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ORIGINAL ARTICLE

Clinicopathological characteristics and prognosis of resected cases of carcinoid tumors of the lung

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Abstract

Background: Lung carcinoid tumors are rare, low-grade, malignant neoplasms with some unclear features. The aim of this study was to analyze clinicopathological features and long-term survival in patients with primary lung carcinoid tumors.

Methods: Patients who underwent surgery in our clinic and were diagnosed with carcinoid tumors, between August 1997 and July 2012, were included in the study. Patient characteristics and clinicopathological factors were retrospectively evaluated.

Results: Bronchial carcinoids comprised only 1.0% of lung cancer cases treated by resection. They are classified into two distinct categories: typical carcinoid (TC) and atypical carcinoid (AC) tumors. AC tumors occurred more frequently in younger patients and in smokers, and had a poorer prognosis than TC tumors. Overall three and five-year survival rates for TC and AC were 92.6% and 81.1%, respectively. Univariate analysis showed that tumor size ($P = 0.012$) and histological type ($P = 0.013$) are prognostic factors. Multivariate analysis revealed that only tumor size ($P = 0.044$) was an independent prognostic factor.

Conclusions: The prognosis for bronchial carcinoid tumors was better than other types of lung cancer and TC was significantly better than AC. Radical lymph node dissection was the best treatment, with complete removal of the tumor. Tumor size was an independent prognostic factor for bronchial carcinoid tumors.

Introduction

Carcinoid tumors are low-grade, slow-growing, malignant neoplasms of neuroendocrine origin with well-differentiated tissue. The most frequent location of carcinoid tumors is the gastrointestinal tract (68–74%), while the second most common location is the respiratory tract (25%). Carcinoid tumors account for only 1.0–2.0% of all lung tumors.[1] Similar to small cell lung cancer, lung carcinoid tumors originate in neuroendocrine Kulchitsky cells of the bronchopulmonary mucosa and submucosal glands. Depending on the degree of mitotic activity and necrosis, they are separated into typical carcinoids (TCs) and atypical carcinoids (ACs). Based on the latest World Health Organization (WHO) classification of bronchopulmonary carcinoids, TC is defined as < 2 mitoses per 2 mm^2 with no necrosis, while AC is defined as ≥ 2 mitoses but < 10 mitoses per 2 mm^2, coagulative necrosis, or both.[2] TC and AC differ in the percentage of lymph node metastasis, which is either low or high, and are accompanied by either rare or common metastatic disease at presentation, respectively.

Because lung carcinoid tumors are rare malignant tumors, factors of clinical manifestation, treatment, and prognosis are not well understood, thus, identifying them from other lesions in the lungs is very difficult. We collected the data of 44 pulmonary carcinoid cases from our hospital to analyze the clinical features and prognostic factors.

Methods

The Human Ethics Committee of Capital Medical University approved this study. Written informed consent was

obtained from all patients at the time of admission. The patient records included in this study were anonymized prior to analysis.

Between August 1997 and July 2012, we performed surgery on 4481 patients with bronchopulmonary neoplasms at the Division of Thoracic Surgery, Beijing Chest Hospital, 44 of which were determined as carcinoid lung tumors (1.0%). An experienced pathologist reviewed all medical records of patients treated surgically for pulmonary carcinoid tumors. Data on age; gender; presenting symptoms; history of smoking; method of diagnosis; tumor size and location; histological type; type of surgical procedure; postoperative complications; and long-term survival were analyzed. Pathological specimens were used to verify the diagnosis of carcinoid tumor established previously and to subclassify the tumor histology further into TC and AC, according to the 2004 WHO classification, based on a 1998 study by Travis *et al.*[3] Pathological diagnosis requires sufficient specimens. Surgical specimens represent the best method to quantify the presence of necrosis and the frequency of mitoses; therefore, we only chose specimens from surgical cases. The tumors were staged according to the seventh edition of the International Classification of Tumor Node Metastasis (TNM; carcinoid lung tumor incidence).

