

# Stage I pure bronchioloalveolar carcinoma: recurrences, survival and comparison with adenocarcinoma of the lung

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## Abstract

**Objective:** Bronchioloalveolar carcinoma (BAC) is considered a subtype of adenocarcinoma of the lung, without pleural, stromal or vascular invasion (World Health Organization (WHO) classification). Previous reports had demonstrated a better prognosis following surgery for patients affected by early stage BAC than those affected by other type of non-small cell lung cancer (NSCLC). We aim to analyse differences between stage I peripheral nodular BAC and stage I peripheral adenocarcinoma of the lung. **Methods:** From January 1, 1993 to December 31, 1999, 1158 patients were submitted to surgical resection for NSCLC. Out of them, 28 patients (2.4%) resulted affected by stage I peripheral pure BAC and 80 (6.9%) by stage I peripheral adenocarcinoma. We made a comparison between these two groups. **Results:** The percentage of females in BAC patients was similar to that registered in adenocarcinoma patients (21.4 vs. 17.5%). No differences were detected between smokers in BAC and adenocarcinoma patients ( $P = 0.331$ ). The upper lobes were the most common sites of the primary tumour in both tumour subtypes (71.4 vs. 67.5%). Relapse of disease was less frequent in BAC than in adenocarcinoma patients (14.2 vs. 33.7%); recurrent disease developed intrathoracic with higher frequency in BAC patients (75 vs. 33.3%). Both 5-year disease-free and long-term survival were significantly higher in patients affected by BAC (81 vs. 51% and 86 vs. 71%, respectively) ( $P < 0.05$ ); when analysis is performed by dividing stage IA from IB tumours, BAC patients resulted to have higher DFS (stage IA, 93 vs. 58% –  $P = 0.044$ ; stage IB, 61 vs. 32.5%) and higher long-term survival (stage IA, 92 vs. 79%; stage IB, 75 vs. 56%). **Conclusion:** Patients with stage I pure BAC have significantly longer disease-free and overall survival than those with similar stage adenocarcinoma. Even if classified as subtype of adenocarcinoma, BAC is characterised by clinical behaviour less aggressive than similar stage adenocarcinoma.

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**Keywords:** Bronchioloalveolar carcinoma; Adenocarcinoma; Prognostic factors; Surgery; Survival

## 1. Introduction

Bronchioloalveolar carcinoma (BAC) is an uncommon primary malignant neoplasm of the lung, and it accounts for 2–14% of all pulmonary malignancies [1,2]. This histological entity is extremely heterogeneous, with different clinicopathological presentations and variable prognosis. According to World Health Organization (WHO) categorisation, BAC is a subtype of adenocarcinoma. The current definition of BAC includes the following: malignant neoplasms of the lung that have no evidence of extrathoracic primary adenocarcinoma, an absence of a central bronchogenic source, a peripheral parenchymal location, no distur-

tion of the pulmonary interstitium and neoplastic cells growing along the alveolar septa. BAC results as a form of adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular or pleural invasion [3]. In the event of an invasive component, the tumour is classified as an adenocarcinoma with a bronchioloalveolar component [3].

BAC was first described by Malassez [4] in 1876, as a bilateral, multinodular form of malignant lung tumour. In 1903, Musser [5] discovered another form: a diffuse, infiltrative type of BAC involving a single lobe or the entire lung simulating pneumonia. In 1953, Storey et al. [6] recognised that the most frequent form was a solitary peripheral pulmonary nodule. BAC in the solitary peripheral nodule form represents the higher percentage of early stage disease; it has better prognosis following curative resection and less

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progress toward diffuse disease; the diffuse form (multinodular, diffuse or infiltrating) tends to be more progressive with a worse prognosis regardless of intervention [7].

Previous reports of patients with resected stage I lung cancer have shown that such patients with BAC live longer than patients with other types of non-small cell lung cancer (NSCLC) [8,9]. However, there is little information on the pattern of recurrent disease and how this is influenced by the surgical approach. We aim to add information on clinical behaviour, the pattern of disease at presentation and recurrence and survival outcomes in patients with early stage BAC and compare these findings with those in patients affected by similar stage of adenocarcinoma.

## 2. Material and methods

From January 1, 1993 to December 31, 1999, 1158 patients were submitted to complete surgical resection of NSCLC at the Department of Thoracic Surgery of the University of Torino. At definitive histological evaluation among 1158 patients, 544 (47%) resulted affected by squamous cell carcinoma, 428 (37%) by adenocarcinoma, 40 (3.4%) by adenocarcinoma with bronchioloalveolar component, 32 (2.8%) by pure BAC, 55 (4.7%) by large cell carcinoma and 59 (5%) by mixed histology lung cancer.

