Clinicopathological aspects of and survival in patients with clinical stage I bronchioloalveolar carcinoma*

Aspectos clínico-patológicos do carcinoma bronquioloalveolar e sobrevida em pacientes no estágio clínico I

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Resumo

Objetivo: Analisar os aspectos clínico-patológicos do carcinoma bronquioloalveolar (CBA) e a sobrevida em uma amostra de pacientes com estadiamento clínico I. **Métodos:** Foram estudados retrospectivamente 26 pacientes com diagnóstico de CBA e estágio clínico I, , segundo a classificação *tumor-node-metastasis* (TNM, tumor-linfonodo-metástase),[15]operados no Instituto de Doenças do Tórax da Universidade Federal do Rio de Janeiro, na cidade do Rio de Janeiro, RJ, entre 1987 e 2007, quanto a variáveis clínico-patológicas e radiológicas, mortalidade e sobrevida. Os dados foram colhidos dos prontuários médicos dos pacientes e analisados estatisticamente. **Resultados:** Houve predomínio de mulheres (n = 16). A idade média ao diagnóstico foi de 68,5 anos. Houve predomínio de tabagistas (69,2%). As formas de apresentação assintomática (84,6%) e nodular (88,5%) foram as mais comuns. Houve predileção pelos lobos superiores (57,7%). O estágio patológico IB foi o mais comum, seguido pelos estágios IA e IIB (46,2%, 38,4% e 15,4%, respectivamente). Não houve óbitos hospitalares. Quatro pacientes faleceram durante o seguimento pós-operatório, com tempo livre de doença médio de 21,3 meses. A taxa de sobrevida global em cinco anos foi 83%. A probabilidade de sobrevida para os pacientes diagnosticados depois de 1999 tendeu a ser maior do que para aqueles diagnosticados até 1999 (taxa de sobrevida em três anos: 92% vs. 68%; p = 0,07). **Conclusões:** Os aspectos clínico-patológicos da amostra estudada foram semelhantes àqueles de estudos anteriores em pacientes com CBA.

Descritores: Adenocarcinoma bronquíolo-alveolar; Carcinoma pulmonar de células não pequenas; Pulmão; Tabagismo.

Abstract

Objective: To analyze the clinicopathological aspects of bronchioloalveolar carcinoma (BAC) and the survival in a sample of patients at clinical stage I. **Methods:** A retrospective study involving 26 patients diagnosed with clinical stage I BAC and undergoing surgery at the Thoracic Diseases Institute of the Federal University of Rio de Janeiro, in the city of Rio de Janeiro, Brazil, between 1987 and 2007. We analyzed clinicopathological and radiological aspects, as well as mortality and survival. The data, which were collected from the medical charts of the patients, were statistically analyzed. **Results:** Females predominated (n = 16). The mean age at diagnosis was 68.5 years. Most patients were active smokers (69.2%). The most common forms of presentation of BAC were the asymptomatic form (84.6%) and the nodular form (88.5%). Involvement of the upper lobes predominated (57.7%). Stage IB was the most common pathological stage, followed by stages IA and IIB (46.2%, 38.4% and 15.4%, respectively). There was no in-hospital mortality. Four patients died during the postoperative follow-up, with a mean disease-free survival time of 21.3 months. The overall five-year survival rate was 83%. The probability of survival for the patients diagnosed after 1999 showed a trend toward an increase when compared with that for those diagnosed up through 1999 (three-year survival rate: 92% vs. 68%; p = 0.07). **Conclusions:** The clinicopathological aspects of this study sample were similar to those of patients with BAC evaluated in previous studies.

Keywords: Adenocarcinoma, bronchiolo-alveolar; Carcinoma, non-small-cell lung; Lung; Smoking.

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Financial support: None.
Submitted: 8 April 2009. Accepted, after review: 14 December 2009.

