J Bras Pneumol. 2019;45(5):e20180140
http://dx.doi.org/10.1590/1806-3713/e20180140

Bronchial carcinoid tumors: second primary neoplasms and outcomes of surgical treatment

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Submitted: 29 April 2018.
Accepted: 9 January 2019.

Study carried out at A.C. Camargo Cancer Center, São Paulo (SP) Brasil.

ABSTRACT

Objective: To analyze determinants of prognosis in patients with bronchial carcinoid tumors treated surgically and the potential concomitance of such tumors with second primary neoplasms. **Methods:** This was a retrospective analysis of 51 bronchial carcinoid tumors treated surgically between 2007 and 2016. Disease-free survival (DFS) was calculated by the Kaplan-Meier method, and determinants of prognosis were evaluated. Primary neoplasms that were concomitant with the bronchial carcinoid tumors were identified by reviewing patient charts. **Results:** The median age was 51.2 years, 58.8% of the patients were female, and 52.9% were asymptomatic. The most common histology was typical carcinoid (in 80.4%). Five-year DFS was 89.8%. Ki-67 expression was determined in 27 patients, and five-year DFS was better among the patients in whom Ki-67 expression was ≤ 5% than among those in whom it was > 5% (100% vs. 47.6%; p = 0.01). Concomitant primary neoplasms were observed in 14 (27.4%) of the 51 cases. Among the concomitant primary neoplasms that were malignant, the most common was lung adenocarcinoma, which was observed in 3 cases. Concomitant primary neoplasms were more common in patients who were asymptomatic and in those with small tumors. **Conclusions:** Surgical resection is the mainstay treatment of bronchopulmonary carcinoid tumors and confers a good prognosis. Bronchial carcinoid tumors are likely to be accompanied by second primary neoplasms.

Keywords: Carcinoid tumor/diagnosis; Carcinoid tumor/surgery; Neoplasms, second primary; Lung neoplasms.

INTRODUCTION

Carcinoid tumors are rare malignant neoplasms originating from neuroendocrine cells. The bronchopulmonary system is the second most common site, harboring 20-25% of carcinoid tumors. Bronchial carcinoid tumors account for 1-5% of all cases of lung cancer.[1-3] Slow growth and a low metastasis rate characterize carcinoid tumors. Histologically, pulmonary carcinoid tumors are classified as typical or atypical according to some characteristics, such as number of mitoses and presence of necrosis.[4] It has been suggested that the classification be changed to well- to moderately differentiated neuroendocrine tumors; however, the World Health Organization classification of tumors maintains the terms typical and atypical carcinoid for bronchial tumors.[4]

Principles of staging and surgical treatment of carcinoid tumors are the same as for other types of lung cancer. However, since carcinoid tumors have a less aggressive behavior, various aspects of clinical and surgical management remain controversial. The most common prognostic determinants are histological classification, tumor size, and Ki-67 expression. However, because most case series are small, there is no consensus regarding determinants of clinical outcomes.[5,6] Another controversial aspect related to carcinoid tumors is their association with second primary neoplasms. Carcinoid tumors from different primary sites have been associated with second primary neoplasms in approximately 20% of cases.[1,7-9]

The objective of the present study was to analyze determinants of prognosis in patients with bronchial carcinoid tumors treated surgically and the potential concomitance of such tumors with second primary neoplasms.

METHODS

This was a retrospective study of data collected from medical charts of patients with a histological diagnosis of bronchial carcinoid tumor submitted to surgical resection at the A.C. Camargo Cancer Center, located in the city of São Paulo, Brazil, between 2007 and 2016. During the study period, pulmonary resections were performed in 1,623 patients, and carcinoid tumor resections were identified in 60. Of those, 3 were excluded because they had not been submitted to complete surgical resection and 6 were excluded because of missing data. Therefore, 51 patients (3.1%) were submitted to complete surgical resection due to bronchial carcinoid tumor and were included in the present study.

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Financial support: None.

