Original Article

Prognostic factors of recurrence and disease-free survival in radically resected pulmonary carcinoids: a real-world analysis

Marc Spils[1], Thomas Klikovits[1], Dagmar Krenbek[2], Maximilian Johannes Hochmair[3], Igor Jankovic[1], Lisa Schulte[1], Tibor Krajc[1], Michal Benej[1], Vladyslav Getman[1], José Ruiz Navarrete[1], Ahmet Akan[1], Michael R. Mueller[1], Clemens Aigner[4], Stefan B. Watzka[1]

[1]Department of Thoracic Surgery and Karl-Landsteiner-Institute, Clinic Floridsdorf, Vienna, Austria; [2]Institute for Pathology, Clinic Floridsdorf, Vienna, Austria; [3]Department of Respiratory and Critical Care Medicine, Karl-Landsteiner-Institute for Lung Research and Pulmonary Oncology, Clinic Floridsdorf, Vienna, Austria; [4]Department of Thoracic Surgery, Vienna General Hospital, Vienna, Austria

Contributions: (I) Conception and design: SB Watzka; (II) Administrative support: L Schulte, A Akan, SB Watzka; (III) Provision of study materials or patients: D Krenbek, I Jankovic, L Schulte, A Akan, MR Mueller, SB Watzka; (IV) Collection and assembly of data: M Spils, A Akan, SB Watzka; (V) Data analysis and interpretation: M Spils, D Krenbek, A Akan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Stefan B. Watzka, MD, BA, MA, FACS. Department of Thoracic Surgery and Karl-Landsteiner-Institute, Clinic Floridsdorf, 68 Bruenner Strasse, 1210 Vienna, Austria. Email: stefan.watzka@me.com.

Background: Pulmonary carcinoids (PCs) are rare neuroendocrine lung tumors which may recur, thus worsening their otherwise favorable overall prognosis. Aiming to identify patients at risk for recurrence, we examined parameters affecting disease-free survival (DFS).

Methods: A retrospective single-center analysis of 82 consecutive patients undergoing curative intent resection for primary PC tumors between 2010 and 2019 was carried out. Kaplan-Meier method was utilized for survival analysis. Independent prognostic factors were determined using multivariable Cox and logistic regression.

Results: During the observation period 82 patients, 48 females (58.5%) and 34 males (41.5%) were operated, representing 84 cases of PCs, 56 typical (TCs) (66.7%) and 28 atypical (ACs) (33.3%) carcinoids. Five-year overall survival was 87.5% and 84.7%, 5-year DFS 97.5% and 74.9% (P=0.012) for TCs and ACs, respectively. Recurrences occurred in one patient (1.8%) with TCs and five patients (17.9%) with ACs (P=0.014). Using multivariable Cox regression, tumor size (cm) remained as an independent prognostic factor for reduced DFS (P=0.018). In logistic regression, nodal involvement (P=0.043) and tumor size (cm) (P=0.023) were independently associated with higher risk of recurrence. Age, sex, smoking, location, and Ki-67 index were not independently associated with recurrence or DFS.

Conclusions: Recurrence in PCs after complete resection is relatively rare. However, DFS is reduced in ACs compared to TCs. Tumor size (cm) and nodal involvement appear as the most important prognostic factors associated with recurrence in PCs, independent of histologic type.

Keywords: Lung cancer; pulmonary carcinoid (PC); recurrence; disease-free-survival (DFS); prognosis

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Introduction

Pulmonary carcinoids (PCs) are rare malignant tumors deriving from neuroendocrine Kulchitsky cells of the bronchopulmonary mucosa and submucosal glands, reflecting 25% of all carcinoid tumors (1,2). According to the current 2015 World Health Organization (WHO) classification of lung tumors, PCs are categorized into typical carcinoids (TCs) and atypical carcinoids (ACs) due to mitotic count and absence/presence of necrosis (3). Moreover, PCs are rare tumors accounting for less than 2%

of all lung tumors (4).

Up to 40% of patients are asymptomatic at time of diagnosis. Accordingly, these tumors are frequently incidental findings on imaging. The most common respiratory symptoms, in descending order, are cough, hemoptysis, poststenotic pneumonia, chest pain and dyspnea. Furthermore, neuroendocrine tumors may synthesize and release different bioactive amines into circulation. Therefore, PCs are rarely diagnosed owing to hormonal hypersecretion causing carcinoid or Cushing syndrome and hardly ever acromegaly (5).

Whenever feasible surgery is the primary treatment of choice for PC with the aim to completely remove the tumor while simultaneously preserving as much functional lung tissue as possible (4).

