Prognostic factors in resected pulmonary carcinoid tumors: A retrospective study with 10 years of follow-up

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Abstract. The objective of the present study was to characterize the difference in 10-year carcinoid-specific survival (CSS) and disease-free survival (DFS) among patients with resected pulmonary typical carcinoid (TC) and atypical carcinoid (AC). Patients diagnosed with pulmonary carcinoid tumors (PCT) between January 1, 1997, and December 31, 2016, were identified. All patients underwent video-assisted thoracoscopic surgery or thoracotomy with thoracic lymphadenectomy. Cumulative CSS was estimated using the Kaplan-Meier model. The analysis of hazard ratios (HRs) and 95% confidence intervals (CIs) was performed using univariate and multivariate Cox proportional hazards models. A total of 404 patients with PCT were included in the present study. The 10-year CSS and DFS rates of patients with AC were significantly worse than those of patients with TC (49.1 vs. 86.8% and 52.2 vs. 92.6%, respectively; P<0.001). In the CSS multivariate analysis, older age and lymph node involvement (HR, 2.45; P=0.022) were associated with worse survival in AC, while age, male sex, M1 stage, cigarette smoking and inadequate N2 lymphadenectomy were associate with worse survival in TC. In the recurrence multivariate analysis, N1-3 stage (HR, 2.62; 95% CI, 1.16-5.95; P=0.018) and inadequate N2 lymphadenectomy (HR, 2.13; 95% CI, 1.04-4.39; P=0.041) were associated with an increase in recurrence in AC, while male sex (HR, 3.72; 95% CI, 1.33-10.42; P=0.010) and M1 stage (HR, 14.93; 95% CI, 4.77-46.77; P<0.001) were associated with an increase in recurrence in TC. In conclusion, patients with AC tumors had significantly worse CSS and DFS rates compared with patients with TC. The degree of nodal involvement in AC was a prognostic marker, in contrast to that in TC. Inadequate lymphadenectomy increased the risk of recurrence in AC and mortality in TC, although surgical approaches did not have a significant impact. The present study therefore emphasizes the importance of mediastinal nodal dissection in patients with PCTs.

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Key words: pulmonary carcinoid tumor, typical carcinoid, atypical carcinoid, prognostic factors, surgery, lymphadenectomy

Introduction

Neuroendocrine tumors (NETs) are a spectrum of malignancies that originate from the neuroendocrine Kulchitsky cells located in the bronchial epithelium (1). These tumors have distinct patterns of behavior, ranging from indolent to highly aggressive patterns, and include large cell neuroendocrine carcinoma and small cell lung cancer (SCLC). Among the NETs, pulmonary carcinoid tumors (PCTs) are a rare subgroup of tumors with an estimated age-adjusted incidence of 1.35 cases per 100,000 individuals in the USA (2), accounting for 20-25% of all NETs. The World Health Organization classifies PCTs into two subtypes depending on the microscopic findings of mitosis and necrosis (3). Typical carcinoid (TC) has fewer than 2 mitoses per 2 mm^2 and a lack of necrosis, while atypical carcinoid (AC) has 2-10 mitoses per 2 mm^2 and/or foci of necrosis.

As surgical resection remains the mainstay of treatment for PCT, multiple retrospective studies can be found in the literature reporting the outcomes of these patients, as well as therapeutic and prognostic factors that are implicated with disease outcomes (1,3). However, PCTs have patterns of

biological behavior that are different in comparison to other types of non-SCLC (NSCLC), and due to this, the surgical approach, in general, can be more aggressive for PCT than for other types of NSCLC. For example, surgery for concomitant N2 disease and resection for patients with distant metastatic disease can be considered more often in PCT than in NSCLC. Additionally, the long-term prognosis of patients with PCT, as well as the effect of adjuvant therapies, under these circumstances is not entirely clear and needs to be better evaluated. The pattern of recurrence (local, regional and distant) for PCT is also different, considering the latency of these tumors. Hence, the relationship between these patterns and survival outcomes should be further analyzed through long-term follow-up.

