)	<0.001	0.51 (0.31–0.83)	0.007
Race					
Black	55 (11.7)				
White	396 (83.9)	1.09 (0.69–1.74)	0.71		
Other	21 (4.4)	1.03 (0.46–2.35)	0.93		
Sex					
Female	327 (69.3)				
Male	145 (30.7)	1.79 (1.32–2.43)	<0.001	1.08 (0.77–1.50)	0.65
Site					
Lower lobe	178 (37.7)				
Main bronchus	23 (4.9)				
Middle lobe	58 (12.3)				
Overlapping lesion of lung	5 (1.1)				
Unknown	79 (16.7)				
Upper lobe	129 (27.3)				
Age, years					
<60	144 (30.5)				
60–79	269 (57.0)	1.32 (0.94–1.84)	0.10	1.35 (0.95–1.92)	0.09
80+	59 (12.5)	1.63 (1.00–2.66)	0.050	2.37 (1.36–4.12)	0.002
Year					
2010–2014	174 (36.9)				
2015–2020	298 (63.1)	1.33 (0.97–1.83)	0.07		
Grade					
I/II	202 (42.8)				
III/IV	15 (3.2)	4.71 (2.47–8.98)	<0.001	2.50 (1.26–4.93)	0.009
Unknown	255 (54.0)	1.77 (1.29–2.42)	<0.001	1.36 (0.97–1.91)	0.07
Size					
<3 cm	231 (48.9)				
≥3 cm	193 (40.9)	2.39 (1.75–3.27)	<0.001	1.48 (1.04–2.09)	0.02
Unknown	48 (10.2)	1.71 (1.01–2.88)	0.04	1.38 (0.81–2.37)	0.23
T stage					
T1	97 (20.6)				
T2	90 (19.1)	1.36 (0.88–2.10)	0.16		
T3	114 (24.2)	0.84 (0.54–1.29)	0.41		
T4	171 (36.2)	0.86 (0.57–1.29)	0.47		

Table 4 (*continued*)

Table 4 (*continued*)

Characteristics	N (%)	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
N stage					
N0	249 (52.8)				
N1	38 (8.1)	2.84 (1.69–4.74)	<0.001	1.84 (1.07–3.18)	0.02
N2	141 (29.9)	4.22 (2.99–5.95)	<0.001	2.46 (1.69–3.57)	<0.001
N3	44 (9.3)	4.27 (2.63–6.92)	<0.001	1.65 (0.96–2.82)	0.68
Radiation					
None/unknown	372 (78.8)				
Yes	100 (21.2)	2.84 (2.10–3.85)	<0.001	1.14 (0.79–1.65)	0.48
Chemotherapy					
No/unknown	308 (65.3)				
Yes	164 (34.7)	2.88 (2.15–3.87)	<0.001	1.38 (0.97–1.97)	0.72
DLN					
No	435 (92.2)				
Yes	37 (7.8)	1.47 (0.88–2.46)	0.14		
Brain					
No	419 (88.8)				
Yes	53 (11.2)	4.03 (2.79–5.84)	<0.001	2.28 (1.45–3.57)	<0.001
Bone					
No	341 (72.2)				
Yes	131 (27.8)	2.43 (1.78–3.31)	<0.001	1.61 (1.16–2.23)	0.004
Liver					
No	317 (67.2)				
Yes	155 (32.8)	2.29 (1.70–3.07)	<0.001	1.37 (0.98–1.92)	0.06
Lung					
No	290 (61.4)				
Yes	182 (38.6)	0.53 (0.38–0.73)	<0.001	0.90 (0.63–1.30)	0.58

n=472, events =182, likelihood ratio test =173.63 on 17 df (P<0.001). CI, confidence interval; CSS, cancer-specific survival; DLN, distance lymph node; HR, hazard ratio; PSM, propensity score matching.

significant differences in P values (P<0.001, P<0.001). Patients who underwent surgery had notably improved OS and CSS compared to those who did not receive surgery.