In general, prognosis of patients diagnosed with PCs is quite favorable. However, chances of cure deteriorate significantly if recurrence occurs. The distinction of distant metastases and locoregional recurrence is of paramount importance, as overall survival is significantly reduced in carcinoids with distant metastases (6).

Hence, the main aim of this retrospective study was to identify risk factors for recurrence and reduced disease-free survival (DFS) in patients diagnosed with PCs who underwent curative intent surgery. Additionally, we aimed to assess the differences between TCs and ACs in terms of epidemiology, tumor characteristics as well as outcomes.

Highlight box

Key findings

- Tumor size (cm) and nodal involvement are the most important prognostic factors for recurrence and reduced disease-free survival (DFS).
- Five-year DFS for cases of nodal involvement (pN1/2) was 73.3% and 93.8% without nodal involvement.
- Five-year DFS for pT1, pT2 as well as pT3 was 97.8%, 87.5% and 40%, respectively.

What is known what is new?

- Recurrence is more frequent in atypical (ACs) compared to typical (TCs) carcinoids.
- Tumor size in cm and nodal involvement are correlated with DFS.

What is the implication and what should change now?

- Nodal involvement and tumor size (cm) may be as important for prognosis as histologic subdivision into TCs and ACs.
- Nodal involvement and tumor size (cm) should be highly considered for determining follow-up frequency as well as the diagnostic approach.

We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1681/rc).

Methods

We performed a retrospective single-center analysis of all consecutive patients diagnosed with PCs who underwent surgery at the Department of Thoracic Surgery at Clinics Penzing and Floridsdorf in Vienna, Austria, from 2010 to 2019. Notably, before 2019 the Department of Thoracic Surgery was located at the Clinic Penzing ("Otto Wagner Spital"), before it has been completely relocated to the newly built site of Clinic Floridsdorf. The study was conducted according to the guidelines of the Declaration of Helsinki (as revised in 2013). The Ethics Committee of the city of Vienna approved the study (No. EK-14-030-VK) and waived the need for informed consent due to the retrospective design. Neoadjuvant or adjuvant therapy (in addition to primary surgery before a potential recurrence), metastatic stage or R1 situations without an additional curative operation were defined as exclusion criteria for this study. It should be noted that a total of 84 carcinoids among 82 patients were observed. Accordingly, one patient presented with metachronous and one with synchronous PCs. Regarding the survival analysis only one case was added for each patient, in either case the one first operated on. Radical resection as well as lymphadenectomy were performed in all cases, following the recommendations of the European Neuroendocrine Tumor Society (ENETS) (7).

Tumors were classified into TC and AC according to the 2015 WHO classification of lung tumors and staged according to the eighth edition of the lung cancer TNM system (3,8). An area of 2 mm^2, corresponding to 10 high-power fields, was examined by the pathologist for mitotic counting. The Ki-67 index was retrospectively extracted from the pathology reports. We used the Ki-67 clone CONFIRM anti-Ki-67 (30-9) from Ventana/Roche (Ventana Medical Systems, Inc. 1910 E. Innovation Park Drive, Tucson, Arizona 85755, USA).

Tumors were defined as peripheral if their location was distal to the segmental bronchus and classified as central if diagnosed specifically at that demarcation or proximal by bronchoscopy. Recurrences were evaluated based on the results of biopsies and specific imaging like computed tomography (CT) scans, magnetic resonance imaging (MRI) or somatostatin receptor scintigraphy (SRS). DFS was calculated from the date of resection until tumor recurrence or date of last follow-up/death. Patients' data

Table 1 Key values as well as frequencies and proportions of epidemiological and clinical parameters

Variables	Total	TC	AC	P value
Cases (patients N=82)	84 (100.0)	56 (66.7)	28 (33.3)	–
Age (years)				
Mean ± SD	58.9±14.2	59.3±14.4	58.2±14.1	0.676
Median (IQR)	63.4 (49.4; 70.0)	63.4 (49.5; 70.2)	63.4 (48.5; 68.9)	–
Sex				0.531
Female	49 (58.3)	34 (69.4)	15 (30.6)	
Male	35 (41.7)	22 (62.9)	13 (37.1)	
Smoking history (N=64)	35/64 (54.7)	24/43 (55.8)	11/21 (52.4)	0.796
Pack years (N=18)				
Mean ± SD	35.0±20.7	32.1±22.3	45.0±10.0	0.198
Median (IQR)	35 (15; 50)	30 (10; 50)	40 (40; 50)	–
Symptoms (N=66)	35/66 (53.0)	22/44 (50.0)	13/22 (59.1)	0.485
Cough	31 (47.0)	19 (43.2)	12 (54.5)	0.383
Pneumonia	22 (33.3)	14 (31.8)	8 (36.4)	0.712
Hemoptysis	10 (15.2)	5 (11.4)	5 (22.7)	0.281
Dyspnea	6 (9.1)	5 (11.4)	1 (4.5)	0.655
Chest pain	2 (3.0)	2 (4.5)	0	0.549
Flush	1 (1.5)	1 (2.3)	0	>0.999
Pleural effusion	2 (3.0)	1 (2.3)	1 (4.5)	>0.999

