Pulmonary Carcinoid: Analysis of a Single Institutional Experience and Prognostic Factors

ARTIGO ORIGINAL

Carcinóide Pulmonar: Análise de Experiência Institucional e Fatores Prognóstico

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ABSTRACT

Introduction: Carcinoid tumors of the lung are rare neoplasms of neuroendocrine origin. According to the World Health Organization, they can be classified into typical carcinoids and atypical carcinoids. The outcome, when compared to other lung neoplasms is usually favorable.

Objectives: To characterize the population of patients with a diagnosis of carcinoid tumor, treated in a single institution and analyze the prognostic factors.

Material and Methods: Retrospective analysis including all the patients with histological diagnosis of lung carcinoid tumor during an 11 year period, in a single institution. The tumors were classified according to the World Health Organization classification of carcinoids tumors in 2004. Staging was made according to the TNM classification of 2009 for non-small lung cancer: T (Tumor); N (Node); M (metastasis).

Results: 59 patients were evaluated, including 53 with typical carcinoids and 6 with atypical carcinoid. 90% of the patients were submitted to surgery. The mean follow-up period was 57 months and the early post-operative mortality rate was 2% (one single case of palliative surgery). Histologic staging showed 49 patients in stage N0, one N1, eight N2 and one N3. The 5-year survival was 79.2%: 80.2% for typical carcinoids and 66.7% for atypical carcinoid ($p < 0.05$). The 5-year survival was 88.1% in T1 patients and 58.2% in T2-T4 patients ($p < 0.01$). In N0 patients, the 5-year survival was 89.7% while in N1-N3 it was 36% ($p < 0.001$). The 5-year survival was 85.9% in M0 disease and 0% in M1 disease ($p < 0.01$). Of the 11 patients who were submitted to adjuvant chemotherapy, 45.4% had atypical tumors.

Discussion: In our sample, surgical treatment was safe, with a low postoperative complication rate. The prognosis was worse for atypical tumors, tumors with more than 3 cm, tumors with nodal involvement or metastasis. The five-year survival for typical carcinoid was excellent (80.2%), in agreement with the literature. For atypical carcinoid, the five-year was 66.7%, also similar to previous studies.

Conclusions: In our institution, most of the lung carcinoids are typical and have an excellent long term survival. The mainstay of treatment is surgical resection. The factors that were related to a poor prognosis were the histological subtype (typical carcinoids versus atypical carcinoids), the size of the tumor, the mediastinal lymphatic involvement and the presence of metastasis.

Keywords: Lung Neoplasms; Carcinoid Tumor; Neoplasm Staging.

RESUMO

Introdução: Os tumores carcinóides pulmonares são tumores raros com origem nas células neuro-endócrinas do pulmão. Classificam-se de acordo com os critérios da OMS em carcinóides típicos ou atípicos. Quando comparados com outros tipos de neoplasia pulmonar, os tumores carcinóides apresentam melhor prognóstico.

Objetivos: Caracterização dos doentes com diagnóstico histológico de tumor carcinóide observados numa instituição. Análise dos fatores que influenciaram o prognóstico.

Material e Métodos: Análise retrospetiva incluindo todos os doentes com diagnóstico histológico de tumor carcinóide pulmonar durante um período de 11 anos numa instituição. Os tumores foram classificados em típicos e atípicos de acordo com a classificação da Organização Mundial de Saúde de 2004. O estadiamento foi feito com base na classificação TNM de 2009 para o carcinoma do pulmão de não pequenas células: T (Tumor); N (Ganglionar); M (Metástase).

Resultados: Foram incluídos 59 doentes: 53 carcinóides típicos e seis carcinóides atípicos. Destes, 90% foram submetidos a cirurgia. O follow-up médio foi de 57 meses. A mortalidade operatória foi de 2% ($n = 1$) tratando-se de cirurgia paliativa para um doente em estádio IV. Em 49 doentes não se verificou envolvimento ganglionar (N0), um doente apresentava doença N1, oito doença N2 e um doente doença N3. A sobrevivência global aos cinco anos foi de 79,2%: 80,2% nos carcinóides típicos e 66,7% nos carcinóides atípicos ($p < 0,05$). Nos doentes T1, a sobrevivência foi de 88,1% e de 58,2% nos T2-T4 ($p < 0,01$). Nos doentes N0 a sobrevivência aos cinco anos de 89,7% e de 36% para os doentes N1-N3 ($p < 0,001$). Os doentes com doença M0 apresentaram uma sobrevivência aos cinco anos de 85,9% sendo de 0% nos doentes M1 ($p < 0,01$). Dos 11 doentes que necessitaram de quimioterapia adjuvante, 45,4% eram carcinóides atípicos.