Introduction

In developed countries, lung cancer is the principal cause of death from malignant neoplasia, in males and females alike.[1] A similar trend has been observed in developing countries. In Brazil, the incidence of lung cancer has increased since 1979; it is currently the leading cause of death from cancer in males and the second leading cause of such death among females.[2]

Bronchioloalveolar carcinoma (BAC), which accounts for approximately 3% of all cases of lung cancer, has received increasing attention from medical researchers in recent years.[3,4] This is attributable to the fact that BAC is one of the few types of lung cancer in which there is a lack of an association with smoking, and that, among females, the incidence of BAC is higher than is that of the other histological types of lung cancer.[4,5] In addition, the lepidic growth pattern of BAC, covering the respiratory epithelium and causing pneumonic or multinodular lesions, is unique.[5] Furthermore, the incidence of BAC has increased in comparison with that of the other histological types, and this has been attributed to the use of HRCT as a diagnostic or screening method, since HRCT can show small pulmonary lesions (ground-glass opacities) that conventional X-rays do not.[6]

In 1999, the World Health Organization (WHO) redefined the histopathological criteria for the diagnosis of BAC, restricting the diagnosis of BAC to patients with noninvasive tumors.[7] This redefinition was associated with an improvement in the clinical prognosis of BAC in comparison with that of forms of adenocarcinoma that were once considered "bronchioloalveolar adenocarcinomas".[8] The redefinition was stimulated by studies in which five-year survival rates for certain types of adenocarcinoma were 100%.[9,10]

EGF-RTwo studies published simultaneously[11,12] reported that BAC and its response to chemotherapy were most commonly associated with EGF-R mutations. Since then, chemotherapeutic agents targeting this cellular pathway have been developed, which can change the prognosis for many patients with BAC, even for those with BAC at more advanced stages.[13]

The most appropriate form of surgical treatment for BAC diagnosed at early stages (tumor ≤ 2 cm in diameter) has recently been discussed, since studies have shown five-year survival rates of nearly 100% in patients submitted to resection of sublobar nodules of 1-2 cm in diameter.[6,10,14]

The purpose of the present study was to analyze the clinicopathological characteristics of BAC—including clinical and radiological presentation, association with smoking, histopathology, treatment, morbidity, mortality and survival (the last having been subdivided into two periods: 1987-1999; and after 1999, when the new WHO definition was published)—in a specific population of patients with clinical stage I BAC submitted to surgical treatment in a thoracic surgery department.

Methods

A retrospective study involving 26 patients diagnosed with clinical stage I BAC in accordance with the tumor-node-metastasis (TNM) staging[15] was conducted by analyzing the data from the medical charts of the patients at the time of diagnosis. All of the patients underwent chest X-ray and bronchoscopy and were operated on by the surgical team of the Department of Thoracic Surgery of the *Hospital Universitário Clementino Fraga Filho* (HUCFF, Clementino Fraga Filho University Hospital) between 1987 and 2007.

We included patients who were diagnosed with BAC in accordance with the WHO criteria (established in 1999 and revised in 2004) and who did not present with stromal, lymphatic or pleural invasion.

We excluded patients in whom diagnosis had been based on cytological examination, as well as those in whom the postoperative follow-up had not been completed (thereby making it impossible to identify the clinical outcome—disease-free survival, recurrence or death).

Due to the low incidence of this histological type, as well as to the interest in comparing survival up through 1999 with survival after 1999, a long-term retrospective study was necessary. Therefore, we began by searching the records of the Department of Pathological Anatomy in order to identify patients who had been diagnosed with primary lung adenocarcinoma. By reviewing the histopathological reports, cytological reports and medical charts, we found 26 patients who met the inclusion criteria.

Data from the medical charts and histopathological reports of the selected patients were collected on a form designed for that purpose. In the cases in which there had been no appointments or entries in the medical chart within the last six months, the patients or their families were contacted via telephone.

The data in the forms were compiled in a spreadsheet and analyzed by the programs MS Excel® 2007 and STATISTICA, version 7 (StatSoft Inc., Tulsa, OK, USA). The normal distribution of the continuous variables was evaluated by the Kolmogorov-Smirnov test. The Student's t-test was used in order to compare patients in terms

Table 1 - Characteristics of the patients under study.