Data are presented as N (%), unless otherwise stated. N = valid data protocols. TC, typical carcinoid; AC, atypical carcinoid; SD, standard deviation; IQR, interquartile range.

were prospectively collected and retrospectively analyzed.

Statistical analysis

Descriptive and inferential statistical analyses were performed using the statistical package IBM SPSS® version 27 (IBM, Armonk, NY, USA). Within the context of inferential statistics, the significance level, corresponding to the probability of type I error, was set at α=5%, therefore an inferential result P≤0.05 within hypotheses-testing is designated as significant. Student's *t*-test and Mann-Whitney's *U* test were used comparing the difference between two sample means of a continuous variable. For analyzing the difference of categorical variables between two groups we used Chi-square and Fisher's exact tests. Kaplan-Meier method was utilized for survival analysis. Independent prognostic factors for DFS and recurrence were determined using multivariable Cox regression and binary logistic regression, respectively. Missing data were treated as unknown. It should be noted that only 60 patients were eligible for Cox regression, as the remaining patients were censored because their follow-up time was shorter than the time to first occurrence of an event.

Results

Sociodemographic characteristics and clinical symptoms

This study included 82 patients, 48 females (58.5%) and 34 males (41.5%) with a mean age of 58.9±14.2 years, representing 84 cases of PCs, 56 TCs (66.7%) and 28 ACs (33.3%). Median follow-up time was 22 months. Symptoms were noted in 53.0% (n=35/66) of the patient collective, cough (n=31; 47.0%) being the most common.

Sociodemographic characteristics and clinical symptoms are displayed in *Table 1*.

Tumor characteristics

Furthermore, tumor-related parameters at time of resection are displayed in *Table 2*. 59.5% (n=50) of PCs were peripherally located, without significant difference between TCs and ACs. Additionally, hormone production was only detected in two (2.4%) cases of TCs; serotonin was expressed in one case and adrenocorticotropin (ACTH) in the other.

Surgical approaches and outcome

Surgical management and outcome parameters are displayed in *Table 3*. Notably, of the six cases with recurrence, three underwent a lobectomy, one a bilobectomy, one a bronchial sleeve lobectomy, and one a lobectomy with a partial vascular sleeve resection. Moreover, all patients underwent also a complete mediastinal lymph node dissection, and all cases were a R0 resection.

A minimally invasive approach [video-assisted thoracoscopic surgery (VATS)] was the preferred procedure (n=45; 53.6%), while thoracotomy was performed in the remaining cases (n=39; 46.4%). Furthermore, in most cases lobectomies (including bilobectomies and sleeve lobectomies) were performed (n=74; 88.1%). Median hospital stay after the procedure was 8 days.

Recurrences occurred in one patient (1.8%) with TCs and five patients (17.9%) with ACs (P=0.014). These appeared primarily as distant metastases (n=6; 7.1%), involving mainly the liver and bones. Only one locoregional recurrence (1.8%) was noted. From the six patients with recurrence, two underwent adjuvant radiotherapy (alone or in combination), four underwent radionuclide therapy, and one underwent complex abdominal metastasectomy.

Throughout the 10-year duration of this study, 10 patients (11.9%) died, only two (2.4%) due to the disease.

Independent prognostic factors influencing DFS and recurrence

Determining prognostic parameters affecting DFS, univariable Cox regression was initially performed. Parameters included in this approach were age, sex, smoking, histology, tumor size (cm), localization, mitotic count, Ki-67 index and nodal involvement. Notably, as almost 80% of our patients had been in stage pT1 (see *Table 2*), we elected to choose 'tumor size in cm' as a more relevant size parameter for subsequent statistical analysis.

Thereafter, multivariable Cox regression was performed including histology, tumor size (cm) and mitotic count. Ultimately, only tumor size (cm) was identified as a statistically significant independent parameter for reduced DFS in radically resected PCs (P=0.018; HR =1.77), shown in *Table 4*.

Moreover, binary logistic regression was utilized to reveal prognostic parameters associated with higher risk of recurrence. In addition, we used the same variables as for the Cox regression. Tumor size in cm (P=0.023; OR =11.88) and nodal involvement (P=0.043; OR =2,695.6) emerged as prognostic factors inducing higher risk of recurrence in radically resected PCs (*Table 5*), which is further illustrated in *Figure 1*.