Chest CT and bronchoscopy were performed in all patients. Tumors were classified as central, when they were directly visualized during bronchoscopy, or peripheral, when they were not. Staging workup was based on chest CT, bronchoscopy, positron emission tomography-CT, brain magnetic resonance imaging, and scintigraphy with radiolabeled octreotide, at the discretion of the attending physician.

Pathologists reviewed all paraffin blocks in order to define the histological diagnosis and classify them as typical or atypical carcinoid tumors in accordance with the criteria established by the World Health Organization.[10,11] Final histological diagnosis and classification were established after analysis of the surgical specimens.

The compiled data included age, gender, smoking history, symptoms, diagnostic method, tumor location, clinical stage, type of surgical resection, tumor size, number of resected mediastinal lymph nodes, histological classification, Ki-67 status, presence of second primary neoplasms, and status in the last follow-up evaluation. Tumor staging was in accordance with the 7th edition of the TNM classification of malignant tumors.[12]

Primary neoplasms that were concomitant with bronchial carcinoid tumors were identified by reviewing patient charts. Depending on when they were diagnosed, concomitant neoplasms were classified as previous to, synchronous with, or subsequent to bronchial carcinoid tumors. Synchronous diagnosis was defined as diagnosis of a second primary tumor within 3 months of the diagnosis of bronchial carcinoid tumor.

All statistical analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as median (minimum-maximum) in order to describe patient characteristics. Differences between categorical variables were assessed by the chi-square test or Fisher's exact test, as appropriate. Survival rates were calculated by the Kaplan-Meier method, and groups were compared by the log-rank test. A p-value < 0.05 was considered statistically significant for all tests.

The study was approved by the local research ethics committee (Protocol no. 1.607.727).

RESULTS

During the study period, 51 patients were identified and included in the analysis. Ages ranged from 16.6 years to 86.1 years (median, 51.2 years). Most of the patients were asymptomatic (52.9%). Among those presenting with clinical manifestations (n = 24), the most common symptoms were pneumonia, in 16; wheezing, in 7; hemoptysis, in 6; dyspnea, in 3; and cough, in 1. Tumor size ranged from 0.4 cm to 7.5 cm (median, 2.5 cm). Other clinicopathological characteristics are shown in Table 1.

All patients were submitted to complete surgical resection. Lobectomy was performed in 43 cases (84.3%); wedge resection, in 4 (7.8%); and pneumonectomy, in 4 (7.8%). In 9 patients (17.6%), a bronchoplastic procedure or a sleeve resection was associated with lobectomy, and pulmonary arterioplasty was performed in 1. The median number of removed lymph nodes was 6 (range, 0-31), lymph node metastasis being found in 3 patients (5.8%). Postoperative length of hospital stay ranged from 3 days to 20 days (median, 6 days). Postoperative complications were identified in 11 patients (21.6%): prolonged air leak, in 3; pleural effusion, in 2; hemothorax, in 1; chylothorax, in 1; pleural empyema, in 1; chronic pain, in 1; wound infection, in 1; and acute abdomen caused by obstruction, in 1. No postoperative mortality occurred.

The follow-up period ranged from 0.3 months to 115.4 months (median, 37.6 months). Systemic recurrence was observed in 3 patients (lung, bone, adrenal gland, and pleura). No local recurrence was observed, and there were no cancer-related deaths.

Five-year disease-free survival (DFS) was 89.8% (Figure 1). Determinants of 5-year DFS are shown in Table 2. Only a high level of Ki-67 expression was related to worse DFS (Figure 2). Patients with Ki-67 expression ≤ 5% showed higher DFS than those with Ki-67 expression > 5%. However, Ki-67 expression was determined in only 27 patients. Although DFS was higher in patients with typical carcinoid tumors than in those with atypical carcinoid tumors (92% vs. 82%), the difference was not significant (p = 0.55).

Second primary neoplasms were observed in 14 patients (27.5%). Of those, 11 were diagnosed with

Table 1. Clinicopathological characteristics of the study patients (N = 51).