There has been a lack of clinical data in these subgroups of patients, thus making identification of prognostic factors and treatment recommendations challenging, since there have been a number of inconsistent findings regarding the prognostic factors associated with recurrence and survival in patients with resected PCT, especially in those cases that are considered as advanced disease. Due to these challenges, a retrospective study was conducted of the Health Science Research (HSR) Study Data Management System (Mayo Clinic, AZ, USA) to characterize the prognostic factors associated with recurrence, survival in resected PCT tumors and the effect of adjuvant therapies.

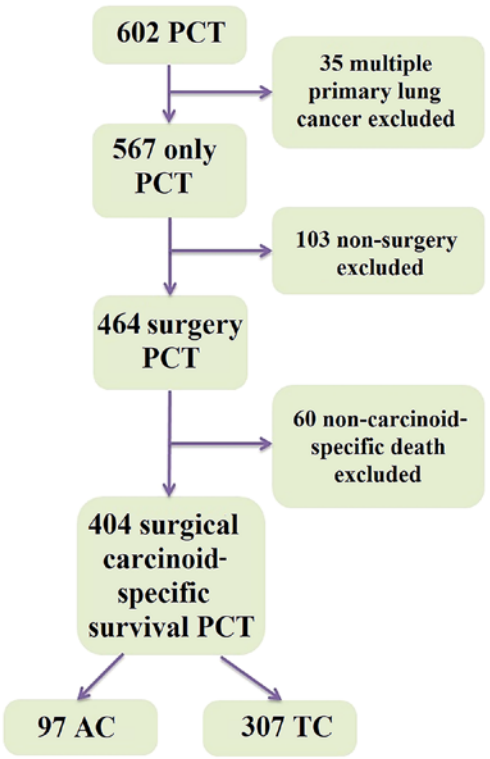

Figure 1. Selection of patients with PCT. AC, atypical carcinoid; PCT, pulmonary carcinoid tumors; TC, typical carcinoid.

Patients and methods

Patients and protocols. Patients with resected PCT were analyzed. All patients underwent video-assisted thoracoscopic surgery or thoracotomy with thoracic lymphadenectomy. Data for patients histologically diagnosed with PCT between January 1, 1997, and December 31, 2016, were retrieved from the lung cancer cohort, where all primary lung cancer patients has been enrolled and followed prospectively (4). Patients with multiple primary lung cancer, non-surgical treatment and non-carcinoid specific death were excluded. Eventually, 404 patients were included in the study. The selection of patients with PCT is shown in Fig. 1.

The clinicopathological characteristics of the patients were collected, including age, sex, BMI, Tumor-Node-Metastasis (TNM) stage, tumor size, tumor lobe location, smoking status, family history of cancer, surgical type and comorbidity. Patients were restaged according to the eighth edition of the TNM staging system of the American Joint Committee on Cancer (5). Classification of smoking was based on the Adult Tobacco Use Information in National Health Interview Survey (6). Adequate mediastinal lymphadenectomy consisted of node resection and mapping (American Thoracic Society map) of at least three N2 groups (7). For the purposes of the present study, if the number of assessed N2 groups was <3, then this was defined as inadequate mediastinal lymphadenectomy. The diagnosis of recurrence was made with a combination of CT images, and/or biopsy of the new suspected site of disease. The survival data of each patient was collected through electronic medical notes, registration database, next-of-kin reports, death certificates, obituary documents filed in the patients' medical records, The Mayo Clinic Institutional Tumor Registry and the Social Security Death Index website (https://socialsecuritydeath-index-search.com).

Statistical analysis. The nominal categorical variables were analyzed by the χ^2 test. The continuous variables were reported as the median and interquartile range, and were evaluated by the unpaired independent sample t-test. For the carcinoid-specific survival (CSS) analysis, the date of cancer-specific death from PCT was the observation endpoint. For the disease-free survival (DFS) analysis, the date of recurrence was the endpoint of observation. Endpoints were analyzed as time-to-event data from the date of surgery to the respective events, which were subject to censoring at the last follow-up if no events were observed. The cumulative survival was estimated using the Kaplan-Meier model and log-rank test. The analysis of hazard ratios (HRs) and 95% confidence intervals (CIs) was performed using univariate (log-rank) and multivariate Cox proportional hazards models. Factors with a P-value of <0.1 in the Cox univariate analysis (log-rank) were included in the multivariate analysis. For all other statistical analyses, P<0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using SAS 9.3 (SAS Institute, Inc.).