Statistical analysis was performed using$\chi 2$ or Fisher's exact tests for nominal variables and the unpaired Student *t*-test for continuous variables. Survival rates were analyzed using the Kaplan–Meier method and compared between groups using the log-rank test. Multivariate analysis was performed according to Cox's proportional hazards model. All statistical analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). A P value < 0.05 was considered statistically significant.

Results

There was a female predominance in the patients with carcinoid lung tumors, with a male to female ratio of 19:25 (1:1.3). Ages ranged between 9 and 71 years (mean 44 ± 14.9). In terms of histological findings, 32 patients (12 men, 20 women, mean age 39 ± 14.1) had TC, while AC was observed in 12 patients (7 men, 5 women, mean age 51 ± 13.4). There were statistically significant differences between the TC and AC groups in terms of mean age, with patients in the AC group tending to be older ($P = 0.010$). The demographic characteristics of the two histologic subtypes are summarized in Table 1.

The most frequently observed complaints were cough (59.1%), hemoptysis (29.5%), and fever (18.2%). Most of the patients with these symptoms had a centrally located tumor. Eight patients (18.2%) were asymptomatic, which is often seen in AC (33.3%), in contrast with TC (12.5%).

Table 1 Clinical characteristics of the patients

Variables	TC	AC	t/χ^2	*P*
Age, year (range)	9–64	28–71	2.698	0.010
Gender (M/F)	12/20	7/5	1.544	0.214
Symptom (None/present)	4/28	4/8	1.338	0.247
Smoking (Never/present)	25/7	4/8	5.927	0.015
Location Central/non-central	28/4	8/4	1.338	0.247
Lateral Left/right lung	13/19	8/4	2.372	0.124
Tumor size < 3 cm/≥ 3 cm	17/15	4/8	1.370	0.242
Lymph node metastasis Absent/present	29/3	9/3	0.726	0.394
Pathological stage I/II and III	26/6	7/5	1.375	0.241

AC, atypical carcinoid; TC, typical carcinoid.

Carcinoid syndrome was not encountered in any of the patients.

Among the 44 carcinoid tumor cases, 15 (34.1%) were smokers. Of the 15 smokers, seven had TC and eight AC. A comparison of smoking habits between the groups showed significant differences, with a smoking habit more commonly observed in the AC group ($P = 0.015$).

Tumors were located in the right lung (54.5%) in 24 patients and in the left lung (45.5%) in 20. Eight lesions were located in the main bronchus (18.2%), 15 in the lower lobe (34.1%), 13 in the upper lobe (30.0%), and seven in the intermediate lobe (15.9%).

The tumors were classified as "central" if visualized directly during bronchoscopy or if associated with atelectasis or obstructive pneumonia and "peripheral" when the tumor was not visible by endoscopy. In our series, 36 tumors (81.8%) were considered to be central and eight (18.2%) peripheral, according to the criteria outlined. Of the 36 centrally located tumors, 28 patients (77.8%) had TC and eight (22.2%) had AC; of the eight peripheral tumors, four (50%) were TC and four (50%) AC. A central tumor was found in 36 of the 44 cases (81.8%) and was more frequently found in cases of TC tumors; however, no statistically significant correlation was found ($P = 0.247$).

Chest X-ray and chest computed tomography (CT) was performed in all patients. In nine patients, chest CT showed enlargement of the mediastinal node, thus, these patients were considered to have preoperative lymph node metastasis. Four of these patients were definitively diagnosed with mediastinal lymph node metastasis; however in three cases, imaging showed normal results, despite subsequent determination that the patients had mediastinal lymph node metastasis.

Bronchoscopy was performed in all patients and endobronchial tumors were directly observed in 36 patients. All patients underwent endoscopic biopsy and brushing for histological diagnostic purposes, and diagnoses were obtained in 19 of the patients preoperatively. Fourteen patients were diagnosed with carcinoid tumors, two with adenocarcinoma, one with squamous cell carcinoma, and one with small cell carcinoma.