Characteristic		n	%	Mean	p
Age, years				68.5	10.9
Gender	Male	10	38.5		
	Female	16	61.5		
Race	White	22	84.6		
	Black	2	7.7		
	Mulatto	2	7.7		
Smoking	Yes	18	69.2		
	No	8	30.8		
	Smoking history, pack-years			52.8	38.4
Symptoms	Yes	4	15.4		
	No	22	84.6		
Bronchoscopy	Normal	22	84.6		
	Abnormal	4	15.4		
Radiology	Nodular	23	88.5		
	Pneumonic	3	11.5		
Location	RUL	7	26.9		
	ML	1	3.8		
	RLL	4	15.4		
	LUL	8	30.8		
	LLL	6	23.1		
cTNM	Ia	12	46.2		
	Ib	14	53.8		
	IIa	0	0		
	IIb	0	0		
pTNM	Ia	10	38.4		
	Ib	12	46.2		
	IIa	0	0		
	IIb	4	15.4		
Histological subtype	Nonmucinous BAC	24	92.3		
	Mucinous BAC	2	7.7		
Surgical procedure	Segmentectomy	1	3.8		
	Lobectomy	21	80.8		
	Bilobectomy	2	7.7		
	Pneumonectomy	2	7.7		
Complications	Hemothorax	2	7.7		
	Pneumonia	1	3.8		
	Air leak > 5 days	4	15.4		
	Dehiscence	1	3.8		
	Residual space	1	3.8		

RUL: right upper lobe; ML: middle lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe; cTNM: clinical tumor-node-metastasis stage; pTNM: pathological tumor-node-metastasis stage; and BAC: bronchioloalveolar carcinoma.

of gender, TNM stage and smoking history, values of $p < 0.05$ being considered significant. The occurrence of the different categorical variables was analyzed with the chi-square test. The descriptive analysis of the data is presented as mean ± SD or as n (%). The disease-free period was measured from the date of the surgical procedure to recurrence or death. The probability of survival was calculated by the Kaplan-Meier method, and survival time was measured from the date of the surgical procedure to the date of death or of the most recent appointment, the last two having been censored. The difference between subgroups in terms of survival was analyzed by the log-rank test.

The present study was approved by the Research Ethics Committee of the HUCFF.

Results

Females predominated in the sample, which comprised 26 patients diagnosed with BAC. The disease occurred principally in the sixth and seventh decades of life. Most patients were White. There was no significant difference ($p = 0.65$) between males and females in terms of the age at the onset of BAC (69.7 ± 10.1 years vs. 67.7 ± 11.5 years). Table 1 shows the characteristics of these patients.

Most patients were active smokers. There was no statistical difference ($p = 0.91$) between smokers and nonsmokers in terms of the mean age at diagnosis (68.3 ± 10.4 years vs. 68.9 ± 12.4 years) or between genders in terms of smoking history ($p = 0.11$).

Although the mean smoking history of N1 patients was greater than that of N0 patients (90.75 ± 31.55 pack-years vs. 41.85 ± 5.57 pack-years), this difference was not statistically significant ($p = 0.14$; Figure 1).

The most common clinical presentation was the asymptomatic form. Among the patients who presented with symptoms in the initial evaluation, cough and hemoptysis were the symptoms identified. All of the patients underwent bronchoscopy, and the results were normal in most. The abnormalities found were exophytic endobronchial lesion and diffuse mucosal hyperemia.

The most common form of presentation on CT scans was a peripheral pulmonary nodule or mass, and only 3 patients presented with the pneumonic form. The site most commonly affected was the left upper lobe, followed by the right upper lobe, the left lower lobe, the right lower lobe and the middle lobe (1 patient).

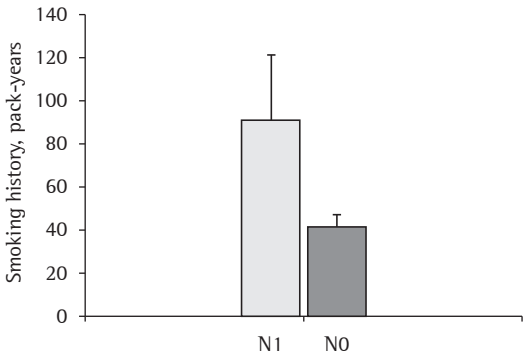

Figure 1 - Mean and standard deviation of the smoking history of patients in relation to lymph node dissemination (N0 or N1).