The diagnosis of BAC was made according to the former description of a peripheral tumour manifesting the growth of well-differentiated cuboidal or columnar tumour cells along intact alveolar walls and no evidence of a primary adenocarcinoma at some extrapulmonary site. The specimens were consistent with the new classification by the WHO, which describes BAC as a form of adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular or pleural invasion [3]. Four patients out of 32 affected by pure BAC received a wedge-resection and so the histological evaluation of segmental lymphnodes was not possible; the other 28 cases were demonstrated to be at

stage I ( $T_1$  or  $T_2-N_0$ ). Among 429 patients affected by adenocarcinoma, 136 received curative resection with hilar and segmental lymphnodes sampling for stage I tumours arising distally to the lobar bronchus; 56 out of them were excluded because of visceral pleural invasion which could result as a negative prognostic factor for these patients.

The study population resulted as follows: 28 patients affected by stage I pure BAC (all in the solitary peripheral nodular form) and 80 affected by peripheral stage I adenocarcinoma without visceral pleural invasion. The medical records of all patients were reviewed for clinical characteristics including age, sex, site of tumour, type of resection. Patients' follow-up was acquired by retrospective chart review. A median follow-up of 4 years (range 0–8.5) was obtained in both groups, which included the time and location of any recurrent disease.

### 2.1. Statistical methods

Comparisons of the groups defined by histology on the basis of clinical and demographic variables, that are categorical, are made by use of a Fisher exact test. For disease-free survival (DFS), time was measured from the operation until recurrence or death. Patients who were alive and disease-free at the most recent follow-up were censored for this analysis. Survival comparisons reported are from a log rank test, and estimates of survival were made by the method of Kaplan and Meier, with the time measured from the date of the initial operation until death or most recent follow-up (censored).

## 3. Results

Twenty-eight patients had a diagnosis of pure BAC and 80 had adenocarcinoma (acinar,  $n = 45$ ; papillary,  $n = 6$ ; solid tumour with mucin,  $n = 23$ ; mixed,  $n = 5$ ; poorly differentiated,  $n = 1$ ); stage I BAC represents 6.4% of all early stage lung cancer (28/436) submitted to surgical management during the same period. The patients' characteristics are outlined in Table 1. The median age at initial presentation was similar both in patients with BAC and in those with adenocarcinoma. The percentage of females in the BAC cohort (21.4%) was quite similar to that registered in the adenocarcinoma cohort (17.5%), and the difference did not reach significant values ( $P = 0.861$ ). Eight patients of the 28 (28.5%) affected by BAC had never smoked as compared with 14 patients (17.5%) in the adenocarcinoma group ( $P = 0.331$ ). The upper lobes were the most common site of the primary tumour in both patients with BAC ( $n = 20$ ; 71.4%) and adenocarcinoma ( $n = 54$ ; 67.5%), with a slight preference for the left side.

During the preoperative evaluation, bronchoscopy was carried out in all patients; when cytology on endoscopic samples such as bronchoalveolar lavage (BAL) or post-bronchoscopy sputum resulted negative or not indicative, CT-scan guided fine needle aspiration biopsy (FNAB)

Table 1  
Patients' characteristics<sup>a</sup>

	BAC		Adenocarcinoma	
	No.	%	No.	%
Patients	28	100	80	100
Age (years)				
Median	62.5	–	63	–
Range	(47.5–73.5)	–	(42–79.5)	–
Sex				
Male	22	78.6	66	82.5
Female	6	21.4	14	17.5
Smoking history				
Non-smokers	8	28.5	14	17.5
Active or ex-smokers	20	71.5	66	82.5

<sup>a</sup> BAC, bronchioloalveolar carcinoma.

Table 2  
Sites of initial progressive disease<sup>a</sup>

	BAC ( <i>n</i> = 4)		Adenocarcinoma ( <i>n</i> = 27)	
	No.	%	No.	%
Intrathoracic recurrences only	3	75	9	33.3
Lung (ipsi- or contralateral)	2	50	4	14.8
Mediastinum	1	25	5	18.5
Extrathoracic metastases only	1	25	18	66.6
Bone	1	25	10	37
Brain	–	–	4	14.8
Liver	–	–	4	14.8
Other	–	–	1	3.7

<sup>a</sup> BAC, bronchioloalveolar carcinoma.

