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Evaluation of radiological and pathological prognostic factors in surgically-treated patients with bronchoalveolar carcinoma ☆

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Abstract

Objective: The incidence of adenocarcinoma and bronchoalveolar carcinoma has increased in recent years. The aim of this study was to retrospectively evaluate radiological and pathological factors affecting survival in patients with bronchoalveolar carcinoma (BAC) or BAC associated with adenocarcinoma who underwent surgical treatment. **Methods**: From May 1988 to September 1999, 49 patients with BAC or BAC and adenocarcinoma underwent surgical treatment. Complete resection was performed in 42 patients. In these patients the impact of the following factors on survival was evaluated: stage, TNM status, radiological and pathological findings (percentage of bronchoalveolar carcinoma in the tumour, presence or absence of sclerosing and mucinous patterns, vascular invasion and lymphocytic infiltration). **Results**: Twenty-nine patients were male and 20 female. Mean age was 63 years. Five-year survival was 54%. Univariate analysis of the patients who underwent complete resection demonstrated a favourable impact on survival in stages Ia and Ib ($P = 0.01$) and in the absence of nodal involvement ($P = 0.02$) and mucinous patterns ($P = 0.02$). Mucinous pattern was also prognostically relevant at multivariate analysis ($P = 0.02$). In the 27 patients with stage Ia and Ib disease, univariate analysis demonstrated that the absence of mucinous pattern ($P = 0.006$) and a higher percentage of BAC ($P = 0.01$) favourably influenced survival. The latter data were also confirmed by multivariate analysis ($P = 0.01$). **Conclusion**: Surgical treatment of early-stage BAC and combined BAC and adenocarcinoma is associated with favourable results. However, the definition of prognostic factors is of utmost importance to improve the results of the treatment. In our series tumours of the mucinous subtype and with a lower percentage of BAC had a worse prognosis.

Keywords: Broncholaveolar carcinoma; Prognostic factors; Radiology; Pathology; Surgery

1. Introduction

The incidence of adenocarcinoma, and especially of its variant bronchoalveolar carcinoma (BAC), has steadily increased in the last few decades. In fairly recent series BAC accounted for over 20% of cases of non-small cell lung cancer (NSCLC) [1,2]. Nevertheless, a number of aspects still need to be clarified regarding the diagnosis and treatment of BAC. BAC is a tumour with a great radiological and clinical variability, and therapeutic results may also vary considerably [3]. In order to improve the results of the treatment of BAC it is essential to identify the clinical, radiological and pathological prognostic factors. To date, however, only a few authors have focused on these prognostic factors, which still remain to be fully defined [4–9]. The aim of this study was therefore to evaluate clinical, radiological and pathological prognostic factors in surgically-resected patients with BAC and BAC associated with adenocarcinoma to arrive at a better understanding of the disease and improved treatment.

2. Materials and methods

From May 1988 to September 1999, 49 patients with BAC and BAC associated with adenocarcinoma underwent surgical treatment at the Department of Thoracic Surgery of the Scientific Institute H San Raffaele, Milan, Italy. Radiologic findings observed at CT scan were classified in three

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categories: solid mass or nodule, diffuse infiltrate and multifocal disease. In selected patients 18-FDG PET scan was also performed. BAC was histologically defined as such when an adenocarcinoma had cylindrical tumour cells growing upon the walls of pre-existing alveoli with preservation of the underlying architecture of the lung, without evidence of primary adenocarcinoma in any extra-pulmonary site. All BAC diagnosed before 1999 were reviewed according to the new World Health Organization (WHO) histological criteria, published in that year, which defined the tumour as pure BAC when the adenocarcinoma had a bronchoalveolar growth pattern and no evidence of stromal, vascular or pleural invasion [10]. If an invasive component was present the tumour was classified as a mixed adenocarcinoma and bronchoalveolar carcinoma. The tumours were staged according to the current international TNM staging system for lung cancer. Formaldehyde-fixed, paraffin-embedded blocks were stained using the hematoxylin–eosin method. The prognostic relevance of the radiological features and of the following histological parameters was assessed in patients that underwent complete surgical resection: percentage of bronchoalveolar carcinoma component in the tumour, stromal or vascular invasion, lymphocytic infiltration and presence of sclerosing or mucinous patterns, the latter evaluated with the PAS method. The percentage of BAC, as histologically defined above, was semiquantitatively analyzed in hematoxylin–eosin stained slides at 100× magnification in relation to the invasive component of adenocarcinoma.

2.1. Statistical analysis

Values were considered as median and range if not normally distributed, and as mean and standard deviation if normally distributed. Mortality rates were computed by Kaplan–Meier survival curves and compared between different groups of risk factors by the log-rank test. Stepwise Cox regression analysis was used to investigate which variables remained independently associated with survival. Risk ratio (R.R.) and 95% confidence intervals (C.I.) were calculated. Two-tailed probability (P) value of 0.05 was considered as indicating statistical significance. The Statistical Analysis System (SAS) program was used.