Characteristic	n	%
Gender		
Female	30	41.2
Male	21	58.8
Smoking		
Yes	16	31.4
No	35	68.6
Clinical manifestation		
No symptoms	27	52.9
Clinical symptoms	24	47.1
Histology		
Typical	41	80.4
Atypical	10	19.6
Affected side		
Right	33	64.7
Left	18	35.3
Location		
Central	34	66.7
Peripheral	17	33.3
Lobe of origin		
Upper	22	43.1
Middle	08	15.7
Lower	21	41.2

typical bronchial carcinoid tumor. Only 5 patients were smokers. Of the 14 patients with second primary neoplasms, 11 (21.5%) had malignant neoplasms and 3 (6.0%) had benign neoplasms. The most common malignant neoplasms were lung adenocarcinoma, in 3, and ovarian carcinoma, in 2. The characteristics of second primary neoplasms are presented in Table 3.

Second primary neoplasms were classified as previous to, synchronous with, and subsequent to bronchial carcinoid tumors in 6 (11.8%), 5 (9.8%), and 3 (5.9%) of the patients, respectively. The median time between the diagnosis of previous primary neoplasms and that of bronchial carcinoid tumors was 20.6 months (range, 7.8-196.8 months), whereas the median time between the diagnosis of subsequent primary neoplasms and that of bronchial carcinoid tumors was 34.7 months (range, 17.8-42.6 months).

Correlations between different characteristics of bronchial carcinoid tumors and concomitant primary neoplasms are shown in Table 4. Concomitant primary neoplasms were found to be most common in asymptomatic patients and in those with small (T1 or T2) bronchial carcinoid tumors (Table 4).

DISCUSSION

Carcinoid tumors comprise 0.5% of all malignant neoplasms, and only 20-25% of those arise from the bronchopulmonary system.[1] Because it is a rare neoplasm, most of the studies on carcinoid tumors are retrospective in nature and include a small number of patients recruited over a long period of time.[5,6] Our study included 51 patients over a period of 10 years, similar to or even greater than other series that reported cases in a single institution.[6,13,14]

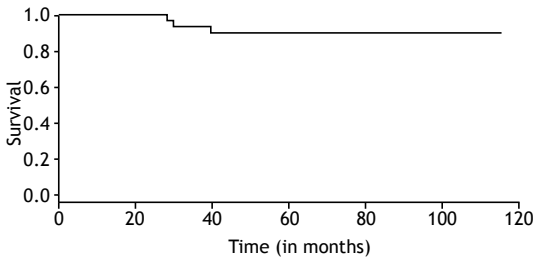

Figure 1. Disease-free survival of patients with bronchial carcinoid tumors submitted to complete surgical resection.

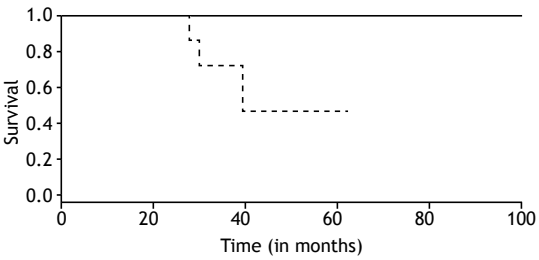

Figure 2. Disease-free survival and Ki-67 expression. Continuous line: Ki-67 ≤ 5%. Dashed line: Ki-67 > 5% (p = 0.01).

Table 2. Univariate analysis of determinants of five-year disease-free survival.

Variable	n	Five-year DFS, %	p
Age, years			
≤ 55	28	88.2	0.64
> 55	23	93.7	
Gender			
Male	21	93.3	0.56
Female	30	85.9	
Smoking status			
Smoker	16	90	0.82
Nonsmoker	35	89.5	
Histology			
Typical	41	92	0.55
Atypical	10	80	
Clinical presentation			
Asymptomatic	27	92.9	0.48
Symptomatic	24	86.7	
Location			
Central	31	88.2	0.64
Noncentral	20	91.7	
T Stage			
T1 and T2	32	90.5	0.95
T3	19	90	
Ki-67 expression			
≤ 5%	19	100	0.01
> 5%	08	47.6	

DTS: disease-free survival; and T: tumor.