Results

Characteristics of PCT. Of the 404 patients with PCT included in the present study, 307 (76.0%) consisted of TC and 97 (24.0%) of AC. The median follow-up time was 89.7 months (range, 57.5-142.3 months). Patients with AC, compared with patients with TC, were older [median age, 62.0 years

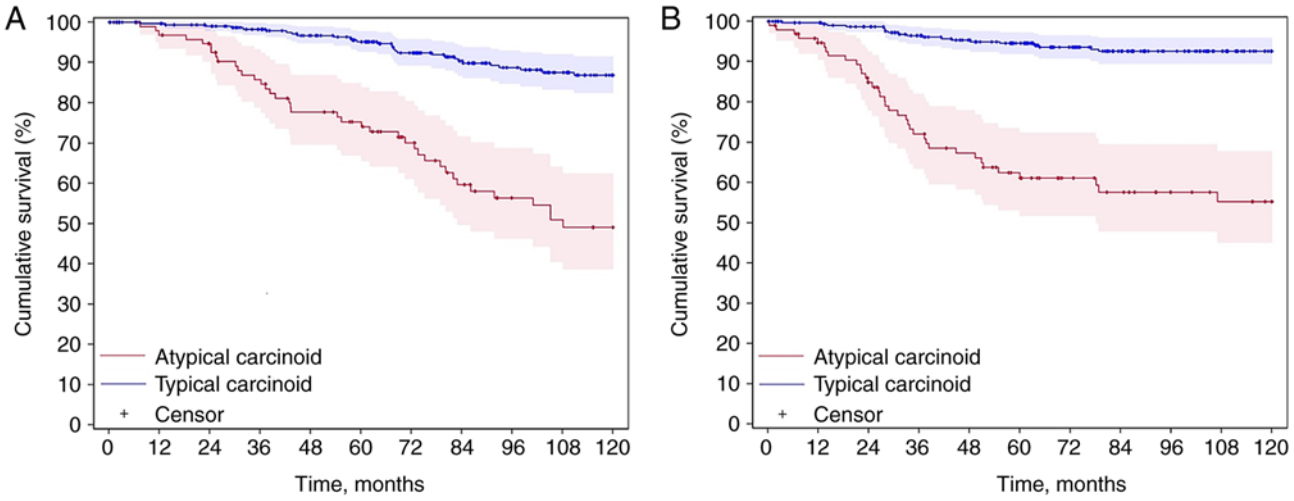

Figure 2. Survival of patients with pulmonary carcinoid tumors. (A) The 10-year carcinoid-specific survival Kaplan-Meier curve (AC vs. TC, 49.1 vs. 86.8%, respectively; P<0.001). (B) The 10-year disease-free survival Kaplan-Meier curve (AC vs. TC, 55.2 vs. 92.6%, respectively; P<0.001). AC, atypical carcinoid; TC, typical carcinoid.

(51.0-70.0 years) vs. 57.0 years (range, 47.0-67.0 years), respectively; P=0.027], with more stage IIIB-IVA cases [IIIB-IVA, 10 (10.3%) vs. 9 (2.9%) respectively; P=0.003], more lymph node involvement [N1-3, 40 (41.2%) vs. 52 (16.9%), respectively; P<0.001], and more distant metastasis [M1, 7 (7.2%) vs. 7 (2.3%), respectively; P=0.021]. The AC subgroup also underwent more extensive surgical resections than the TC subgroup [pneumonectomy, 10 (10.3%) vs. 6 (2.0%); bi-lobectomy, 7 (7.2%) vs. 15 (4.9%); P<0.001]. The recurrence rate was higher in patients with AC compared with that in patients with TC [38 (39.2%) vs. 19 (6.2%); P<0.001]. Baseline characteristics and surgical treatment details are provided in Table I.