Discussão: Na nossa série, a cirurgia no tumor carcinóide pulmonar demonstrou-se segura, com uma baixa taxa de complicações no pós-operatório. Observou-se pior prognóstico em doentes com tumor carcinóide atípico, tumores com mais de 3 cm, com envolvimento ganglionar ou presença de metástase. A sobrevivência aos cinco anos nos tumores carcinóides típicos foi excelente (80,2%), correspondente à encontrada na literatura. No tumor carcinóide atípico, a sobrevivência aos cinco anos foi de 66,7% também concordante com os dados obtidos em estudos anteriores.

Conclusões: Os tumores carcinóides pulmonares são na maioria carcinóides típicos com uma excelente sobrevivência a longo prazo. A cirurgia de ressecção é o tratamento de eleição nestes doentes. Os fatores relacionados com um pior prognóstico foram o subtipo histológico (carcinóides típicos versus carcinóides atípicos), o tamanho do tumor, o envolvimento ganglionar e a presença de

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metástases.

Palavras-chave: Neoplasias do Pulmão; Tumor Carcinóide; Estadiamento.

INTRODUCTION

Pulmonary carcinoid tumours are rare well-differentiated neuroendocrine tumours of the lung, corresponding to 0.4 to 3% of resected lung tumours and 23 to 30% of all neuroendocrine lung tumours.[1,2] There are two types (typical and atypical) according to the 2004 World Health Organization (WHO) histological criteria. Typical carcinoid tumour is above 5 mm in size, presents with < 2 mitoses/2 mm^2 and necrosis is absent. In atypical carcinoid tumours there are 2-10 mitoses, necrosis or architectural distortion.[3] From a clinical perspective, these are usually central tumours progressing to bronchial obstruction. The most common symptoms include a cough or haemoptysis, although many patients present with no symptoms.[4,5] They can affect people of all ages and there are no differences regarding gender. As regards outcome, when compared to other non-small cell lung carcinoma, carcinoid tumours usually present a favourable outcome upon surgical resection. Typical carcinoid tumours are rarely invasive and have a five-year survival rate between 87 and 100%[6-7] while atypical carcinoid have a higher risk of invasion and five-year survival rate between 25 and 69%.[8,9] Few studies have assessed the outcome of carcinoid tumours according to the histological subtype, type or surgery, size of the tumour, lymphatic invasion and the presence of distant spread, following the new TNM classification.[10,11] Our study aimed to characterise patients with carcinoid tumours and to analyse the factors that affected the outcome of patients attending to a tertiary healthcare unit.

MATERIAL AND METHODS

This was a retrospective study involving all patients diagnosed with lung carcinoid tumour attending a Hospital Unit in *Centro Hospitalar e Universitário de Coimbra* between 1999 and 2010. Data were obtained from patient's clinical record and included different epidemiological and clinical variables (including history and physical examination), technical procedures (including bronchoscopy, transthoracic biopsy and surgery) as well as outcome data. The histological diagnosis was confirmed by a neuroendocrine carcinoma-experienced pathologist and tumours were classified according to the WHO criteria.[3] Staging was carried out based on 2009 TNM classification for non-small cell lung cancer: T (Tumour); N (Nodes); M (Metastases).[12,13] The statistical analysis used IBM's version 17 SPSS software. The five-year survival was estimated following the Kaplan and Meier method. Statistical significance was considered for $p < 0.05$.

RESULTS

Our study included 59 patients (33 male) and the mean age of the patients was 54.5 ± 14.5 (16 - 79) (Fig. 1).

According to the histological classification, 53 patients presented with a typical carcinoid tumour (TC) and six with an atypical carcinoid (AC). The description of our group of patients is shown in Table 1.