The aim of surgical treatment was to achieve complete resection of the primary tumor with a negative margin. In addition to the three patients who underwent thoracoscopic surgery, posterolateral thoracotomy was also performed. Parenchyma-sparing procedures, such as segmentectomy or sleeve lobectomy, were applied in eligible cases. Lobectomy was the most frequently performed procedure; 18 standard lobectomies and eight sleeve lobectomies were performed (Table 2). Pneumonectomy was performed in 10 cases (22.7%); the tumor was located in the main bronchus with obstructive pneumonia or atelectasis in seven; and the tumor invaded the pulmonary arterial trunk in three cases. Systematic radical mediastinal lymphadenectomy was performed for all cases. Standard resection was performed in 33 (75%) carcinoid tumor patients and parenchyma-sparing resection (segmentectomy, sleeve lobectomy, and bronchoplasty) in 11 patients (25%).

No operative or postoperative mortality was observed. Postoperative complications were observed in six patients (13.7%), including persistent air-leakage (2 patients), pneumonia (2), arrhythmia (1), and wound infection (1). Postoperative complications occurred less frequently in the TC (9.4%) compared with the AC group (25%).

According to the seventh edition of the International Classification of TNM, the majority of the patients (n = 33) were in stage I, six were in stage II, and five were in stage III. Lymph node metastasis was confirmed in six cases (3 N1, 3 N2). Pathologic stage distribution revealed that significantly more patients with TC presented with stage I (81.3%) than those with AC (58.3%); however, there was no statistically significant difference between them (P = 0.214).

Table 2 Surgical treatment

Surgery procedure		Total (n = 44)	%
Standard resection	VATS lobectomy	3	6.8
	Lobectomy	15	34.1
	Bilobectomy	5	11.4
	Pneumonectomy	10	22.7
Parenchyma-sparing resection	Sleeve lobectomy	8	18.2
	Segmentectomy	1	2.3
	Bronchoplasty	2	4.5

VATS, video-assisted thoracoscopic surgery.

Follow-up evaluations were performed from 8–126 months (mean 59) until the end of January 2014. Survival was measured from the time of diagnosis. Histological subtypes, postoperative treatment, and patient characteristics were analyzed.

Twenty of the patients treated with resection received postoperative adjuvant platinum-based chemotherapy or/and radiotherapy. Nine patients received adjuvant chemotherapy with a regimen of etoposide plus cisplatin, 10 patients received carboplatin plus vinorelbine (6) or paclitaxel (4), and one patient underwent radiation therapy. There was no difference in survival between patients treated with or without chemotherapy (P = 0.157).

The size of the tumor varied from 1 cm to 14 cm in maximum dimension, with a tumor size of ≥ 3 cm in 52.3% of cases. Univariate analysis showed that the prognosis for patients with a tumor size of ≥ 3 cm was significantly worse than for patients with a tumor size < 3 cm (P = 0.012).

Univariate analysis showed that tumor size (P = 0.012) and histological type (P = 0.013) are prognostic factors (Table 3). The five-year survival rates of TC and AC were 88.1 and 50%, respectively (Fig 1). Multivariate analysis revealed that only tumor size (P = 0.044) was an independent prognostic factor (Table 3).

Discussion

Carcinoids were first reported in 1888 by Lubarch and can occur in different parts of the body; however, most are located in the digestive tract. Bronchial carcinoids are rare, accounting for only 25–30% of all carcinoid tumors and constituting 2–5% of all lung cancers.[2,4,5] Bronchial carcinoids can be divided into TC with low-grade malignancy and AC with moderate malignancy. According to the 1999 WHO classification, TC, AC, small cell lung carcinomas, and large cell neuroendocrine carcinomas are defined as neuroendocrine pulmonary tumors.

Bronchial carcinoid incidence is low; our cohort of 44 cases accounts for 1.0% of lung cancer patients hospitalized over the same period in our institution, similar to the reported incidence of 1.0–2.0% in published studies.[6] The mean age of onset in our group was only 44 years (range 9–71), while the mean age of onset of other types of lung cancer, such as lung squamous cell carcinoma or adenocarcinoma, is later than in pulmonary carcinoid tumors.[7]

Aydin *et al.* reported that the average age of patients with TC was higher than AC (50 vs. 42 years); however our results determined an average age of 51 for AC patients and 39 for TC.[8] Single factor analysis shows a significant difference, which is consistent with a recent report by Herde *et al.*[9]