Analysis of OS and CSS using Cox regression (univariate and multivariate) after PSM in patients

Tables 5,*6* illustrate the results of Cox regression analyses (univariate and multivariate) for OS and CSS in patients with metastatic PC after PSM. The multivariate Cox regression model included only variables that demonstrated statistical significance with a P value less than 0.05 in univariate analyses. N2 was identified as an independent predictor for OS and CSS (P=0.001, P<0.001) in patients with metastatic PC based on the outcome analysis using multivariate Cox regression. Surgery (P=0.02) was an independent predictor for OS, while it did not show significance for CSS (P=0.11). T2 (P=0.01), T3 (P=0.02), T4 (P<0.001), N3 (P=0.02), chemotherapy (P=0.01), and bone metastasis (P=0.02) were independent predictors for

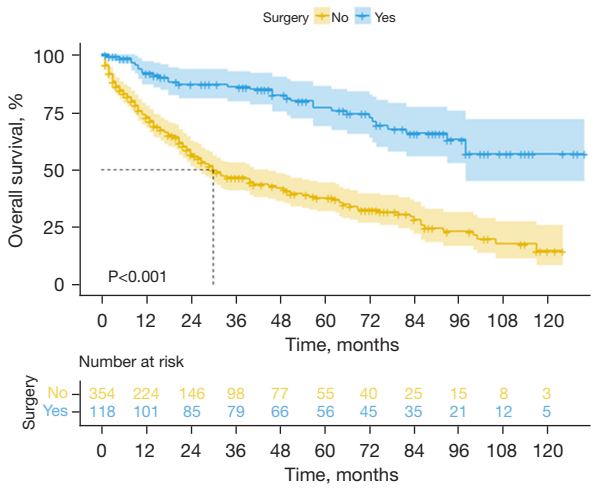

Figure 2 Overall survival of patients with metastatic pulmonary carcinoid tumors before propensity score matching.

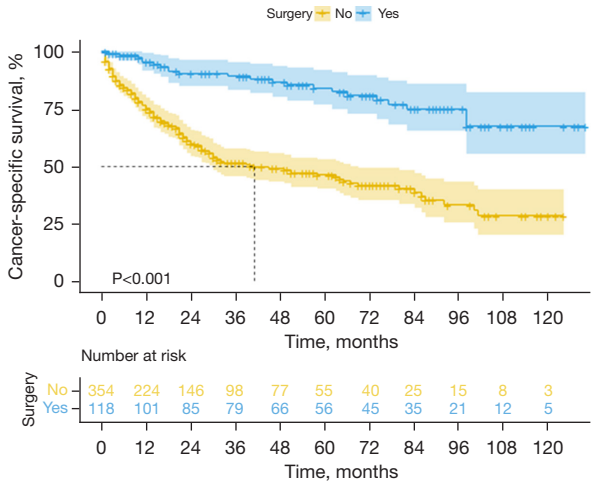

Figure 3 Cancer-specific survival of patients with metastatic pulmonary carcinoid tumors before propensity score matching.

CSS but not for OS. Race, sex, primary tumor site, age, year of diagnosis, histological grade, tumor size, T stage, lymph node dissection, and postoperative adjuvant therapy were not associated with patient prognosis.

Survival outcomes and CSS after PSM

Figures 4,5 illustrate the K-M survival curves of OS and CSS in patients after PSM, and P values exhibited significant differences (P=0.02, P=0.02). Patients who received surgery showed significantly enhanced OS and CSS in contrast to those who did not undergo surgery.