Major patient's presentation symptom was a cough (47%), chest pain (34%), dyspnoea (29%), haemoptysis (15%) and Cushing's syndrome (2%), while 29% of the patients were asymptomatic. This neoplasm was diagnosed on chest CT-scan with a central nodule in 51% of the patients, a peripheral nodule in 34% and an image of atelectasis in 15%. From those patients presenting with central nodules (n = 30), most were located to the right upper and lower lobe. Tumour locations are shown in Table 2.

When symptoms were compared to tumour location (central *vs*. peripheral), haemoptysis was more frequent in those patients with central tumours (p = 0.012). No statistical significant differences were found regarding dyspnoea, cough or chest pain.

Tumour staging is shown in Table 3. The absence of lymphatic invasion was found in 49 patients (N0). In the group of patients with TC (n = 53 patients), 47 patients (89%) did not show any lymphatic involvement (N0), while in the AC group (6 patients), half of the patients presented in the N2 or N3 staging category.

As regards diagnosis, flexible bronchoscopy was performed in 69% (n = 41) of the patients and the tumour was identified in 90% of these (therefore considered as central).

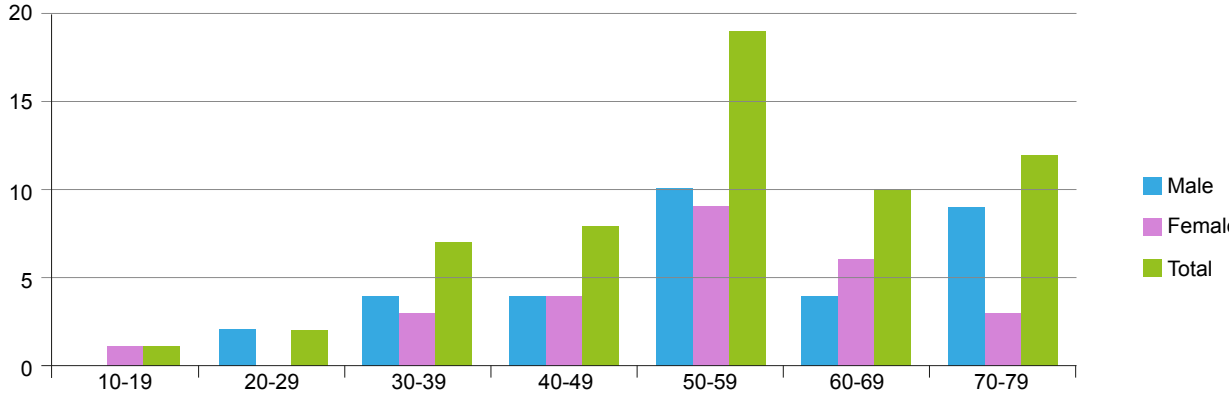

Figure 1 - Age and gender distribution of our group of patients

Table 1 - Histological, clinical and radiological characteristics

Histological, clinical and radiological characteristics		
Histological	***n***	**%**
Typical carcinoid	53	89.8%
Atypical carcinoid	6	10.2%
Symptoms		
Cough	28	47.0%
Chest pain	20	34.0%
Dyspnoea	17	29.0%
Haemoptysis	9	15.0%
Cushing's Syndrome	1	2.0%
Asymptomatic	17	29.0%
Radiology		
Central nodule	30	51.0%
Peripheral nodule	20	34.0%
Atelectasis	9	15.0%

Table 2 - Location of bronchial carcinoid tumours

Location of bronchial carcinoid tumours		
Location	*n*	%
Right main bronchus	2	3.4%
Left main bronchus	5	8.5%
Right upper lobe	11	18.7%
Middle lobe	10	16.9%
Right lower lobe	10	16.9%
Left upper lobe	13	22.0%
Left lower lobe	8	13.6%
TOTAL	**59**	**100%**

In central tumours (*n* = 37), 83% were TC. All these patients underwent a bronchial biopsy: a carcinoid tumour was identified in 76% of the patients, an inconclusive histological result was obtained in 21% and another lung neoplasm subtype was found in 3% of the patients. Trans-thoracic needle biopsy was performed in 12% of the patients and in 86% of these a carcinoid tumour was identified and showed another type of lung neoplasm in 14% of the patients.