In the present study, most of the carcinoid tumors were classified as typical, with no clinical manifestations, and the size of the tumor was small. The same characteristics have been described in different studies, suggesting that carcinoid tumors have an indolent clinical behavior.[5,14] Clinical manifestations have been reported in 40-50% of cases,[2,7,15] the most common being recurrent pneumonia, hemoptysis, wheezing, dyspnea, and cough, as in our study.

Surgical resection is the mainstay curative treatment of bronchial carcinoid tumors; however, there are some questions regarding the extent of resection and the role of mediastinal lymphadenectomy.[16,17]

Table 3. Characteristics of second primary neoplasms in patients with bronchial carcinoid tumors.

Primary site and type	n
Benign neoplasms	
Parotid adenoma	1
Bronchial neurofibroma	1
Parathyroid adenoma	1
Malignant neoplasms	
Lung, adenocarcinoma	3
Ovarian, serous carcinoma	2
Colorectal, adenocarcinoma	1
Melanoma	1
Palate, squamous cell carcinoma	1
Thyroid, papillary carcinoma	1
Testis, germ cell tumor	1
Cervix, squamous cell carcinoma	1

Some authors have suggested sublobar resection as an appropriate surgical approach for peripheral typical bronchial carcinoid tumors. Nevertheless, other authors recommend lobectomy/pneumonectomy regardless of the histological type.[18-20] Given that all of the aforementioned studies were retrospective in nature and compared heterogeneous groups of patients, it is difficult to draw any definitive conclusions about the extent of surgical resection to treat bronchial carcinoid tumors.[16] Sublobar resection could be an adequate procedure for small peripheral typical bronchial carcinoid tumors. In addition, pneumonectomy should be avoided when performing bronchoplasty or arterioplasty.[1,19-21]

There are no definitive studies addressing the role of mediastinal lymphadenectomy in long-term survival. One group of authors found mediastinal lymph node metastases in 11.1% of cases, and most of the cases classified as N2 (83.3%) were not identified during preoperative evaluation.[22] Because mediastinal lymph node metastases appear to be a determinant of prognosis, resection of mediastinal lymph nodes could be important for adequate pathological staging and treatment.

As in other studies,[13,17,18] lobectomy was the most common type of surgical intervention performed (in 84.3% of cases) in the present study. In order to avoid pneumonectomy, a bronchoplastic procedure was performed in 9 cases (17.6%), and arterioplasty was necessary in 1 patient. Mediastinal lymphadenectomy is our standard approach for all lung cancers. However, in our series of bronchial carcinoid tumors, no lymph

Table 4. Correlation of clinicopathological variables between patients with bronchial carcinoid tumors with and without second primary neoplasms.

Variable	Second primary neoplasms		p
	Yes	No	
Age, years			
≤ 55	5 (17.9%)	23 (82.1%)	0.09
> 55	9 (39.1%)	14 (60.9%)	
Gender			
Male	8 (38.1%)	13 (61.9%)	0.15
Female	6 (20.0%)	24 (80.0%)	
Smoking status			
Smoker	5 (31.2%)	11 (68.8%)	0.68
Nonsmoker	9 (25.7%)	26 (74.3%)	
Histology			
Typical	13 (31.7%)	28 (68.3%)	0.25
Atypical	1 (10.0%)	9 (90.0%)	
Clinical presentation			
Asymptomatic	10 (30.3%)	23 (69.7%)	0.05
Symptomatic	4 (22.2%)	14 (77.8%)	
Location			
Central	7 (22.6%)	24 (77.4%)	0.33
Noncentral	7 (35.0%)	13 (65.0%)	
T Stage			
T1 and T2	12 (37.5%)	20 (62.5%)	0.05
T3	2 (10.5%)	17 (89.5%)	

T: tumor.

nodes were removed in 3 patients. Those patients were older and underwent sublobar resection of small and peripheral tumors. Metastases were found in only 3 (5.8%) of the patients submitted to mediastinal lymphadenectomy. Despite these controversial aspects, we believe that lobectomy associated with mediastinal lymphadenectomy should be performed in all patients with adequate clinical performance, regardless of histological type and absence of lymph node metastases in clinical staging. We recommend this approach because sometimes complete histological classification is only obtained after complete resection and analysis of an entire specimen. The possible presence of clinically unsuspected lymph node metastases demands lymphadenectomy.