Before surgery, all of the patients had clinical stage I BAC—in accordance with the TNM staging[15]—without mediastinal lymph node enlargement on CT scans. In addition, only 1 patient had been diagnosed with neoplasia in the preoperative period, which means that the remaining 25 were diagnosed in the perioperative period. Therefore, routine preoperative mediastinoscopy was not performed.

All 26 patients underwent surgery, and the mean length of hospital stay was 11 ± 9 days, ranging from 5 to 40 days. Most of the surgical procedures performed were anatomical resections, lobectomy with mediastinal lymphadenectomy being the most common.

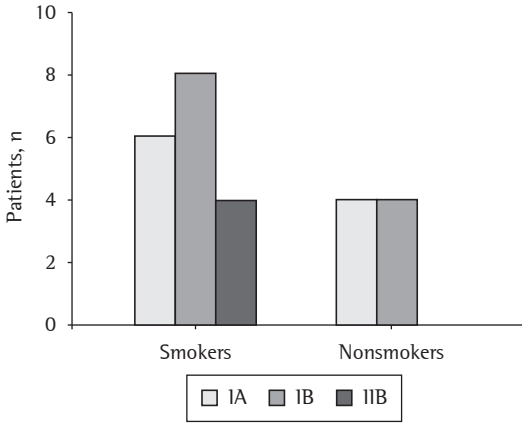

Figure 2 - Relationship between the pathological tumor-node-metastasis stage and the number of smoking or nonsmoking patients.

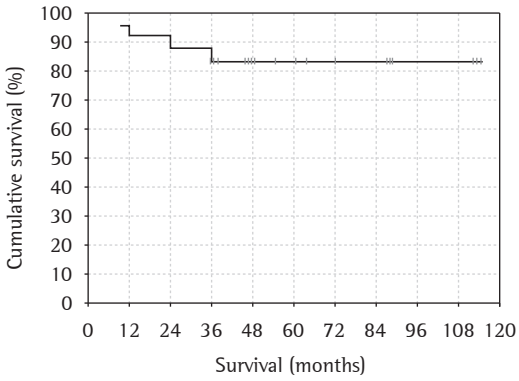

Figure 3 - Probability of overall survival of the study sample (Kaplan-Meier).

Upper bilobectomy, middle bilobectomy, right pneumonectomy and left pneumonectomy were performed in 1 patient each. Another patient presented with functional limitation, as detected by spirometry, and was therefore submitted to left lower lobe anterior segmentectomy.

The most common histological subtype was nonmucinous BAC. The pathological stage was different from the clinical stage in 4 patients (15.4%), which was due to the detection of positive lymph nodes at level 10 or higher in the surgical sample, characterizing what the TNM staging refers to as N1.

According to the evaluation of the surgical sample and of the mediastinal lymph nodes that were resected, the pathological stages were as follows: stage IA in 10 patients (38.4%); stage IB in 12 patients (46.2%); and stage IIB in 4 patients (15.4%). All of these were T2N1 (Figure 2). No stage IIA cases (T1N1) were observed.

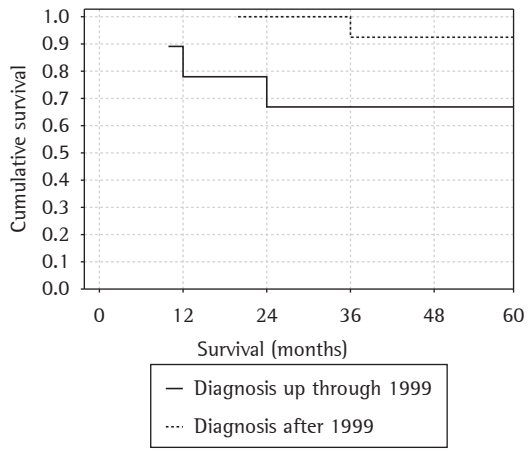

Figure 4 - Probability of survival (Kaplan-Maier) before and after 1999, based on the study sample (p = 0.07).