3. Results

Twenty-nine patients were male and 20 female. Mean age was 63 years (36–77). A pure BAC pattern was observed in two patients and a mixed adenocarcinoma and BAC in 47. At CT scan examination 30 patients had a nodule or a mass lesion, eight a diffuse lesion and 11 a multifocal tumour. An 18-FDG PET scan was performed in three patients; it gave a correct diagnosis in one patient and a false negative result in the evaluation of the primary tumour and in the evaluation of mediastinal nodal involvement and adrenal metastases in the remaining two patients. Preoperative symptoms were present in 21 patients (Table 1). A preoperative diagnosis was obtained in 29 patients, by means of CT-guided needle biopsy in 25, bronchoscopy in three and sputum cytology in one patient.

Eight patients underwent a wedge resection, 35 a lobectomy, one a pneumonectomy and five an exploratory thoracotomy. There was no perioperative mortality. A complete surgical resection was performed in 42 patients, and their postoperative stage was Ia in 14 patients, Ib in 13, IIa in seven, IIb in four, IIIa in two and IV in two. Histological examination performed on these 42 patients showed a mucinous subtype of BAC (13 patients), localized scarring within the tumour (27 patients), vascular invasion (14 patients) and lymphocytic infiltration (23 patients). The percentage of BAC in the tumour was also assessed in the 42 patients and in particular in the 27 patients with stage Ia and Ib tumours, 11 of whom had a percentage of BAC $\leq 50\%$, while the remaining 16 had a percentage $>50\%$.

Five-year survival in the 49 patients was 54% and 58% in the 42 patients who had a complete resection. Ten patients underwent postoperative oncological treatments (radiotherapy in five, chemotherapy in two and combined radio- and chemotherapy in three). Seventeen patients had a recurrence of their disease. The site of relapse was local in ten patients and distant in seven (brain metastases in three patients and bone metastases in four).

Statistical analysis was performed in the 42 patients who underwent a complete resection. No significant difference in survival was observed on the basis of preoperative symptoms and radiological appearance, in particular there was no difference in survival when nodular tumours were compared with diffuse or multifocal lesions. No statistically significant correlation was found between radiological appearance and percentage of BAC in the tumour. Univariate analysis indicated that patients with stage Ia and Ib tumours ($P = 0.01$) (Fig. 1), N0 status ($P = 0.02$) (Fig. 2) and absence of a mucinous pattern ($P = 0.02$) (Fig. 3) had a significantly higher survival. No statistical correlation was found between survival and sclerosing pattern, lymphocytic infiltration and vascular invasion. The absence of a mucinous pattern was the only factor that remained statistically significant after multivariate analysis ($P = 0.02$) (R.R. 0.27; 95% C.I. 0.08–0.91).

Table 1
Preoperative symptoms in patients with bronchoalveolar carcinoma and bronchoalveolar carcinoma associated with adenocarcinoma (more than one symptom in some patients)

Preoperative symptoms	Number of patients
No symptoms	27
Cough	13
Thoracic pain	3
Loss of weight	3
Hemoptysis	3
Dyspnea	2
Pneumonia	1

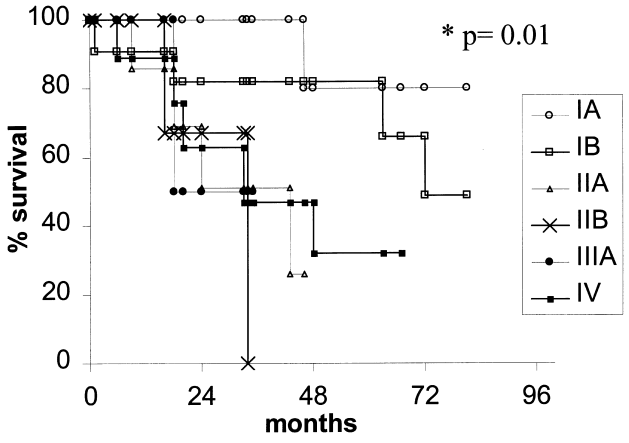

Fig. 1. Survival according to postoperative stage. *Significant difference between stages Ia and Ib and other stages ($P = 0.01$).

In the 27 patients with stage Ia and Ib disease univariate analysis also demonstrated that the absence of a mucinous pattern ($P = 0.006$) and the presence of a higher percentage of a BAC component in the tumour ($P = 0.01$) favourably influenced survival. After multivariate analysis the percentage of BAC in the tumour was the only factor to remain statistically significant ($P = 0.01$), the risk ratio being 0.93 for each 10% increase in BAC (95% C.I. 0.89–0.98).