Discussion

The incidence of TC in the U.S. is 0.77 per 100,000 individuals, while the incidence of AC is 0.22 per 100,000 individuals (8). Over the last thirty years, there has been a significant rise of 6% each year in the number of PC cases, as reported by the SEER database (25). The behavior of PC, a neuroendocrine tumor, is relatively passive when compared to lung adenocarcinoma or squamous cell carcinoma (26). The primary approach for treating early-stage PC involves complete surgical removal while saving as much healthy lung tissue as possible. A study has demonstrated high five-year survival rates of 94% and 67% for TC and AC, respectively (27).

Upon diagnosis, 24% of individuals with metastatic disease present with pulmonary symptoms such as cough, hemoptysis, pain, atelectasis, or lung infection (28). In North American registries, the 5-year survival rate for patients with metastatic pancreatic cancer stands at 27% (10), and the optimal approach to managing the tumor site for many other neuroendocrine tumors, including the role of surgical resection of the primary tumor, is a subject of debate. This is connected to the gradual development of PC and its ability to secrete substances, potentially impacting QoL through conditions like sepsis or cardiac carcinoid syndrome. Retrospective research has explored the effectiveness of removing the primary tumor in cases of small bowel (29) or pancreatic neuroendocrine tumors. Yet, based on our understanding, there is a scarcity of research on surgery for the primary tumor in metastatic PC.

No curative treatment is available for metastatic PC, and adjuvant therapy has no clear effect on patients with advanced PC. There is a lack of extensive prospective studies demonstrating advantages in contrast to non-small cell lung cancer (NSCLC). There are conflicting suggestions in guidelines about the use of adjuvant therapy for N2-positive AC, with some noting the lack of data (30). Insufficient information leads other recommendations to advise against the application of adjuvant therapy for all stages (31). The current research findings align with the idea that radiotherapy and chemotherapy did not independently impact patient survival rates in the study, as indicated by multifactorial Cox regression analysis after PSM (P=0.80 for radiotherapy and P=0.12 for chemotherapy). The main objectives in late-stage illness are to manage both tumor progression and symptoms. Treatment approaches are commonly shaped by past encounters with neuroendocrine

Table 5 Univariate and multivariate Cox regression analysis of OS in patients after PSM

Characteristics	N (%)	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Surgery					
No	82 (50.0)				
Yes	82 (50.0)	0.55 (0.32–0.93)	0.02	0.51 (0.29–0.93)	0.02
Race					
Black	12 (7.3)				
White	140 (85.4)	1.64 (0.51–5.25)	0.40		
Other	12 (7.3)	1.45 (0.32–6.52)	0.62		
Sex					
Female	128 (78.0)				
Male	36 (22.0)	1.38 (0.75–2.57)	0.30		
Site					
Lower lobe	61 (37.2)				
Main bronchus	6 (3.7)				
Middle lobe	27 (16.5)				
Overlapping lesion of lung	2 (1.2)				
Unknown	29 (17.7)				
Upper lobe	39 (23.8)				
Age, years					
<60	66 (40.2)				
60–79	94 (57.3)	1.28 (0.74–2.22)	0.37		
80+	4 (2.4)	0.85 (0.11–6.41)	0.87		
Year					
2010–2014	79 (48.2)				
2015–2020	85 (51.8)	1.02 (0.56–1.88)	0.94		
Grade					
I/II	79 (48.2)				
III/IV	2 (1.2)	2.92 (0.39–21.94)	0.29		
Unknown	83 (50.6)	1.52 (0.89–2.60)	0.12		
Size					
<3 cm	98 (59.8)				
≥3 cm	58 (35.4)	1.22 (0.70–2.14)	0.48		
Unknown	8 (4.9)	1.56 (0.55–4.40)	0.40		
T stage					
T1	26 (15.9)				
T2	26 (15.9)	0.92 (0.37–2.28)	0.86		
T3	57 (34.8)	1.10 (0.53–2.27)	0.80		
T4	55 (33.5)	0.45 (0.19–1.04)	0.06		

Table 5 (*continued*)

Table 5 (*continued*)