CSS analysis. The CSS of AC was inferior to that of TC; the 10-year CSS rates were 49.1 vs. 86.8% (P<0.001), respectively (Fig. 2A). Univariate and multivariate analyses are found in Table II. For AC, univariate analysis of CSS revealed that age (HR, 1.03; 95% CI, 1.00-1.05; P=0.002), N1-3 stage (HR, 2.39; 95% CI, 1.34-4.26; P=0.002), M1 stage (HR, 2.59; 95% CI, 1.09-6.15; P=0.025), family history of lung cancer (HR, 0.16; 95% CI, 0.02-1.20; P=0.042), pneumonectomy/bi-lobectomy (HR, 2.18; 95% CI, 1.08-4.42; P=0.086) and inadequate N2 lymphadenectomy (HR, 1.78; 95% CI, 0.99-3.22; P=0.049) were all P<0.10 so were included in the multivariate analysis. For the multivariate analysis, age (HR, 1.04; 95% CI, 1.01-1.07; P=0.001) and N1-3 stage (HR, 2.45; 95% CI, 1.14-5.30; P=0.022) were independent risk factors. For TC, univariate analysis of CSS determined that age (HR, 1.06; 95% CI, 1.04-1.09; P<0.001), male sex (HR, 1.86; 95% CI, 1.06-3.26; P=0.028), T2-4 stage (HR, 1.70; 95% CI, 0.94-3.09; P=0.077), N1-3 stage (HR, 2.23; 95% CI, 1.15-4.35; P=0.015), M1 stage (HR, 9.99; 95% CI, 4.42-22.66; P<0.001), upper lobe location (HR, 1.25; 95% CI, 0.68-2.30; P=0.086), cigarette smoking [former smoker (HR, 2.13; 95% CI, 1.15-3.95); current smoker (HR, 1.86; 95% CI, 0.81-4.27); P=0.044] and inadequate N2 lymphadenectomy (HR, 3.14; 95% CI, 1.74-5.66; P<0.001) were all P<0.10 so were included in the multivariate analysis. For the multivariate analysis, age (HR, 1.07; 95% CI, 1.04-1.10; P<0.001), male sex (HR, 2.03; 95% CI, 1.10-3.75; P=0.026), M1 stage (HR, 4.63; 95% CI, 1.73-12.38; P=0.005), cigarette smoking [former smoker (HR, 2.14; 95% CI, 1.12-4.11); current smoker (HR, 2.50; 95% CI, 1.03-6.08); P=0.032] and inadequate N2 lymphadenectomy (HR, 3.45; 95% CI, 1.85-6.43; P<0.001) were significant risk factors.

Tumor recurrence analysis. The DFS of AC was inferior to that of TC; the 10-year DFS rates were 55.2 vs. 92.6% (P<0.001), respectively (Fig. 2B). Univariate and multivariate analyses are found in Table III. For AC, the univariate analysis revealed that N1-3 stage (HR, 3.61; 95% CI, 1.86-7.01; P<0.001), M1 stage (HR, 2.51; 95% CI, 0.97-6.46; P=0.049), pneumonectomy/bi-lobectomy (HR, 2.42; 95% CI, 1.15-5.12; P=0.030) and inadequate N2 lymphadenectomy (HR, 1.95; 95% CI, 1.02-3.73; P=0.039) were all P<0.10 so were included in the multivariate analysis. For the multivariate analysis, N1-3 stage (HR, 2.62; 95% CI, 1.16-5.95; P=0.018) and inadequate N2 lymphadenectomy (HR, 2.13; 95% CI, 1.04-4.39; P=0.041) were independent risk factors for recurrence. For TC, the univariate analysis showed that male sex (HR, 4.19; 95% CI, 1.59-11.03; P=0.002), overweight/obese BMI (HR, 0.45; 95% CI, 0.17-1.16; P=0.090), N1-3 stage (HR, 2.42; 95% CI, 0.92-6.36; P=0.065) and M1 stage (HR, 31.22; 95% CI, 10. 95-88.99; P<0.001) were all P<0.10 so were included in the multivariate analysis. For the multivariate analysis, male sex (HR, 3.72; 95% CI, 1.33-10.42; P=0.010) and M1 stage (HR, 14.93; 95% CI, 4.77-46.77; P<0.001) were independent risk factors for recurrence.