Survival analysis

First, we used the Kaplan-Meier approach for comparing the overall and DFS between TC (n=55) and AC (n=27) (*Figure 2*). Mantel-Cox's log-rank test revealed no significant difference (P=0.543) in terms of overall survival. Five-year overall survival was 87.5% and 84.7% for TCs and ACs, respectively.

Five-year DFS was 97.5% and 74.9% (P=0.012) for TCs and ACs, respectively.

We then examined the influence of nodal involvement as well as the pT category on DFS. We found that nodal involvement (P=0.041) and the pT category (P<0.001) significantly influenced DFS (*Figure 3*).

Five-year DFS for cases of nodal involvement (pN1/2, n=12) was 73.3% and 93.8% without nodal involvement (n=70). Furthermore, 5-year DFS for pT1 (n=64), pT2 (n=12) as well as pT3 (n=6) was 97.8%, 87.5% and 40%, respectively.

Discussion

PCs are rare neuroendocrine tumors of the lung, accounting for approximately 2% of all lung malignancies (1,4). Compared to other lung malignancies like small cell lung cancer (SCLC), adenocarcinoma or squamous cell carcinoma, these tumors behave less aggressively and exhibit better overall survival. However, if recurrence occurs, their otherwise favorable prognosis is significantly worsened (6). Therefore, the main aim of this study was to identify parameters influencing DFS and recurrence rate in patients who underwent radical resection for TCs and ACs.

Table 2 Key values as well as frequencies and proportions of tumor-related parameters

Variables	Total	TC	AC	P value
Cases (patients N=82)	84 (100.0)	56 (66.7)	28 (33.3)	–
Localization				0.432
Central	34 (40.5)	21 (37.5)	13 (46.4)	
Peripheral	50 (59.5)	35 (62.5)	15 (53.6)	
Primary tumor site				
Right	52 (61.9)	33 (58.9)	19 (67.9)	0.427
Left	32 (38.1)	23 (41.1)	9 (32.1)	
Main bronchus	2 (2.4)	2 (3.6)	0	0.550
Bronchus intermedius	3 (3.6)	3 (5.4)	0	0.547
Upper lobe	24 (28.6)	15 (26.8)	9 (32.1)	0.608
Middle lobe	14 (16.7)	9 (16.1)	5 (17.9)	>0.999
Lower Lobe	41 (48.8)	27 (48.2)	14 (50.0)	0.877
Tumorlets	8 (9.5)	5 (8.9)	3 (10.7)	>0.999
Pleural invasion	1 (1.2)	1 (1.8)	0	>0.999
Mitotic count (per 10 high-power fields)				
Mean ± SD	2.06±3.15	0.77±0.60	4.64±4.41	<0.001**
Median (IQR)	1.0 (1.0; 2.5)	1.0 (0; 1.0)	3.5 (2.5; 5.0)	–
Ki-67 index (%) (N=62)				
Mean ± SD	4.23±4.48	2.34±1.71	7.91±5.82	<0.001**
Median (IQR)	2.0 (1.0; 5.0)	2.0 (1.0; 2.0)	7.0 (5.0; 10.0)	–
Hormone production	2 (2.4)	2 (3.6)	0	0.550
Serotonin	1 (1.2)	1 (1.8)	0	>0.999
ACTH	1 (1.2)	1 (1.8)	0	>0.999
Tumor size (cm)				
Mean ± SD	2.29±1.23	2.05±0.92	2.78±1.60	0.058
Median (IQR)	2.0 (1.5; 2.6)	1.9 (1.5; 2.5)	2.5 (1.5; 3.6)	–
pT				0.019*
T1	66 (78.6)	48 (85.7)	18 (64.3)	
T2	12 (14.3)	7 (12.5)	5 (17.9)	
T3	6 (7.1)	1 (1.8)	5 (17.9)	
Nodal involvement	12 (14.3)	8 (14.3)	4 (14.3)	>0.999
pN				>0.999
N0	72 (85.7)	48 (85.7)	24 (85.7)	
N1	7 (8.3)	5 (8.9)	2 (7.1)	
N2	5 (6.0)	3 (5.4)	2 (7.1)	

Data are presented as N (%), unless otherwise stated. *, P≤0.05; **, P≤0.01. N = valid data protocols. TC, typical carcinoid; AC, atypical carcinoid; SD, standard deviation; IQR, interquartile range; ACTH, adrenocorticotropin.