Table 3 Univariate and multivariate analysis of prognostic factors for survival

Variables	Univariate		Multivariate	
	P	HR	95%CI	*P*
Male versus female	0.998	—	—	—
Age (years) < 60 versus ≥ 61	0.806	—	—	—
Smoker versus non-smoker	0.959	—	—	—
Chemoradiotherapy versus no chemoradiotherapy	0.132	—	—	—
Histological type (TC vs. AC)	0.013	0.395	0.149–1.047	0.062
Tumor size (< 3 cm vs ≥ 3 cm)	0.012	0.351	0.126–0.974	0.044

AC, atypical carcinoid; CI, confidence interval; HR, hazard ratio; TC, typical carcinoid.

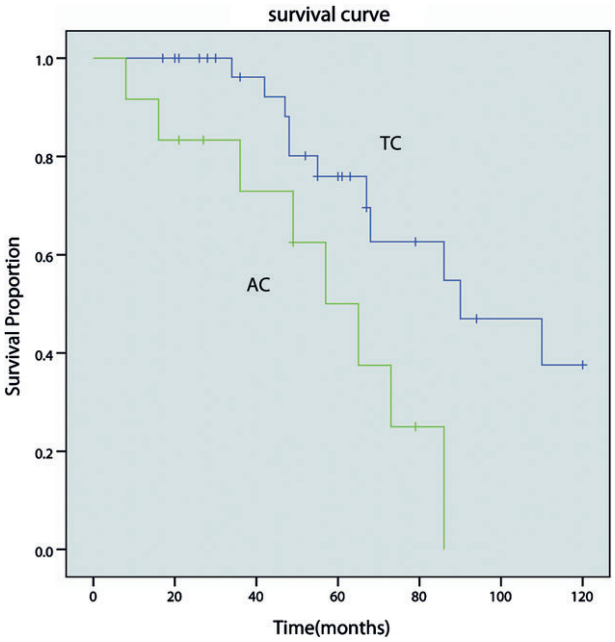

Figure 1 Kaplan–Meier survival curves for patients with typical carcinoids (TC) and atypical carcinoids (AC) ($P = 0.013$).

There were 15 smokers in the present study, accounting for 34.1% of the total cohort. We found an increased proportion of smokers in AC compared with TC patients. Univariate analysis showed that this result was statistically significant ($P = 0.015$).

The majority of patients with carcinoid tumors present with symptoms. In our study, respiratory symptoms, such as cough and hemoptysis, were most common, accounting for 81.8%; however, 18.2% were asymptomatic, thus, the bronchial carcinoids in these patients were found incidentally.

The incidence of carcinoid syndrome in lung carcinoids is 2–5%, according to related reports.[10] Carcinoid syndrome is derived from poor liver inactivation of a variety of hormone-like substances secreted by tumors; therefore, it is more likely to occur in liver metastases and/or abnormal liver function. Carcinoid syndrome was not detected in any of the patients in our study; our patients were surgical cases and we excluded those with liver metastases.

With a ratio of TC to AC of 32:12, our study included significantly more AC cases compared with results from Thomas *et al.* (88:12) and Fink *et al.* (90:10), but similar to some recent studies.[11–13] The number of samples in our study was small; therefore, a large-scale epidemiological survey is needed.

The five-year survival rate in TC patients is greater than 90%, as a result of the low degree of malignancy; however, 12% of TC patients already have metastasis at the date of admission. AC patients experience a higher degree of invasiveness and a poor clinical prognosis; approximately 50% of AC patients have mediastinal lymph node metastasis, and the five-year survival rate is only 40–75%.[14] The five-year survival rates of patients with TC and AC in the present study were 87.0 and 55.6%, respectively, different results from those reported in literature.

An epidemiological survey showed that bronchial carcinoid tumors most often occur in the right lobe, accounting for 59.0%; TC are mainly central located; and AC are usually displayed as peripheral tumors.[6,15] In our study, bronchial carcinoid tumors were located in the right lung in 24 cases (54.5%), in the center in 36 (81.8%) and in peripheral lung parenchyma in eight (18.2%). Central TC tumors accounted for 77.8% and peripheral AC tumors 50%, consistent with the literature.