Discussion

This was a retrospective study, with the objective to evaluate additional risk factors associated with the survival of patients with resected PCT. To the best of our knowledge, these factors are not entirely clarified and are still a matter for discussion in multidisciplinary tumor boards. Using the HSR Study Data Management System, the patterns of these tumors were analyzed, which typically required a long-term follow-up to verify potential effects on the therapeutic strategies employed

Table I. Characteristics of 404 surgical patients with pulmonary carcinoid tumors.

Characteristics	Atypical carcinoid (n=97)	Typical carcinoid (n=307)	P-value
Median age (interquartile range), years	62.0 (51.0-70.0)	57.0 (47.0-67.0)	0.027
Sex, n (%)			0.442
Female	67 (69.1)	199 (64.8)	
Male	30 (30.9)	108 (35.2)	
BMI, n (%)			0.141
Missing	5 (5.2)	10 (3.2)	
Underweight	2 (2.1)	2 (0.7)	
Normal	28 (28.9)	68 (22.1)	
Overweight	36 (37.1)	111 (36.2)	
Obese	26 (26.8)	116 (37.8)	
T stage, n (%)			0.105
T1	56 (57.7)	216 (70.4)	
T2	30 (30.9)	63 (20.5)	
T3	8 (8.2)	17 (5.5)	
T4	3 (3.1)	11 (3.6)	
N stage, n (%)			<0.001
N0	57 (58.8)	255 (83.1)	
N1	19 (19.6)	25 (8.1)	
N2	20 (20.6)	26 (8.5)	
N3	1 (1.0)	1 (0.3)	
M stage, n (%)			0.021
M0	90 (92.8)	300 (97.7)	
M1	7 (7.2)	7 (2.3)	
TNM stage, n (%)			0.003
I-IIIA	87 (89.7)	298 (97.1)	
IIIB-IVA	10 (10.3)	9 (2.9)	
Tumor side, n (%)			0.744
Left	38 (39.2)	126 (41.0)	
Right	59 (60.8)	181 (59.0)	
Tumor lobe, n (%)			0.487
Upper	36 (37.1)	90 (29.3)	
Middle	16 (16.5)	65 (21.2)	
Lower	43 (44.3)	144 (46.9)	
Main bronchus	2 (2.1)	8 (2.6)	
Smoking status, n (%)			0.337
Never smoker	48 (49.5)	162 (52.8)	
Former smoker	32 (33.0)	109 (35.5)	
Current smoker	17 (17.5)	36 (11.7)	
Family history of lung cancer, n (%)			0.593
No	91 (93.8)	283 (92.2)	
Yes	6 (6.2)	24 (7.8)	
Family history of other cancer, n (%)			0.494
No	69 (71.1)	207 (67.4)	
Yes	28 (28.9)	100 (32.6)	
Surgical type, n (%)			<0.001
Pneumonectomy	10 (10.3)	6 (2.0)	
Bi-lobectomy	7 (7.2)	15 (4.9)	
Lobectomy	61 (62.9)	182 (59.3)	
Sub-lobectomy	17 (17.5)	75 (24.4)	
Sleeve resection	2 (2.1)	29 (9.4)	

Table I. Continued.

Characteristics	Atypical carcinoid (n=97)	Typical carcinoid (n=307)	P-value
N2 lymphadenectomy, n (%)			0.312
Inadequate (<3 groups)	37 (38.1)	100 (32.6)	
Adequate (≥3 groups)	60 (61.9)	207 (67.4)	
Recurrence, n (%)			<0.001
No	59 (60.8)	288 (93.8)	
Yes	38 (39.2)	19 (6.2)	
Comorbidity, n (%)			0.158
Missing	0 (0.0)	2 (0.7)	
No	11 (11.3)	21 (6.8)	
Yes	86 (88.7)	284 (92.5)	

TNM, Tumor-Node-Metastasis.

Table II. Survival analysis of 404 patients with pulmonary carcinoid tumors using univariate and multivariate Cox models.