4. Discussion

Bronchoalveolar carcinoma is a tumour with unique clinicopathological features [3]. Although the incidence of BAC has markedly increased in recent decades, studies which have focused on the prognostic factors of this tumour are still scant and a number of points still remain to be clarified.

One of the most outstanding features of BAC is the heterogeneneity of its clinical behaviour. The term BAC

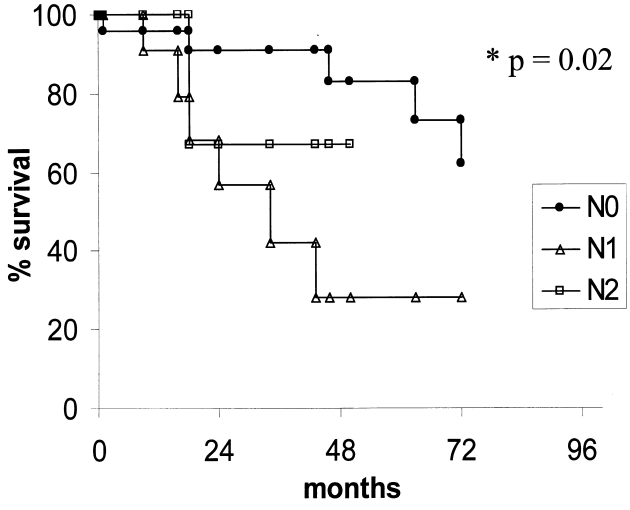

Fig. 2. Survival according to N status. *Significant difference between N0 and N1 and between N0 and N2 ($P = 0.02$).

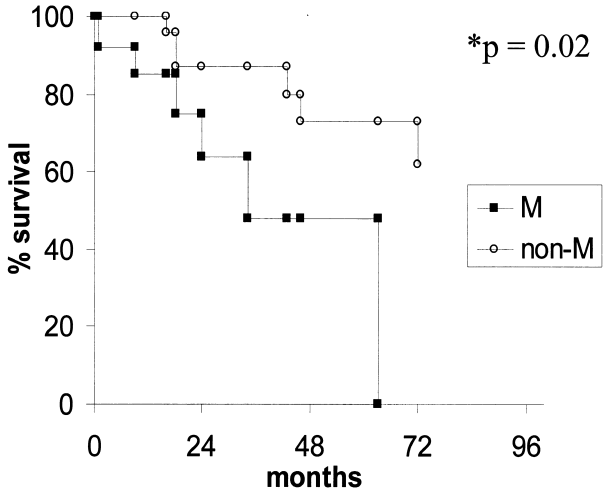

Fig. 3. Survival according to mucinous pattern. *Significant difference between mucinous (M) and non-mucinous subtypes (non-M) ($P = 0.02$).

encompasses lesions with an extremely indolent behaviour as well as extremely aggressive tumours. The results of the treatment vary accordingly, favourable results being observed after surgical resection of small peripheral lesions and discouraging results reported in patients with diffuse or multifocal tumours [5]. The indications for surgical treatment of BAC have also been rather heterogeneous, sometimes tailored to the single patient [11]. It would therefore seem of utmost importance to identify the clinical, radiological and pathological prognostic factors that could help to differentiate the different tumour subtypes in order to clarify the indications for BAC treatment.

The histological definition of BAC is still open to debate [12,13]. According to the 1999 WHO criteria, pure BAC is defined as an adenocarcinoma with a pure bronchoalveolar growth pattern and no evidence of stromal, vascular or pleural invasion. In the event of an invasive component, the tumour is classified as an adenocarcinoma with a bronchoalveolar carcinoma component [10].

The radiological features of BAC are varied, ranging from a solitary pulmonary nodule or solid mass to diffuse pulmonary involvement, found more frequently in tumours of the mucinous subtype [14]. BAC is also characterized by its potential multifocality, which has been explained both by the lymphatic and aerogenous spread of the tumour and by its multiclonal origin [5,15]. The presence of a diffuse and multifocal radiological appearance has in some reports been associated with a dismal prognosis [6,8]. Unlike these reports we did not find any correlation between radiological data and survival in our series, although this may have been influenced by the relatively small number of patients. In fact, tumours of the mucinous subtype, which frequently have a diffuse radiological appearance, were associated with a worse prognosis in our study.

The role of other diagnostic techniques in the evaluation of BAC has only been preliminarily evaluated. Initial experience with PET scan is extremely discouraging. In

accordance with previous reports [16], we observed false negative results using PET scan in the evaluation of BAC. This occurred both in the assessment of the primary lesion and in the evaluation of mediastinal and adrenal metastases. Although requiring confirmation in larger series, these data call for careful consideration especially in the light of the growing use of PET scan in evaluating lung cancer. Nuclear magnetic resonance (NMR) has also been recently used in the evaluation of BAC. This technique seems to be able to demonstrate the presence of mucin, which could prove to be an important factor since some series report a worse prognosis in BAC with a mucinous differentiation [17].