There were no deaths related to the surgical treatment. Surgical complications occurred in 8 patients. Most of these complications were minor complications, such as air leak through the chest tube for more than 5 days, persisting residual space and surgical wound dehiscence. Major complications included postoperative hemothorax in 2 patients, both of whom required a second surgical procedure, and pneumonia with respiratory failure.

All of the patients completed the postoperative follow-up. During the follow-up period, 4 patients died (in months 10, 12, 24 and 36, respectively). The three-year mortality rate was 15.4%.

The mean survival was 57 months, ranging from 10 to 244 months (95% CI: 38 ± 75 months). The mean follow-up period was 5.3 years (Figure 3). Patients diagnosed up through 1999 were compared with those diagnosed after 1999 in terms of the probability of survival. The probability of survival for the patients diagnosed after 1999 showed a trend toward an increase, although the difference was not statistically significant (p = 0.07; Figure 4).

Disease recurrence was observed in 6 patients (23%), 4 of whom presented with intrathoracic tumors (66.7%). The disease-free survival time for these patients ranged from 10 to 36 months (mean, 21.3 ± 9.8 months). The sites of recurrence were the spinal column (n = 2; 7.7%), the contralateral lung (n = 2; 7.7%), ipsilateral pleural effusion (n = 1; 3.8%) and local pulmonary recurrence (n = 1; 3.8%).

The 2 patients with recurrence in the contralateral lung underwent segmentectomy and survived (for 38 and 61 months, respectively). In patients with distant recurrence, chemotherapy with cisplatin (n = 1; 3.8%) and conventional radiotherapy (n = 3) were used due to, respectively, metastases to the spinal column (n = 2; 7.7%) and recurrence in the bronchial stump (n = 1; 3.8%).

Discussion

In recent decades, BAC, which is a subtype of adenocarcinoma, has received increasing attention. This is because studies have found that the clinical, radiological, epidemiological and biological characteristics of BAC are some-

what different from those of other types of non-small cell lung cancer (NSCLC), even when BAC is compared with all other adenocarcinomas.[1,8,9,16-19]

In our patient sample, the mean age was similar to that found in larger studies involving patients with BAC[8,20] and quite similar to the mean age at the onset of NSCLC in general, which ranges from 60 to 69 years.[21] As has been demonstrated in patients with stage IA NSCLC, being over 67 years of age is prognostic of poor survival.[22] However, the mortality rate reported in the present study (15.4% in 3 years) did not confirm that finding.

The predominance of females with BAC in the present study is consistent with the findings of larger studies involving patients with BAC.[16,17] However, other studies have reported a predominance of males.[8,18,23] It is speculated that EGF-R mutation is one of the determining factors of the predominance of females among patients with BAC.[23]

The incidence of smoking was similar to that described in the literature for BAC, which, like adenocarcinomas in general, has been characterized as the histological type of NSCLC that shows the weakest association with smoking.[24] However, the incidence of BAC is directly related to the duration of exposure to smoking and to pack-years, the relative risk decreasing in proportion to the time elapsed since smoking cessation. In the present study, it was impossible to confirm, statistically, that smoking history is associated with BAC that is more severe. However, the mean smoking history of N1 patients was considerably greater than was that of N0 patients.

The most common form of clinical presentation of BAC was the asymptomatic form. Cough was the most common symptom, and all of the symptomatic patients presented with alterations that were detectable by bronchoscopy. Therefore, bronchoscopy is an indispensable test in the preoperative staging, especially in symptomatic patients.

In patients with mucus hypersecretion, BAC is described as the most probable histological type.[25] However, since nonmucinous/nodular BAC clearly predominated in the study sample (and since the study sample comprised patients with BAC at earlier stages), mucus hypersecretion was not observed. The pneumonic form was observed on the CT scans of 3 patients. However, the diagnosis of mucinous BAC was confirmed in only 2.

The spectrum of presentation of BAC ranges from a peripheral solitary pulmonary nodule to multiple, bilateral pulmonary lesions with pleural effusion. The predominance of the nodular presentation in the present study is explained not only by the method used for selecting the sample, which was composed of patients with early-stage BAC, but also by the fact that the nodular presentation is the most common radiological presentation.[16] The pneumonic forms are commonly related to the mucinous subtype, presenting more aggressive behavior and worsening survival.[26] There were only 3 cases of this form in the present study.