were utilised. In the BAC population, the endoscopic findings were normal in all cases and BAL or sputum cytology revealed diagnosis of BAC in eight cases (28.5%); the other 20 patients were subsequently submitted to CT-scan guided FNAB which revealed BAC in nine cases (32.2%), not specified NSCLC in five (17.8%) and not diagnostic specimen in six (21.4%). In the adenocarcinoma population, the endoscopic findings were normal in all cases and BAL or sputum cytology revealed diagnosis of adenocarcinoma in 27 cases (33.75%); the other 53 patients were submitted to CT-scan guided FNAB which revealed adenocarcinoma of the lung in 29 cases (36.25%), not specified NSCLC in 17 (21.25%) and not diagnostic specimen in seven (8.75%). Patients without preoperative diagnosis were submitted to open biopsy of the pulmonary nodule and after frozen section examination, they were submitted to lobar or sublobar anatomic resection during the same surgical procedure.

Twenty-seven patients (96.4%) with BAC received lobectomy with mediastinal, hilar and segmental lymph nodes dissection compared with 79 patients (98.7%) with adenocarcinoma. One patient with BAC had segmentectomy with mediastinal, hilar and segmental lymphnodes

dissection, such as one affected by adenocarcinoma. BAC resulted to be at stage IA (T<sub>1</sub>N<sub>0</sub> because T < 3 cm in maximum diameter) in 19 patients (67.8%) and stage IB (T<sub>2</sub>N<sub>0</sub> because T > 3 cm in diameter) in nine; adenocarcinoma were stage IA in 53 cases (66.3%) and stage IB in 27.

Four of the 28 patients (14.3%) with BAC had recurrent disease compared with 27 of the 80 patients (33.75%) with adenocarcinoma. These results are summarised in Table 2. The 5-year DFS in patients with BAC and adenocarcinoma was 81 and 55%, respectively (*P* = 0.009) (Fig. 1). There was significant difference in DFS in patients with stage IA BAC vs. those with stage IA adenocarcinoma (5-year DFS: 93 vs. 58%, respectively; *P* = 0.043) (Fig. 2). Quite significant difference was registered in DFS in patients with stage IB BAC vs. same stage adenocarcinoma (5-year DFS: 61 vs. 32.5%; *P* = 0.064) (Fig. 3).

The recurrences within the patients with resected BAC occurred predominantly within the thorax (75%) compared with patients with adenocarcinoma (33.3%) (*P* = 0.295). In contrast, extrathoracic metastases were more common in the patients (18 of 27 patients, 66.7%) with adenocarcinoma. Of these patients with recurrent adenocarcinoma, 37% had metastases to bone (*n* = 10), 14.8% to brain (*n* = 4), 14.8% to liver (*n* = 4), and 3.7% to other sites (*n* = 1). These findings are summarised in Table 2. The sites of recurrent disease for stage IA and IB diseases are illustrated in Table 3. Patients with BAC lived longer (5-year survival 86%) than patients with adenocarcinoma (5-year survival 71%) after resection of their disease, and the difference resulted significant (*P* = 0.014) (Fig. 4). Five-year survival rate was 92% for patients affected by stage IA BAC vs. 79% for patients affected by same stage adenocarcinoma (*P* = 0.08); 5-year survival rate was 75% for patients affected by stage IB BAC vs. 56% for patients affected by same stage adenocarcinoma (*P* = 0.07).

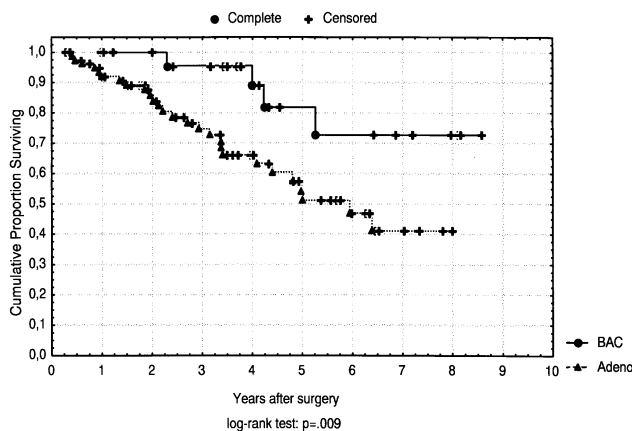


Fig. 1. Postoperative DFS in patients with pathologic stage I BAC compared with patients with same stage adenocarcinoma (patients at risk at 5-year: BAC, *n* = 8; adenocarcinoma, *n* = 15).