Table 3 Key values as well as frequencies and proportions of surgical management and outcome parameters

Variables	Total	TC	AC	P value
Cases (patients N=82)	84 (100.0)	56 (66.7)	28 (33.3)	–
Surgical approach				0.643
Thoracotomy	39 (46.4)	25 (44.6)	14 (50.0)	
VATS	45 (53.6)	31 (55.4)	14 (50.0)	
Surgical resection				0.701
Lobectomy	60 (71.4)	39 (69.6)	21 (75.0)	
Bilobectomy	7 (8.3)	5 (8.9)	2 (7.1)	
Sleeve lobectomy	7 (8.3)	6 (10.7)	1 (3.6)	
Bronchial sleeve resection	2 (2.4)	0	2 (7.1)	
Pneumonectomy	1 (1.2)	0	1 (3.6)	
Wedge resection	3 (3.6)	3 (5.4)	0	
Segmentectomy	4 (4.8)	3 (5.4)	1 (3.6)	
Hospital stay (days)				
Mean ± SD	9.8±8.4	9.5±7.4	10.2±10.2	0.720
Median (IQR)	8.0 (6.0; 10.0)	8.0 (6.0; 10.0)	8.0 (6.5; 10.0)	–
Recurrence	6 (7.1)	1 (1.8)	5 (17.9)	0.014*
Locoregional recurrence	1 (1.2)	1 (1.8)	0	>0.999
Distant metastasis	6 (7.1)	1 (1.8)	5 (17.9)	0.014*
Liver metastasis	4 (4.8)	0	4 (14.3)	0.011*
Brain metastasis	1 (1.2)	1 (1.8)	0	>0.999
Bone metastasis	3 (3.6)	0	3 (10.7)	0.034*
Pancreatic metastasis	1 (1.2)	0	1 (3.6)	0.333
Adrenal metastasis	1 (1.2)	0	1 (3.6)	0.333
Mortality	10 (11.9)	5 (8.9)	5 (17.9)	0.290
Dead for disease	2 (2.4)	0	2 (7.1)	0.175
Dead for other causes	8 (9.5)	5 (8.9)	3 (10.7)	
Alive with disease	3 (3.6)	1 (1.8)	2 (7.1)	0.257

Data are presented as N (%), unless otherwise stated. *, P≤0.05. N = valid data protocols. TC, typical carcinoid; AC, atypical carcinoid; VATS, video-assisted thoracoscopic surgery; SD, standard deviation; IQR, interquartile range.

Patient demographics and clinical presentation

In this study we present a male:female ratio of 0.71, which is within the range of other studies describing a slight predominance in female patients (2). Moreover, our patient collective consisted of a reasonably high proportion of ACs (66.7%), considering that ratios of 8–10:1 between TCs and ACs are commonly described in the literature (4,5).

We did not find any difference between the two histologic subtypes regarding age. In contrast, Caplin *et al.* described that the mean age for TCs is 45 years, as ACs generally occur one decade later (4).

Symptoms were recognized in 53.0% of the cohort, cough (47.0%) being the most frequent. These findings are consistent with previous reports claiming that up to 40–50%

Table 4 Univariable and multivariable Cox regression based on the outcome parameter "disease-free survival" (N=60)

Prognostic factors	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)	1.056	0.973–1.146	0.192	–	–	–
Male sex	1.270	0.254–6.345	0.771	–	–	–
Smoking	0.455	0.082–2.514	0.367	–	–	–
Atypical carcinoid	9.429	1.097–81.017	0.041*	4.273	0.365–49.97	0.247
Tumor size (cm)	2.042	1.340–3.111	<0.001**	1.766	1.103–2.826	0.018*
Peripheral location	0.322	0.059–1.766	0.192	–	–	–
Mitotic count	1.114	1.020–1.217	0.016*	0.985	0.878–1.106	0.801
Ki-67 index (%) (N=41)	1.118	1.005–1.243	0.041*	–	–	–
Nodal involvement (N1/2)	4.537	0.911–22.601	0.065	–	–	–

Data are presented as N (%), unless otherwise stated. *, P≤0.05; **, P≤0.01. N = valid data protocols. HR, hazard ratio; CI, confidence interval.