Since bronchial carcinoid tumors usually have a less aggressive biological behavior, the overall survival is good. Various studies have reported low rates of recurrence and 5-year overall survival higher than 80%.[5,18,21]

Some prognostic factors can help predict more aggressive biological behavior among bronchial carcinoid tumors. Atypical carcinoid tumors and lymph node metastasis are described as factors associated with a worse prognosis.[5,15,21,23] Histology is considered to be an independent prognostic factor in most studies.[2,5,15,19,21,24] Contrary to what has been described in most studies,[5-7,11,21] 5-year DFS was not significantly different between typical (92%) and atypical (80%) carcinoid tumors in our study. According to Cardilo et al.,[24] histology is not an independent determinant of survival. Kornerup et al.[25] evaluated 68 patients with carcinoid tumors and found no differences in overall survival between typical and atypical tumors. With regard to histology, our results are inconsistent with those of other studies.[5-7,11,21] This might be due to the fact that there were few (only three) recurrent events and the median follow-up period was short (i.e., 37.6 months) in our study.

In our study, Ki-67 expression was the only variable associated with prognosis. Because determination of Ki-67 expression is not routinely performed at our institution, data on Ki-67 expression were available for 27 patients only, and any statistical analysis of a small group of cases should be cautiously interpreted. Nevertheless, DFS was significantly higher in patients with Ki-67 expression < 5% in our sample. Kornerup et al.[25] also found that the histological classification (typical or atypical tumors) had no influence on the outcomes, but Ki-67 expression was an important prognostic factor. Similarly, Zahel et al.[26] questioned the reliability of that histological classification to determine the biological behavior of pulmonary carcinoid tumors. They concluded that Ki-67 expression and mitotic count are better predictors of the clinical behavior of these tumors.[25,26] Because of those controversies, prognostic factors in patients with bronchial carcinoid tumors should be continuously evaluated.

The occurrence of second primary neoplasms in patients with carcinoid tumors has been described over the years. Berge and Linel[8] were the first to describe it, in 1976; they found second primary neoplasms in 40.7% of the patients in their retrospective study. However, neoplasms were incidentally found in 44.5% of autopsies, a proportion that is similar to that reported for second primary neoplasms in patients with carcinoid tumors and suggests that the incidence of second primary malignant neoplasms in patients with carcinoid tumors is no higher than that reported for patients with other cancers.[8] Nevertheless, other, more recent studies have shown that the prevalence of patients with carcinoid tumors and second primary neoplasms ranges from 18% to 25%.[9,27-29]

Our study found a strong association between bronchial carcinoid tumors and other primary neoplasms (27.5%). Most of the bronchial carcinoid tumors were identified after detection of other neoplasms and were small and asymptomatic. These findings suggest that bronchial carcinoid tumors constituted incidental findings in patients with previous neoplasms. This remains to be explained. It might be a simple association, or, as some authors have suggested,[30] the high frequency of concomitant neoplasms might be the result of mitogenic activity of growth factors secreted by carcinoid tumors.

The present study has some limitations that should be considered: its retrospective nature, the small number of cases over a long period of time, the small number of recurrent events, and the short follow-up period.

In conclusion, the present study showed that bronchial carcinoid tumors are rare neoplasms and that complete surgical resection offers a good prognosis. Although additional studies are needed in order to identify determinants of prognosis, mitotic activity, as measured by Ki-67 expression, seems to be an important prognostic factor. Bronchial carcinoid tumors are likely to be accompanied by second primary neoplasms. The reasons for this association remain unclear, and additional studies are needed to address this question.

ACKNOWLEDGMENTS

We would like to thank A.C. Camargo Cancer Center Research Nurse Ana Carolina Scintini for data collection and tabulation.

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