#### 4. Discussion

Currently, BAC is pathologically classified as a subtype

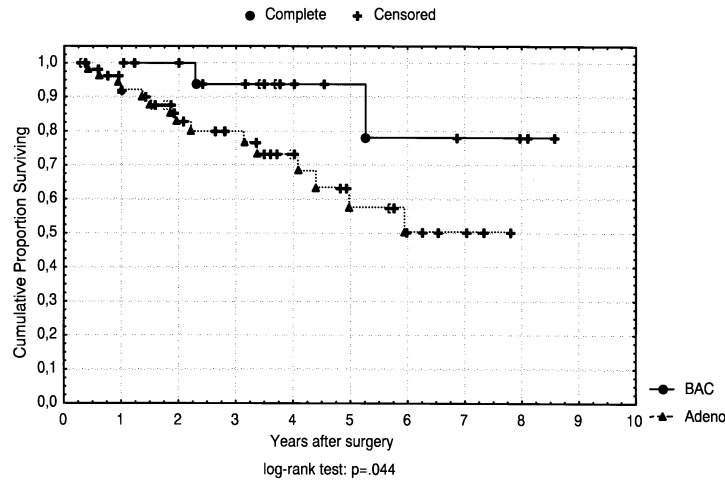


Fig. 2. Postoperative DFS in patients with pathologic stage IA BAC compared with patients with same stage adenocarcinoma (patients at risk at 5-year: BAC,  $n = 5$ ; adenocarcinoma,  $n = 10$ ).

of the adenocarcinoma, although BAC is a unique and distinct type of primary pulmonary cancer and has numerous distinguishing clinical features from adenocarcinoma [3]. BAC can coexist with adenocarcinoma and overlap within the same tumour often occurs. Carretta et al., referred about 49 patients: two patients with pure BAC and 47 with adenocarcinoma with BAC component; they noted that the presence of higher percentage of BAC component in the adenocarcinoma favourably influenced survival [10]. The most frequent form of BAC at presentation is a single, peripheral nodule or mass which was referred to be related with a good prognosis; other less frequent forms at presentation are the diffuse, infiltrative type and the multinodular, often bilateral, type [7].

In this study, we focused on the stage I pure BAC and we compared it with same stage adenocarcinoma of the lung, excluding those cases with both BAC and adenocarcinoma aspects. Many studies reported data on patients with stage I BAC [1,8,9,11–15]. The majority of them focused on symptoms at presentation, pathologic features of BAC and radi-

ologic features as prognostic factors. Data on the recurrence rates and sites of recurrent disease in patients with early stage BAC, such as comparisons between stage I BAC and adenocarcinoma are rare.

The present study adds information about the sites of disease at initial presentation, the pattern of surgical resection and subsequent recurrent disease and survival of patients with early stage nodular BAC and adenocarcinoma. BAC continues to be the least common type of bronchogenic carcinoma. The prevalence of BAC in our stage I lung cancer series is in accordance with the literature (6.4%). In our study, women accounted for 21.4%, which is much lower than the mean previously reported by other authors (approximately 44%) [9,14,16]. The reason for this difference is unclear. In our previous study of 436 resections for non-small cell bronchogenic carcinomas (all histological types together) only 12.6% were females.

The impact of cigarette smoking on induction of BAC is somewhat controversial [16,17]. Some investigators have stated that BAC occurs most commonly in smokers, while others have demonstrated up to 30% of patients diagnosed with BAC were lifelong non-smokers, with perhaps another 30–40% having been former or intermittent smokers [18]. In the series of Breathnach et al., the percentage of non-smokers in BAC patients (33%) was significantly higher

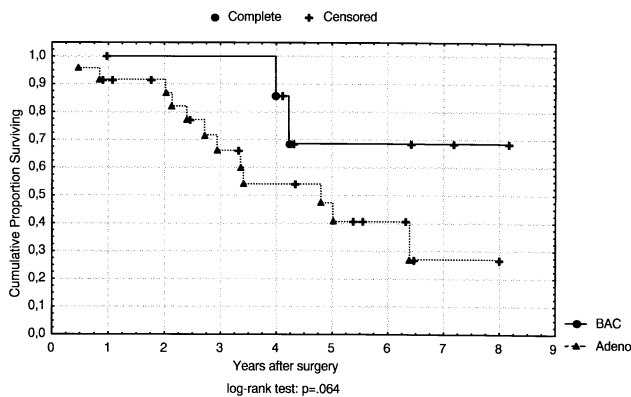


Fig. 3. Postoperative DFS in patients with pathologic stage IB BAC compared with patients with same stage adenocarcinoma (patients at risk at 5-year: BAC,  $n = 3$ ; adenocarcinoma,  $n = 6$ ).