	Atypical carcinoid (n=97)				Typical carcinoid (n=307)			
	Univariate		Multivariate		Univariate		Multivariate	
Factors	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.03 (1.00-1.05)	0.002	1.04 (1.01-1.07)	0.001	1.06 (1.04-1.09)	<0.001	1.07 (1.04-1.10)	<0.001
Sex		0.946				0.028		0.026
Female	-				-		-	
Male	0.98 (0.51-1.86)				1.86 (1.06-3.26)		2.03 (1.10-3.75)	
BMI[a]		0.419				0.353		
Underweight/ normal	-				-			
Overweight/ obese	0.68 (0.37-1.25)				0.73 (0.38-1.42)			
T stage		0.159		0.483		0.077		0.154
T1	-		-		-		-	
T2-4	1.51 (0.85-2.67)		1.33 (0.60-2.91)		1.70 (0.94-3.09)		1.62 (0.85-3.11)	
N stage		0.002		0.022		0.015		0.092
N0	-		-		-		-	
N1-3	2.39 (1.34-4.26)		2.45 (1.14-5.30)		2.23 (1.15-4.35)		2.06 (0.92-4.60)	
M stage		0.025		0.604		<0.001		0.005
M0	-		-		-		-	
M1	2.59 (1.09-6.15)		1.33 (0.46-3.82)		9.99 (4.42-22.66)		4.63 (1.73-12.38)	
Tumor side		0.852				0.167		
Left	0.95 (0.52-1.70)				1.48 (0.84-2.60)			
Right	-				-			

Table II. Continued.

	Atypical carcinoid (n=97)				Typical carcinoid (n=307)			
	Univariate		Multivariate		Univariate		Multivariate	
Factors	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Tumor lobe		0.506				0.086		0.062
Upper	0.69 (0.36-1.30)				1.25 (0.68-2.30)		2.13 (1.10-4.13)	
Middle/main bronchus	0.78 (0.34-1.76)				0.42 (0.16-1.10)		0.80 (0.28-2.24)	
Lower	-				-		-	
Smoking status		0.740				0.044		0.032
Never smoker	-				-		-	
Former smoker	1.27 (0.67-2.42)				2.13 (1.15-3.95)		2.14 (1.12-4.11)	
Current smoker	1.22 (0.56-2.67)				1.86 (0.81-4.27)		2.50 (1.03-6.08)	
Family history of lung cancer		0.042		0.065		0.921		
No	-		-		-			
Yes	0.16 (0.02-1.20)		0.21 (0.03-1.66)		1.05 (0.42-2.65)			
Family history of other cancer		0.756				0.314		
No	-				-			
Yes	1.10 (0.60-2.00)				0.74 (0.41-1.33)			
Surgery type		0.086		0.148		0.151		
Pneumo/bi-lobectomy	2.18 (1.08-4.42)		2.15 (0.88-5.27)		2.01 (0.77-5.25)			
Lobectomy/ sleeve	-		-		-			
Sub-lobectomy	1.20 (0.56-2.55)		1.50 (0.61-3.71)		1.64 (0.88-3.04)			
N2 Lymphadenectomy		0.049		0.335		<0.001		<0.001
Inadequate	1.78 (0.99-3.22)		1.44 (0.69-3.00)		3.14 (1.74-5.66)		3.45 (1.85-6.43)	
Adequate	-		-		-		-	
Comorbidity		0.925				0.436		
No	1.04 (0.44-2.47)				0.57 (0.14-2.37)			
Yes	-				-			

[a]15 missing BMI were not analyzed using the Cox model. CI, confidence interval; HR, hazard ratio.

and the prognostic factors identified. It was found that the 10-year CSS and DFS rates for patients with TC were 86.8 and 92.6%, respectively. In patients with AC, however, the 10-year CSS and DFS rates were 49.1 and 55.2%, respectively. These findings corroborate the well-known body of evidence in the literature showing that AC carries a worse prognosis compared with TC (1,2).

In the present study, it was also found that age and lymph node involvement were associated with inferior CSS in AC, while age, male sex, distant metastasis, cigarette smoking and

Table III. Recurrence analysis of 404 patients with pulmonary carcinoid tumors using univariate and multivariate Cox models.