Since the inclusion criterion was aimed at selecting patients at early stages, all of the patients under study were at clinical stage I. However, pathological staging revealed that 4 patients (15.39%) had N1 lymph node metastases, characterizing stage IIB due to T2N1M0.

The discrepancy between clinical staging and pathological staging is known and is attributable to the presence of metastases in lymph nodes ≤ 1 cm in diameter or, in the case of lymph nodes > 1 cm, by false-negative mediastinoscopy results, either due to inappropriate sampling or to anatomical limitations of the method. It should be highlighted that, in the present study, the lymph nodes that were affected were located in the hilar or intrapulmonary region (at level 7 or higher) and were inaccessible to cervical mediastinoscopy.[27] Therefore, preoperative mediastinoscopy would not have changed the staging in any of the patients under study, and the indiscriminate use of this procedure in patients with indeterminate pulmonary nodule is unjustified outside the scope of research.

Lobectomy is considered a surgical procedure that provides satisfactory oncologic results with acceptable functional loss for most patients with NSCLC. The lymphatic drainage and the lymph nodes are removed *en bloc* with the tumor, which often guarantees disease-free margins and reduces the probability of local recurrence.[16,18] Therefore, only 1 patient was surgically treated with segmentectomy, since the risk of a lobectomy was high due to the low functional reserve of the patient. The remaining patients underwent lobectomy, bilobectomy or pneumonectomy.

The surgical mortality related to pulmonary resection due to cancer ranges from 2.4% to 4%, and it can be as high as 9% when only pneumonectomy is considered.[16] No intraoperative deaths occurred in the present study. The postoperative complications observed in the present study were consistent with those reported in larger studies,[16] the most severe being hemothorax and pneumonia-related respiratory failure, which resulted only in longer hospital stays.

The 6 patients (23.1%) who presented with disease recurrence did so within the first 24 postoperative months. Of the 6 patients, 2 presented with recurrence in the contralateral lung and, after having undergone segmentectomy of the new lesions, remained free of any signs of recurrence, surviving for 31 and 68 months, respectively. Therefore, in patients with local pulmonary recurrence, resection should be considered.[16,28] Intrathoracic recurrence was observed in 66.7% of the cases under study, which confirmed that the potential for lymphatic and hematogenous dissemination of BAC is lower.[29]

The probability of five-year survival was above 80%, even considering that some of the patients under study were at stage IIB, at which the expected five-year survival for NSCLC patients is approximately 40%.[15] The mean survival rates for patients with stage I or stage II BAC are expected to be 92% and 63%, respectively; some studies evaluating patients with lesions < 2 cm in diameter have reported three-year survival rates of 100%.[30]

The survival curves showed a trend toward an increase in survival for patients who underwent surgery after 1999. However, this difference lacked statistical significance, probably due to the small size of the sample, which consisted of only 26 patients and in which there were only 4 deaths during the study period. According to the inclusion criterion, patients were classified according to the same histopathological criteria, and therefore, theoretically, there should have been no discrepancies among the diagnoses. Nevertheless, we believe that the trend toward an increase in survival for patients who underwent surgery after 1999 is due to the fact that the histopathological tests conducted after 1999 were more efficient in identifying for small signs of stromal invasion in the entire resected lesion, signs that would have sufficed to consider the lesion an invasive adenocarcinoma. One group of authors[8] analyzed 626 cases of BAC at all stages and noted this trend, which was attributed to the fact that, after 1999, in accordance with the new WHO definition, only in situ tumors were considered to be BAC, thereby excluding invasive adenocarcinomas, which are known to have a worse prognosis.

In the present study, most of the BAC patients were female smokers who presented clinically with the asymptomatic form. The nodular form affecting the upper lobes was the most common radiological presentation of BAC, showing the predominance of the nonmucinous histological subtype in the sample.

The clinical TNM staging was in disagreement with the pathological staging in 4 patients, due to N1 lymph node metastases. Anatomical resection was the surgical treatment that was most widely used, and lobectomy was the most common surgical procedure. The incidence of major surgical complications was low, and no surgical deaths occurred. Three-year mortality was 15.4%.

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