Table 5 Univariable and multivariable binary logistic regression based on the outcome parameter "recurrence"

Prognostic factors	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Age (years)	1.049	0.973–1.131	0.210	–	–	–
Male sex	1.452	0.275–7.668	0.661	–	–	–
Smoking	0.375	0.063–2.219	0.280	–	–	–
Atypical carcinoid	12.273	1.355–111.152	0.026*	9.005	0.365–49.977	0.424
Tumor size (cm)	3.426	1.648–7.122	<0.001**	11.878	1.412–99.916	0.023*
Peripheral location	0.326	0.056–1.893	0.212	–	–	–
Mitotic count	1.527	1.095–2.128	0.012*	1.842	0.938–3.617	0.076
Ki-67 index (%) (N=41)	1.254	1.053–1.494	0.011*	–	–	–
Nodal involvement (N1/2)	7.444	1.300–42.628	0.024*	2,695.6	1.296–∞	0.043*

Data are presented as [N (%)], unless otherwise stated. *, P≤0.05; **, P≤0.01. N = valid data protocols. OR, odds ratio; CI, confidence interval.

of patients are asymptomatic at time of diagnosis (5).

Controversy surrounds the question whether a history of smoking, considered one of the strongest risk factors for SCLC or large cell neuroendocrine carcinoma (LCNEC) (9), may also be associated with the development of PCs. In our cohort, 54.7% of patients did smoke at time of diagnosis or had a smoking history. Nevertheless, no conclusions concerning the risk potential of tobacco consumption can be drawn, since the number of cases is far too small and a comparison with a healthy cohort was not established.

Tumor characteristics

In general, PCs have been reported to be centrally localized, Detterbeck *et al*. indicated a percentage of 70% (10). However, in more recent studies, the ratios have converged or even shown a higher proportion of peripherally located PCs (11,12). These discrepancies may be explained by the fact that no uniform definition has been established for "central" and "peripheral". This study reveals a predominance of peripheral tumors (59.5%). Although no

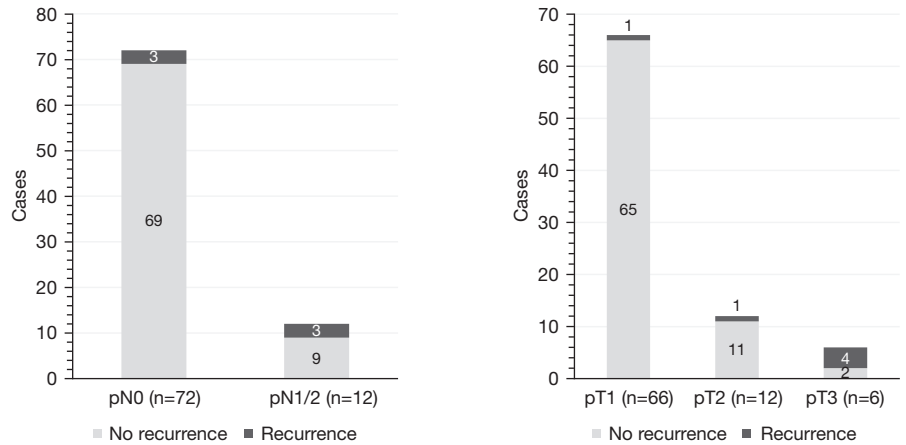

Figure 1 Frequencies of recurrence considering nodal involvement and pT category.

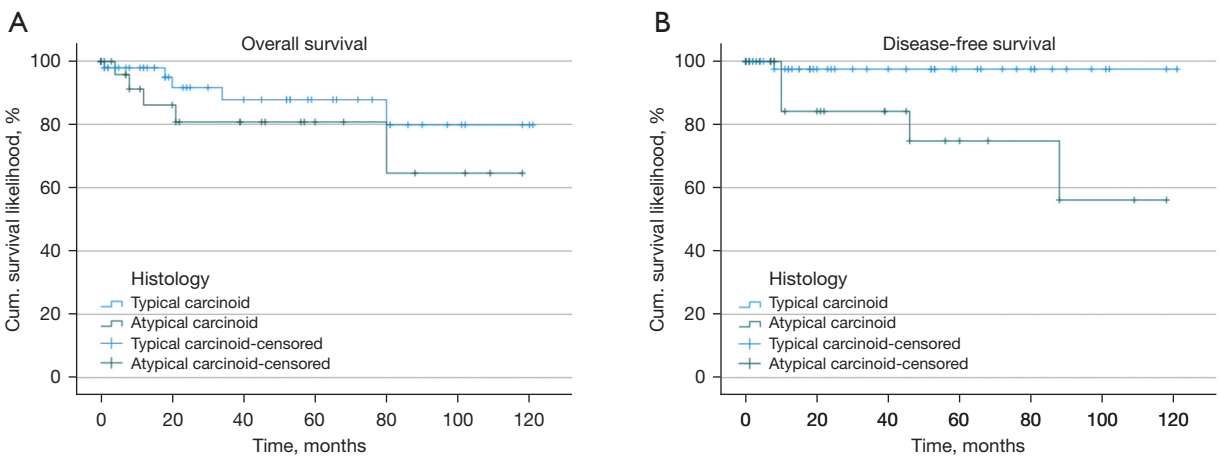

Figure 2 Kaplan-Meier estimator for overall survival (A) and disease-free survival (B) considering typical carcinoids (N=55) and atypical carcinoids (N=27). Cum., cumulative.