Most patients (*n* = 53; 90%) underwent surgery. The presence of an invasive cancer was the most frequent cause for non-surgical therapy (four patients); one patient underwent endoscopic therapy and one patient refused surgery. The surgical procedure involved a lobectomy in 64% of the patients, atypical sublobar resection in 26%, pneumectomy in 7% and bilobectomy in 4%. Radical mediastinal lymphadenectomy was also performed in all the patients. Operative mortality was 2% (one patient) and related to palliative surgery in a 57-year old patient with single contralateral lung invasion. Surgery involved the removal of a large right hilar mass with mediastinal and right atrial compression. Postoperative complications were observed in 24% of the patients: pleural effusion (*n* = 6; 10%), pneumothorax (*n* = 5; 8%), empyema (*n* = 1; 2%) and haemorrhage (*n* = 1; 2%), with a mean 57-month follow-up (0 - 144). Fifteen patients died due to neoplasm-related (*n* = 9) and non-related causes (*n* = 6; three patients died due

Table 3 - Tumour staging

Variable		*n*	%
Primary tumour	T1a	25	42.4%
	T1b	16	27.1%
	T2a	10	17.0%
	T2b	2	3.4%
	T3-T4	6	10.1%
Lymphatic invasion (Nodes)	N0	49	83.0%
	N1	1	1.7%
	N2	8	13.6%
	N3	1	1.7%
Distant spread (Metastases)	M0	55	93.0%
	M1	4	7.0%
Stage	I	49	83.0%
	II	1	1.7%
	III	5	8.5%
	IV	4	6.8%

Table 4 - Patient's survival

		n	Mortality	Five-year survival	*p*
Gender	Male	33	33.3%	71.2%	
	Female	26	15.4%	90.4%	**> 0.05**
Age	16-40	11	9.0%	90.9%	
	41-60	30	23.3%	77.1%	
	> 60	18	38.9%	76.2%	**> 0.05**
Subtype	Typical	53	20.8%	80.2%	
	Atypical	6	66.7%	66.7%	**< 0.05**
Tumour	T1	41	14.6%	88.1%	
	T2-T4	18	50.0%	58.2%	**< 0.01**
Lymphatic invasion	N0	49	16.3%	89.7%	
	N1-N3	10	70.0%	36.0%	**< 0.001**

to myocardial heart infarction and three due to ischaemic stroke). From the deceased patients, 11 presented with TC and four with AC. Eight patients presented with an invasive cancer: two with AC and six with TC. From those with TC, four presented with lung invasion and two with liver invasion. The patients with AC presented with lung invasion.

We did not find any differences regarding survival between the patients who underwent an atypical sub-lobar resection and those who underwent a lobar resection (*Log-rank*; $p = 0.359$).

A 79.2% five-year overall survival was found (Table 4): 71.2 % in male patients and 90.4% in female patients ($p > 0.05$). In this study, a 90.9%, 77.1% and 76.2% five-year survival respectively related to the patient's age group (16-