Bronchoscopy is an important method to diagnose lung cancer because the bronchial lumen can be observed and the biopsy directly performed. In the present study, all patients underwent bronchoscopy, with 32 cases (81.8%) of endoscopically visible lesions. Only 19 cases were correctly diagnosed, while 13 cases were misdiagnosed. These results suggest that diagnosis made with bronchoscopy tissue alone is still difficult and sometimes secondary examination or more precise diagnostic methods are necessary.

At present, the opinions of authors as to whether intraoperative lymph node dissection is worthwhile are inconsistent.[16–18] Many authors believe that lymph node dissection for lung carcinoid tumors, especially for TC, is not useful for prolonging the mean survival of patients.

Our study found that preoperative diagnosis of carcinoids is difficult to obtain, and, thus, misdiagnosis can occur. Cases are often preoperatively diagnosed by imaging as having no lymph node metastasis, but are then confirmed by pathology to have lymph node metastasis. Therefore, we believe that it is necessary to perform a systemic lymph node dissection, regardless of histological type.

Radical surgery is the best way to treat lung carcinoid tumors, and limited resection should be performed, when possible, for known carcinoid tumors. However, the type of surgical approach to use is still controversial. Some authors have suggested parenchymal sparing resections for confirmed TCs, while others adhere to anatomical resections independent of the histological subtype, given a sufficient functional reserve.[19–21] We prefer bronchial sleeve resection or sleeve lobectomy over pneumonectomy because these methods result in no local recurrence, are not accompanied by postoperative complications, and yield a good survival rate.

In the present study, six patients received preoperative neoadjuvant chemotherapy and 20 received adjuvant therapy, including chemotherapy, radiotherapy, or a combination. Univariate analysis showed that patients treated with postoperative chemoradiotherapy did not have a better prognosis than those not treated with postoperative chemoradiotherapy. In a study by Wirth *et al.* of 18 pulmonary carcinoid tumor cases, the response rates for chemotherapy and chemoradiotherapy were 20% and 22%, respectively, both of which are lower than for other types of lung cancer.[22] In our opinion, there is no clear evidence demonstrating the benefit of chemotherapy for patients with carcinoid tumors. Thus, in the treatment of early stage tumors, we believe chemotherapy can be abandoned.

A recent SEER group study demonstrated a five-year survival rate of 73.5% for lung carcinoid tumors.[23] Zhong *et al.* reported three, five, and 10-year survival rates for 131 cases of pulmonary carcinoid tumors of 96.0%, 86.9%, and 70.6%, respectively.[4] Our data showed three and five-year survival rates of 92.6% and 81.1%, respectively, which is consistent with the literature. Schrevens *et al.* reported that histological type and lymph node metastasis were independent prognostic factors.[24] In our group, univariate analysis showed that tumor size ($P = 0.012$) and histological type ($P = 0.013$) are prognostic factors. Multivariate analysis revealed that only tumor size ($P = 0.044$) was an independent prognostic factor. Although our univariate analysis showed histological type ($P = 0.013$) as a prognostic factor, multivariate analysis showed no significant difference between histological type, probably because of the small number of samples in our study, and the fact that the proportion of AC patients was higher. TC cases also showed tumor invasion with lymph node metastasis. The overall survival in patients with pulmonary carcinoid tumors was longer than for other types of lung cancer and at an early tumor stage, the prognosis was better.

Pulmonary carcinoid tumors are a special kind of lung neuroendocrine tumors. Compared with other types of lung cancer, pulmonary carcinoid tumors are well differentiated, less invasive, and slow growing, with a better prognosis. They are classified into two distinct categories: typical and atypical carcinoid tumors. AC tumors manifest in a lower proportion of patients, at an earlier age of onset, in a higher proportion of smokers, and carry a poorer prognosis than TC. Radical surgery with operative lymph node dissection is the best treatment, and can cure the tumor completely. However, in patients with lymph node metastasis, the rationality for adjuvant chemoradiotherapy or targeted therapy should be explored.

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Disclosure

No authors report any conflict of interest.

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