	Atypical carcinoid (n=97)				Typical carcinoid (n=307)			
	Univariate		Multivariate		Univariate		Multivariate	
Factors	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.01 (0.98-1.03)	0.173			1.02 (0.98-1.05)	0.292		
Sex		0.842				0.002		0.010
Female	-				-		-	
Male	0.93 (0.46-1.88)				4.19 (1.59-11.03)		3.72 (1.33-10.42)	
BMI[a]		0.116				0.090		0.163
Underweight/ normal	-				-		-	
Overweight/ obese	0.56 (0.28-1.10)				0.45 (0.17-1.16)		0.47 (0.17-1.30)	
T stage		0.422		0.661		0.414		0.663
T1	-		-		-		-	
T2-4	1.30 (0.68-2.46)		0.83 (0.37-1.89)		1.47 (0.58-3.74)		1.26 (0.45-3.53)	
N stage		<0.001		0.018		0.065		0.167
N0	-		-		-		-	
N1-3	3.61 (1.86-7.01)		2.62 (1.16-5.95)		2.42 (0.92-6.36)		2.14 (0.76-5.99)	
M stage		0.049		0.275		<0.001		<0.001
M0	-		-		-		-	
M1	2.51 (0.97-6.46)		1.91 (0.63-5.85)		31.22 (10.95-88.99)		14.93 (4.77-46.77)	
Tumor side		0.726				0.583		
Left	1.12 (0.59-2.14)				14.93 (0.52-3.16)			
Right	-				-			
Tumor lobe		0.198				0.618		
Upper	0.51 (0.24-1.07)				0.74 (0.26-2.13)			
Middle/main bronchus	0.78 (0.33-1.84)				0.55 (0.15-1.98)			
Lower	-				-			
Smoking status		0.809				0.369		
Never smoker	-				-			
Former smoker	1.07 (0.53-2.20)				1.95 (0.72-5.23)			
Current smoker	1.34 (0.56-3.21)				1.90 (0.49-7.34)			
Family history of lung cancer		0.459				0.780		
No	-				-			
Yes	0.59 (0.14-2.44)				1.23 (0.28-5.33)			

Table III. Continued.

	Atypical carcinoid (n=97)				Typical carcinoid (n=307)			
	Univariate		Multivariate		Univariate		Multivariate	
Factors	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Family history of other cancer		0.631				0.934		
No	-				-			
Yes	1.18 (0.60-2.31)				1.04 (0.41-2.65)			
Surgery type		0.030		0.355		0.295		
Pneumo/bi-lobectomy	2.42 (1.15-5.12)		1.88 (0.80-4.41)		1.46 (0.33-6.37)			
Lobectomy/ sleeve	-		-		-			
Sub-lobectomy	0.77 (0.29-2.03)		0.83 (0.28-2.49)		0.37 (0.08-1.60)			
N2 Lymphade-nectomy		0.039		0.041		0.002		0.138
Inadequate	1.95 (1.02-3.73)		2.13 (1.04-4.39)		2.13 (1.54-9.98)		2.12 (0.78-5.79)	
Adequate	-		-		-		-	
Comorbidity		0.485				0.807		
No	1.40 (0.54-3.58)				0.78 (0.10-5.83)			
Yes	-				-			

[a]15 missing BMI were not analyzed using the Cox model. CI, confidence interval; HR, hazard ratio.

inadequate mediastinal lymphadenectomy were associated with worse CSS in TC. Regarding recurrence, lymph node involvement and inadequate mediastinal lymphadenectomy were associated with inferior DFS in AC, while male sex and distant metastasis were associated with inferior DFS in TC. The identified prognostic factors of the present study are similar to those of previous reports in the literature. The average age at the time of diagnosis is ~45 and 55 years for patients with TC and AC, respectively (8,9). Age (<45 years) is an important prognostic factor associated with a good prognosis in PCT (10). Moreover, some studies report a higher prevalence of smoking in patients with AC compared to TC. As previously published, most patients with TC are female and are never-smokers (11,12). Furthermore, it has been reported that the prognosis of female patients with PCT is worse than that of male patients (13).