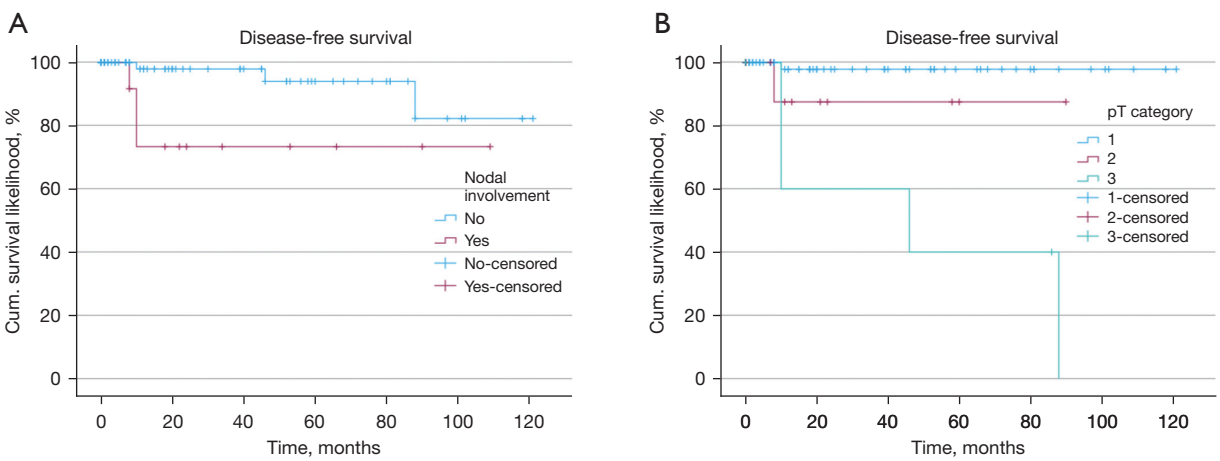

Figure 3 Kaplan-Meier estimator for disease-free survival considering nodal involvement (A) and the pT category (B). Cum., cumulative.

statistically significant difference was evident between TCs, a tendency of TCs toward peripheral localization is notable. Additionally, the majority of our cases occurred in the right lung, which is well described in preceding studies (13,14).

Our findings regarding Ki-67 (*Table 2*) are in accordance with the current 2015 WHO guidelines, which indicate a Ki-67 index of 0–5% and 6–20% for TCs and ACs, respectively (3).

Previous studies have shown that ACs compared to TCs present larger tumors as well as higher prevalence of nodal metastases (15,16). Concerning tumor size (cm), a statistically significant difference in pT stage for TCs and ACs was observed, whereas tumor size in cm was tending in the same direction, however not statistically significant. Impressively, 17.9% of ACs were resected at stage pT3 contrasting to only 1.8% of TCs. Regarding nodal involvement we report the same percentage of TCs and ACs (14.3%) already developed lymph node metastases at time of resection. Thus, no difference was ascertained in our study, which is in contrast to most results in the literature suggesting that lymph node metastasis is significantly more frequent in ACs compared to TCs (12,17). It may be contended, though, that our results are quite in line with what can be expected, namely because tumor size and lymph node involvement are established prognostic factors. However, as almost 80% of our cases had pT1 tumors, and 85% were in a pN0 situation, focusing on T and N factors alone would therefore not have fully captured the strong prognostic relevance of tumor size and lymph node involvement. Thus, for PCs the adoption of 'tumor size in cm' seems to be a more relevant prognostic parameter than T stage. We believe, this insight is a new knowledge.

Treatment

Furthermore, there is an ongoing debate regarding the best surgical approach in the literature. In recent studies, VATS has been associated with advantages over thoracotomy regarding pain and postoperative complications (18). We report a predominance of patients being treated by using VATS over thoracotomy, which was primarily utilized for large as well as centrally located tumors. In our study, the procedure of choice was a lobectomy. Based on the literature, it is unclear whether sublobar resection achieves the same outcome for PCs as lobectomy. Several previous papers declared no difference (19), whereas others reported the superiority of lobectomy (6,17). Xu *et al.* demonstrated no statistically significant difference for overall survival in PCs ≤3 cm in a large-scale study comparing lobectomy and sublobar resection (20). Similarly, Ernani *et al.* did not observe improved overall survival for lobectomy compared with sublobar resection in non-metastatic ACs (21).