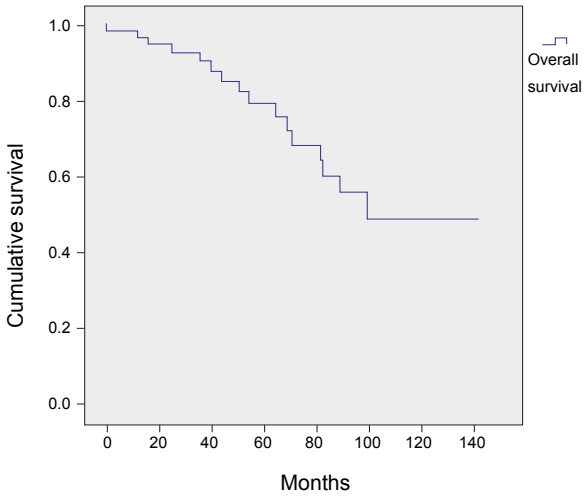

Figure 2 - Carcinoid tumours – overall survival curve

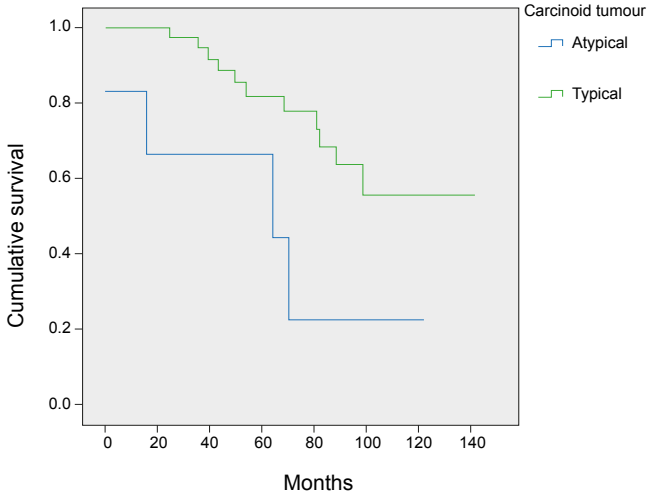

Figure 3 - Survival curve in patients with TC *vs.* AC

40; 41-60; > 60 years of age)at the time of diagnosis (p > 0.05). An 80.2 and 66.7% five-year survival was found in TC and AC patients, respectively (p < 0.05). An 88.1% five-year survival was found in patients with T1 tumours (less than 3 cm in size) whereas in the remaining patients (T2-T4) it was 58.2% (p < 0.01). Stage N0 patients showed 89.7% five-year survival which was 36% in the remaining patients (N2-N3) (p < 0.001). Stage M0 patients showed 85.9% whereas stage M1 patients showed 0% five-year survival (p < 0.01).

These results are shown in Table 3. The analysis of survival using Kaplan-Meier curves is shown in Fig. 2 and 3.

From the 11 patients with an indication to adjuvant chemotherapy, 45.4% were AC-patients. Chemotherapy involved the use of cisplatin and etoposide in all patients.

DISCUSSION

In our study, as expected [3,12], bronchopulmonary carcinoid tumours predominantly affected patients in their fifties, in a younger age group than patients with other lung neoplasms,, Similarly, a 1.26 male-to-female ratio was found, in line with what has been found by Filosso *et al.* (1.33 ratio) and by Cardillo *et al.* (1.11).[14-16] Most patients were symptomatic (71%), corresponding to a slightly higher percentage than what has been previously described.[16,17] As regards primary location, most tumours were located in the upper lobes, unlike some clinical series that found the middle lobe as the predominant location for lung carcinoid tumours.[18]

Bronchoscopy is a crucial test for a patient's evaluation as carcinoid tumours frequently present as central tumours. In our group of patients, 90% presented with central tumours, allowing for bronchial biopsies to be performed, contributing in turn to a timely diagnosis. However, the histological diagnosis based on the bronchial biopsy needs to be confirmed by the examination of the surgical sample. As previously described, the histological examination of the bronchial biopsy showed unspecific changes in 21% of the patients and another lung neoplasm subtype in 3%. Trans-thoracic needle biopsy showed to be important in peripheral tumours, not accessible by the bronchoscopy approach.

Most tumours considered as central (endoscopically visible tumours) were TC. Although the reason for this association is not be explained, this has already been described in other previous clinical series.[1]

Surgical resection is the treatment of choice for lung carcinoid tumours. From the 53 patients who underwent surgery, 6 presented with lymphatic invasion (11%). Atypical sublobar resection in patients with central TC and no lymphatic invasion allows for optimal long-term survival.[2,17] Radical mediastinal lymphadenectomy should always be performed, although there are few studies regarding this issue.[19,20]

In our group of patients, surgery was found to be a safe approach, with a low rate of postoperative complications.

Atypical carcinoid tumours show higher risk of invasion and worse outcome than TC tumours. A worse outcome was found in patients with AC, in tumours with more than 3 cm in size, with lymphatic invasion and with distant spread. An excellent five-year survival was found in patients with TC (80.2%), in line with the literature.[1,6] A 66.7% five-year survival was found in patients with AC, also in line with previous studies.[3,6]

No differences were found between atypical sub-lobar resection *vs.* lobar resection regarding patient's survival.

We should note that the fact that our study was carried out between 1999 and 2010 may represent a limitation, because other diagnostic and staging methods that have been introduced thereafter have changed clinical practice and will be the object of further studies.

CONCLUSION

Our group of patients showed similar characteristics to those previously described. Most patients presented with resectable carcinoid tumours and with a favourable outcome. Typical carcinoid tumours with no lymphatic invasion were the most frequently found subtypes. Histology (TC *vs.* AC), tumour's size, lymphatic invasion and the presence of distant spread were the factors related to worse outcome.

CONFLICTS OF INTEREST

The authors declare that there was no conflict of interest in writing this manuscript.

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