Characteristics	N (%)	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
N stage					
N0	115 (70.1)				
N1	14 (8.5)	3.92 (1.84–8.33)	<0.001	1.96 (0.81–4.79)	0.13
N2	32 (19.5)	3.62 (1.98–6.62)	<0.001	3.32 (1.63–6.77)	0.001
N3	3 (1.8)	4.18 (0.99–17.63)	0.052	3.96 (0.79–19.96)	0.09
Radiation					
None/unknown	144 (87.8)				
Yes	20 (12.2)	2.65 (1.43–4.93)	0.002	1.12 (0.45–2.80)	0.80
Chemotherapy					
No/unknown	124 (75.6)				
Yes	40 (24.4)	3.72 (2.20–6.30)	<0.001	1.85 (0.84–4.04)	0.12
DLN					
No	156 (95.1)				
Yes	8 (4.9)	0.84 (0.20–3.43)	0.80		
Brain					
No	158 (96.3)				
Yes	6 (3.7)	5.19 (2.03–13.27)	<0.001	2.22 (0.63–7.82)	0.21
Bone					
No	135 (82.3)				
Yes	29 (17.7)	2.53 (1.35–4.77)	0.004	1.53 (0.72–3.24)	0.26
Liver					
No	114 (69.5)				
Yes	50 (30.5)	2.89 (1.65–5.04)	<0.001	1.11 (0.53–2.34)	0.78
Lung					
No	87 (53.0)				
Yes	77 (47.0)	0.50 (0.30–0.86)	0.01	0.82 (0.44–1.53)	0.54

n=164, events =58, likelihood ratio test =44.81 on 10 df (P<0.001). CI, confidence interval; DLN, distance lymph node; HR, hazard ratio; PSM, propensity score matching.

tumors in the gastrointestinal or pancreatic areas (32). Octreotide or lanreotide is frequently advised for severe cases due to the common occurrence of somatostatin receptors (SSTRs) in PC (5,30,31).

Therefore, it is important to assess how well surgical procedures work for this group of patients. The study investigated the survival prospects of patients with metastatic PC who had surgery as opposed to those receiving no surgery, utilizing data from the SEER database. In our study, 79.45% of patients who underwent surgical intervention had a tumor T-stage of ≥T2, and 47.2% had an N-stage of ≥N1. Prior research has indicated that approximately 30% of patients are asymptomatic at presentation (33). This can be attributed to the fact that symptoms in patients with PC often manifest at more advanced stages. Our multifactorial Cox regression analysis demonstrated that OS was comparable across different T-stages, corroborating the findings of Yaldız *et al.* that the size of the tumor was not a strong indicator of prognosis (34,35). Regarding the N-stage, the hazard ratio (HR) increased with higher

Table 6 Univariate and multivariate Cox regression analysis of CSS in patients after PSM

Characteristics	N (%)	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Surgery					
No	82 (50.0)				
Yes	82 (50.0)	0.51 (0.28–0.94)	0.03	0.57 (0.28–1.15)	0.11
Race					
Black	12 (7.3)				
White	140 (85.4)	1.95 (0.47–8.08)	0.35		
Other	12 (7.3)	2.33 (0.43–12.75)	0.33		
Sex					
Female	128 (78.0)				
Male	36 (22.0)	1.73 (0.89–3.36)	0.10		
Site					
Lower lobe	61 (37.2)				
Main bronchus	6 (3.7)				
Middle lobe	27 (16.5)				
Overlapping lesion of lung	2 (1.2)				
Unknown	29 (17.7)				
Upper lobe	39 (23.8)				
Age, years					
<60	66 (40.2)				
60–79	94 (57.3)				
80+	4 (2.4)				
Year					
2010–2014	79 (48.2)				
2015–2020	85 (51.8)	0.91 (0.47–1.78)	0.78		
Grade					
I/II	79 (48.2)				
III/IV	2 (1.2)	3.06 (0.40–23.11)	0.27		
Unknown	83 (50.6)	1.28 (0.71–2.33)	0.41		
Size					
<3 cm	98 (59.8)				
≥3 cm	58 (35.4)	1.65 (0.89–3.05)	0.10		
Unknown	8 (4.9)	1.71 (0.51–5.67)	0.38		
T stage					
T1	26 (15.9)				
T2	26 (15.9)	0.84 (0.33–2.15)	0.72	0.26 (0.09–0.77)	0.01
T3	57 (34.8)	0.86 (0.40–1.83)	0.69	0.36 (0.15–0.87)	0.02
T4	55 (33.5)	0.23 (0.08–0.63)	0.004	0.10 (0.03–0.30)	<0.001