Outcome and prognostic factors

Recurrences occurred significantly more frequent in ACs compared to TCs. In accordance, Filosso *et al.* described recurrence rates of 5% for TCs and 20% for ACs after radical resection (22). Metastases primarily appeared as distant metastases, mainly involving the liver and bones. Locoregional recurrence was noted only once.

We observed a 5-year overall survival of 87.5% and 84.7% for TCs and ACs, respectively. According to the 5- and 10-year overall survival rates reported in the literature, the long-term survival for PCs after primary resection in our cohort is reasonably good. Indeed, in the literature the 5- and 10-year overall survival for TCs has been found to be 86% to 93% and 76% to 88% (12,23,24), respectively, compared with a 5-year overall survival of 80% to 87% and a 10-year overall survival of 43% to 69% for ACs (6,15,24,25). Cañizares *et al.* presented that 5-year overall survival of ACs is dramatically shortened to only 39% following distant metastasis. Furthermore, they stated that median survival is reduced to 38 months in ACs developing distant metastasis, compared with 180 months in disease-free patients (6). Consequently, focusing on prognostic factors influencing DFS to find patients at risk of recurrence is necessary to further improve the outcome. Our survival analysis revealed significantly reduced DFS for ACs compared to TCs, 5-year DFS was 97.5% for TCs and 74.9% for ACs, which is consistent with preceding studies indicating 5-year DFS of 82% to 99% and 72% to 81% for TCs and ACs, respectively (26-28).

Only tumor size (cm) proved to be an independent statistically significant factor associated with reduced DFS in the performed multivariable Cox regression. Tumor size (cm) and nodal involvement were independently and statistically significantly associated with higher risk of recurrence in radically resected PCs, as determined by multivariable logistic regression. In recent studies, which also identified advanced age and male sex as prognostic factors, competing risk model nomograms (29) and scores (30) were developed to evaluate long-term survival. When using these models, we highly recommend including lymph node involvement and tumor size (cm) as prognostic factors for the calculation of long-term survival, regardless

of histologic type.

We report 5-year DFS, independently of the histologic subtype, for pT1, pT2 and pT3 being 97.8%, 87.5% and 40%, respectively, which clearly illustrates the influence of tumor size (cm). Studies describing the impact of tumor size (cm) or pT stage on 5-year DFS are scarce to nonexistent in the literature. Lee *et al.* reported 5-year DFS of 90.6% and 81.2% for pT1 and pT2–4, respectively, which is in accordance with our findings (26). Hence, PCs presenting at pT1/2 are considered having a very good prognosis. Further growth of the tumor indicates significantly worsened prognostic outcome for stage pT3. Furthermore, we determined 5-year DFS of 93.8% for PCs staged pN0 compared to 73.3% for those displaying nodal involvement (pN1/2). Similar results have been obtained in previous studies. Cusumano *et al.* described 5-year DFS of 99%, 88%, and 60% for pN0, pN1, and pN2, respectively (27). Additionally, Lee *et al.*, who divided their cohort for statistical analysis into groups characterized by pN1/2 and pN0, described 5-year DFS as 89% for pN0 and 78% for pN1/2 (26).

Limitations

The most important limitations for the present work arise from the fact that this is a single center study with a comparatively small number of cases. However, since this is a single center study from the largest thoracic surgical center in Austria, with all consecutive patients included, this is only a relative limitation. Moreover, the published references with more included patients are either multicentric studies, or are based on large population databases, like Surveillance, Epidemiology, and End Results (SEER), National Cancer Database or similar. Due to the relatively small number of cases, only few recurrences could be detected, which complicates the identification of prognostic factors. Data of approximately 10 years were conducted in this retrospective study. Therefore, we were unable to report all parameters for each patient and had to deal with the difficulties of missing data.

Conclusions

In conclusion, PCs represent an infrequent tumor entity characterized by fairly good prognosis. However, if recurrence occurs, especially in case of distant metastasis, the overall outcome is remarkably reduced. Hence, the main aim to continuously improve the outcome of patients diagnosed with TCs or ACs is to identify parameters influencing DFS and recurrence rate after radical resection.

Recurrence after complete resection is relatively rare, but more frequent in ACs compared to TCs. Thus, DFS is evidently reduced in ACs. Nodal involvement and tumor size (cm) appear to be the most important prognostic factors associated with recurrence of resected PCs. Regarding the frequency of nodal involvement, no difference between TCs and ACs was observed. Conversely, a tendency toward higher pT stages for ACs became apparent.

Therefore, we suggest that these parameters should be highly considered for determining follow-up frequency as well as the diagnostic approach. To confirm and strengthen our results, further comparable studies with large sample sizes are required.

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Footnote

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