Table 3  
Sites of recurrence with particular focus on the initial disease stage<sup>a</sup>

		Intrathoracic		Extrathoracic	
		N	%	N	%
BAC	T <sub>1</sub>	2	10.5	–	–
	T <sub>2</sub>	1	11	1	11
Adeno	T <sub>1</sub>	6	11.3	9	17
	T <sub>2</sub>	3	11	8	33.3

<sup>a</sup> BAC, bronchioloalveolar carcinoma; Adeno, adenocarcinoma.

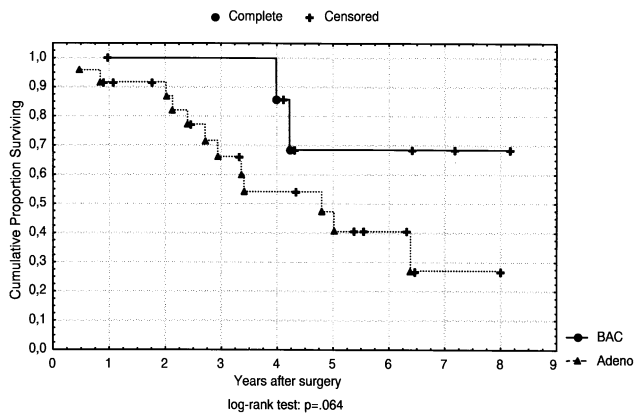


Fig. 4. Postoperative overall survival in patients with stage I BAC compared with those with stage I adenocarcinoma (patients at risk at 5-year: BAC,  $n = 9$ ; adenocarcinoma,  $n = 17$ ).

than that in adenocarcinoma patients (9%); the same author referred an high predominance of females [19]. Two recent case-control studies have suggested an association between duration and intensity of cigarette smoking and the development of BAC [17,20]. Many previous studies reported about the site of disease at presentation in patients with BAC in the solitary nodule form, even if they did not specify the number of patients with stage I disease: solitary nodules resulted most commonly found in the upper lobes (46–64%) [19]. Our data similarly show the involvement of the upper lobes being the most common site of disease at presentation, both in patients with BAC and adenocarcinoma.

The treatment approaches for patients with BAC are similar to those used in patients with other types of NSCLC and depends on the stage of disease. For patients with early stage (I and II) disease, surgical resection is the treatment of choice. The extent of resection has been somewhat controversial. Some investigators have suggested that patients treated with less than a lobectomy have higher recurrence rates and have a worse prognosis; others have advocated lung-sparing procedures (wedge or segmentectomy) given the propensity of the disease to recur in a multifocal fashion [21]. However, most commonly performed surgical procedures in patients undergoing resection for BAC is lobectomy with between 56 and 87% patients treated in this manner while limited resections are performed in 3–39% patients submitted to surgical treatment for stage I BAC [14,15,19].

Few studies compare recurrence rates after resection in patients with early stage BAC and those with adenocarcinoma. Grover et al., reported about a significantly higher recurrence rate in patients with adenocarcinoma than in those with BAC [9]. Heikkilä et al. referred about 39% intrathoracic recurrence in patients affected by BAC and 13% in adenocarcinoma ( $P = 0.025$ ); 29% of patients with BAC and 69% with adenocarcinoma had extrathoracic recurrences, respectively ( $P = 0.001$ ) [16]. Breathnach et al., compared patients of similar stage BAC and adenocar-

cinoma and referred the greater tendency for intrathoracic recurrence to develop with few extrathoracic metastases in patients with BAC [19]. In our study, patients affected by BAC showed higher tendency to intrathoracic recurrences, ipsi- or contralateral, than adenocarcinoma patients; while distant metastases are more frequent in adenocarcinoma. Patients affected by stage I BAC had higher 5-year DFS rate than those affected by same stage adenocarcinoma; when stage IA and IB diseases are separately analysed, BAC demonstrated higher DFS rates (for stage IA disease, the difference reaches significant values; this is probably related to the number of cases representing the two cohort of patients).

Many studies report on median and 5-year overall survival in patients with stage I BAC. The reported 5-year survivals range from 54 to 81% [1,8,9,12,14,15,19]. Two of these studies compared their patients with BAC to those with stage I adenocarcinoma (81–83% and 65–63%, respectively) [1,19]. These findings are nearly identical to those reported in our series. Our results reach significant difference. Five-year overall survival rates of patients affected by both stage IA and IB BAC are higher than those of patients affected by adenocarcinoma (the differences do not reach significant values probably because of the small number of complete observations in each group during the follow-up period). These data support the belief that patients with peripheral nodular early stage BAC have a better prognosis than patients with similar stage adenocarcinoma.

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