Table 6 (*continued*)

Table 6 (*continued*)

Characteristics	N (%)	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
N stage					
N0	115 (70.1)				
N1	14 (8.5)	5.78 (2.59–12.90)	<0.001	1.83 (0.67–4.99)	0.24
N2	32 (19.5)	4.86 (2.45–9.66)	<0.001	5.11 (2.19–11.96)	<0.001
N3	3 (1.8)	6.20 (1.43–26.86)	0.01	9.13 (1.38–60.47)	0.02
Radiation					
None/unknown	144 (87.8)				
Yes	20 (12.2)	3.63 (1.90–6.93)	<0.001	1.50 (0.57–3.96)	0.41
Chemotherapy					
No/unknown	124 (75.6)				
Yes	40 (24.4)	5.48 (3.02–9.93)	<0.001	3.14 (1.27–7.74)	0.01
DLN					
No	156 (95.1)				
Yes	8 (4.9)	1.07 (0.26–4.43)	0.92		
Brain					
No	158 (96.3)				
Yes	6 (3.7)	6.36 (2.45–16.53)	<0.001	1.91 (0.48–7.64)	0.36
Bone					
No	135 (82.3)				
Yes	29 (17.7)	2.96 (1.51–5.82)	0.002	2.53 (1.10–5.81)	0.02
Liver					
No	114 (69.5)				
Yes	50 (30.5)	3.60 (1.94–6.69)	<0.001	0.92 (0.38–2.23)	0.85
Lung					
No	87 (53.0)				
Yes	77 (47.0)	0.38 (0.20–0.71)	0.002	0.76 (0.37–1.56)	0.45

n=164, events =45, likelihood ratio test =73.04 on 13 df (P<0.001). CI, confidence interval; CSS, cancer-specific survival; DLN, distance lymph node; HR, hazard ratio; PSM, propensity score matching.

N-stages in the Cox regression analysis. Aydin *et al.* and Yaldız *et al.* also highlighted the importance of considering lymph node involvement as a key factor that influences long-term survival outcomes (34,36). Furthermore, we discovered that in this cohort, bone metastasis became a significant predictor of CSS following PSM, while metastasis from other sites did not demonstrate the same significance—a result in alignment with a previous study (35). Interestingly, while in certain reviews of NSCLC cases, it was noted that those with liver metastases had the least favorable prognosis, and our findings revealed that, following PSM, patients with bone metastases exhibited worse CSS compared to those with liver metastases. This conclusion aligns with the findings of Zhang *et al.* (35), suggesting that liver metastases in patients with PC may be more amenable to complete surgical resection compared to bone metastases.

Moreover, study results suggest that undergoing surgery following PSM independently influences OS in these individuals. OS and CSS were enhanced in patients receiving surgery compared to those who did not, both pre-