Surgery remains the main treatment of BAC [6,8]. In our experience surgical treatment of early-stage BAC and of mixed adenocarcinoma and BAC tumours was associated with a favourable long-term survival. However, the definition of prognostic factors is essential to achieve further improvement in the treatment of early-stage tumours and to reach satisfactory results in more advanced cases.

In our series postoperative TNM and nodal status significantly influenced prognosis at univariate analysis. Patients without nodal involvement had a significantly higher survival in comparison to patients with metastases to N1 or N2 lymph nodes, in accordance with previous reports [7,8]. The prognostic relevance of the histological features of BAC tumours is controversial [5,7,8]. In our experience BAC with a mucinous differentiation had a significantly lower survival, as demonstrated by multivariate analysis. The data are of interest since the presence of mucin can be detected by preoperative radiological examinations such as NMR. It has also been shown that mucinous BAC has a higher metabolic uptake in those patients who have a positive PET scan [16]. In contrast to other series, we did not find any correlation between survival and presence of vascular invasion, sclerosis or lymphocytic infiltration, although the role of these factors may have been underestimated due to the relatively small size of the sample [18].

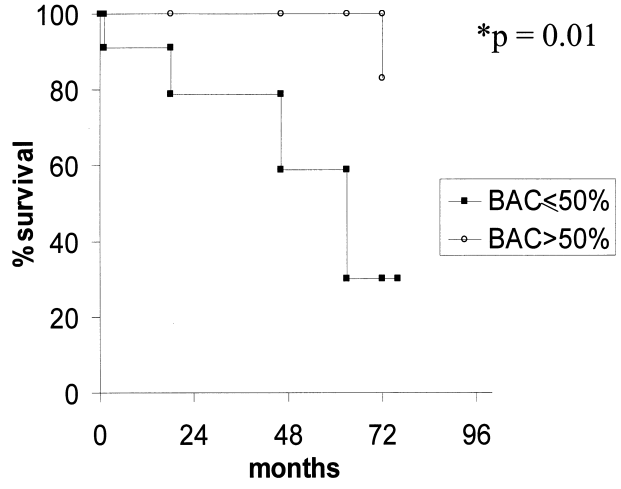

Fig. 4. Survival in stage Ia and Ib patients according to the percentage of BAC in the tumour. Significant difference between tumours with >50% of BAC component and tumours with ≤50% of BAC component ($P = 0.01$).

According to the current WHO histological definitions, most BAC tumours are classified as a combination of classic adenocarcinoma and BAC. In a recent report the percentage of the BAC component in mixed tumours significantly influenced survival in patients with peripheral adenocarcinomas, those with a higher percentage of BAC having a better survival [19]. In our series these data were confirmed in stage I patients, since patients with a higher percentage of BAC had a significantly higher survival at multivariate analysis. The 5-year survival in patients with a BAC component higher than 50% was 83%, compared to a 29% 5-year survival in patients with a BAC component equal or less than 50% ($P = 0.01$) (Fig. 4). This factor could be of interest in identifying patients with early-stage adenocarcinoma that have a higher risk of recurrence.

In conclusion, the surgical treatment of early-stage BAC and mixed adenocarcinoma and BAC is associated with favourable results. However, the definition of prognostic factors is essential to further improve these results and to obtain satisfactory survival rates in more advanced stages. In our series tumours of the mucinous subtype and with a lower percentage of BAC had a worse prognosis. If confirmed by further studies, our data may contribute to identifying patients at a higher risk of tumour recurrence, in whom new therapeutic strategies should be evaluated.

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Appendix A. Conference discussion

Dr. P. Macchiarini *(Hannover, Germany)*: I have two questions. You have an almost 20% incomplete resection rate, which is very high. Do you have any explanation for that?

The second question, your group is doing lung transplantation, and I just wanted to know what your thoughts are concerning lung transplantation in these histological types.

Dr. Carretta: The first question: our patients who had an incomplete resection included those with a very advanced disease in whom we performed an exclusively diagnostic procedure. However, in our Department the overall incidence of exploratory thoracotomy in oncologic general thoracic surgery is around 2%. The second question, my group is not performing at this time lung transplantation, but from the literature we know that most of the patients that were submitted to lung transplantation due to bronchoalveolar carcinoma had tumour recurrence some years after transplantation. The question is whether this was donor- or recipient-related, and this question, as far as I know, has still not been answered. Anyway, most of these patients had tumour recurrence after transplantation. So I think it's a very difficult indication to be supported.