TC is an indolent malignancy and excellent long-term outcomes can be achieved. The 10-year CSS of 86.8% observed in the present study is very similar to the results previously reported by other groups (14-16). In the present study, the median age of diagnosis was 57.0 years, and the majority of the patients presented with T1 (70.4%) and N0 (83.1%) stage disease. In the cohort, a 16.9% incidence of nodal involvement (8.8% N2-N3) was found, which is very similar to the findings reported by Kneuertz *et al* (17), where ≥10 lymph nodes were evaluated. The impact of nodal involvement in TC remains controversial and, in the present study, it was demonstrated that nodal involvement was an independent prognostic factor for TC prognosis. However, other studies have questioned the prognostic significance of nodal involvement in PCT (18,19). Martini *et al* (14) found no survival difference in patients with N1 or N2 disease. Kneuertz *et al* (17) found nodal involvement to be associated with worse overall survival only in tumors >2 cm. In a study by Lou *et al* (16), only 2% of patients with TC without nodal disease had recurrence, while there was increased recurrence in positive nodal disease following surgery. Regarding the surgical approach, the most common type of procedure in patients with TC in the present study was lobectomy (59.3%), followed by sublobectomy (24.4%). Despite a previous study demonstrating that sublobar resection does not seem to compromise oncological outcomes compared with lobar resection, assuming complete resection and adequate mediastinal staging is performed (15), no significant difference in the prognosis of patients with TC who underwent different lung resections (P>0.05) was found in the present study, which may be due to the small sample size. Mediastinal

lymphadenectomy (≥3 groups) was performed in 67.4% of the patients with TC and was associated with a better prognosis compared with inadequate mediastinal lymphadenectomy. Given that lymphadenectomy has not been a routine practice in patients with TC, most previous studies did not address the role of lymphadenectomy in this subgroup of patients. Based on these results, it can be suggested that a complete lymphadenectomy should always be performed in order determine the staging and improve the prognosis of patients with TC.

In two small previous retrospective analyses of TC and AC, the 10-year survival rates for AC ranged from 59-69%, which were higher than the CSS rate of 49.1% reported in the present study, likely owing to the differences in sample size and the characteristics of the patients enrolled (20,21). The sample size was larger and there were more patients with lymph node involvement in the present study, which was also a factor affecting prognosis. In another larger study (n=507) utilizing the Surveillance, Epidemiology and End Results database, patients with AC had a 10-year survival rate of 59% after surgery, which may have been influenced by a lower proportion of nodal involvement (N1-3, 33.5%) compared with the nodal status of the cohort in the present study (N1-3, 41.2%) (22). Lymph node metastases have been shown to be associated with an inferior survival rate in patients with AC (19). In a recent national study of surgically managed AC (n=816), no significant difference in mortality was observed between lobectomy and sublobectomy (23). Similar to TC, it can be suggested that the extent of lymphadenectomy in AC seems to be more important than the extent of lung resection.

In a study examining disease recurrence in patients with TC and AC following surgery, there did not appear to be a significant difference in the recurrence rate of AC with positive nodes versus negative nodes (16). This is in contrast to the findings in the present study, which may be attributed to the inclusion of patients with higher nodal status, as well as data regarding inadequate N2 lymphadenectomy, which was shown to increase recurrence risk. In a retrospective Spanish study, a univariate analysis found that sublobar resections in AC were associated with increased rates of recurrence compared with lobar resections (24). These observed findings, in conjunction with increased recurrence risk with inadequate lymphadenectomy, reinforce the suggestion that mediastinal staging and mediastinal dissection are needed to improve the prognosis of patients with PCT.

Limitations of the present study largely derive from its retrospective nature. Additionally, being a tertiary referral center could result in more patients who are medically complex and/or with advanced stage PCT. Additional prospective studies are necessary to validate the findings as well as to determine the appropriate surgical approach for these patients. Furthermore, recurrence type may also be associated with prognosis, which is not the subject of the present study, but is of note. This will be investigated further in later work.

In conclusion, in the present study, patients with AC tumors had significantly worse CSS and DFS rates compared with patients with TC. The degree of nodal involvement in AC was a prognostic marker, in contrast to that in TC. Inadequate lymphadenectomy increased the risk of recurrence in AC and mortality in TC. However, the type of surgery did not have a significant impact. The present study emphasizes the importance of mediastinal nodal dissection in patients with PCT.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LD, VE, AL, SES and DEJ designed the study. SDC, SEB, DW, YHL, JAW and PARS performed the acquisition of data, and DS, KRS and PY performed analysis and interpretation of data. LD, VE, AL, SES and DEJ prepared and wrote the original draft of the manuscript. SDC, SEB, DW, YHL, JAW and PARS reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. DS, KRS and PY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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