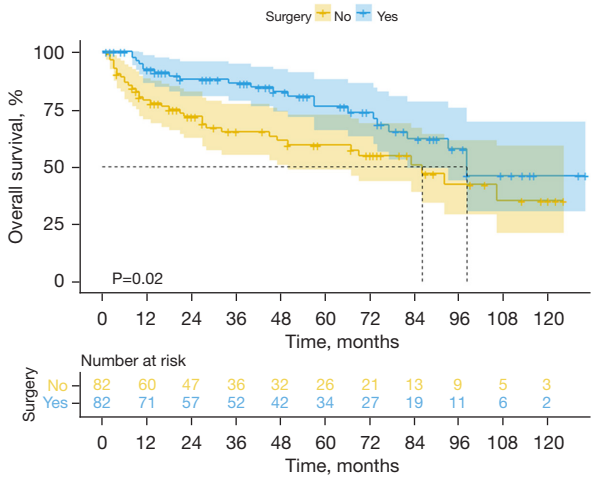

Figure 4 Overall survival of patients with metastatic pulmonary carcinoid tumors after propensity score matching.

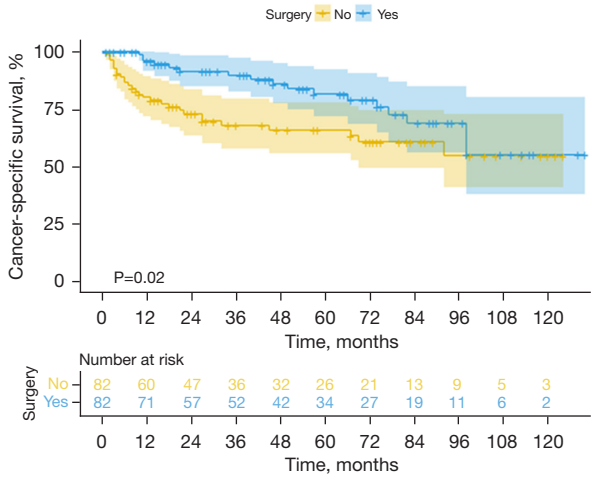

Figure 5 Cancer-specific survival of patients with metastatic pulmonary carcinoid tumors after propensity score matching.

and post-PSM. Surgery notably relieved lung symptoms and was more efficacious in the management of carcinoid syndrome in patients with PC compared to no surgery. The removal of the primary tumor may lead to the resolution of the obstruction in the bronchial tubes, which in turn could alleviate symptoms like cough, infection, collapsed lung, and coughing up blood. It might also help in reducing the tumor burden that circulates in the body, thereby lowering the chances of carcinoid syndrome. The results hold substantial clinical significance for patients with PC, as many individuals can achieve prolonged survival even in the metastatic stage (37). These findings further demonstrate the value of primary tumor resection in patients with metastatic PC.

This study has several limitations that warrant consideration. Firstly, due to its retrospective design, the study is subject to inherent biases, including selection bias and information bias. Our team is working on conducting prospective studies to further validate the conclusions presented herein. However, the rarity of PC poses a significant challenge and necessitates a longer preparation period. Secondly, the SEER database, which primarily collects data on cancer incidence and survival in the United States, includes only a small proportion of the Asian population. This introduces heterogeneity within the patient cohort, and it remains unclear whether the findings of this study are fully generalizable to domestic populations in China. Thirdly, the inherent limitations of the SEER database may have prevented us from comprehensively accounting for certain confounding factors or biases. Lastly, while this study highlights the survival benefit of primary tumor resection in patients with metastatic PC, it does not explore the impact of specific surgical techniques or chemotherapy on patient outcomes. The low incidence of PC and the even rarer occurrence of metastatic cases limit the sample size available for analysis. After PSM, each of the surgical and non-surgical groups comprised 82 patients, which is insufficient to support further subgroup or categorical analyses.

Conclusions

The prognostic importance of surgical intervention in PC patients was clarified through the PSM study using SEER database data. Surgical resection at the primary site has been shown to significantly enhance the OS and CSS in this population. Therefore, aggressive surgical management should be considered for individuals with metastatic PC. In any case, more randomized controlled trials are essential to analyze the efficacy and proper indications for surgery in these specific patients.

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None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2024-1935/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-2024-1935/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 and its subsequent amendments.

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