

ORIGINAL ARTICLE

Clinical presentation, treatment options and outcome in patients with bronchioalveolar carcinoma

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Summary

Purpose: To determine the characteristics of bronchioalveolar carcinoma (BAC) as a special clinical and pathological entity and to evaluate the effects of treatment options on survival of BAC patients.

Patients and methods: The study was partially retrospective and partially prospective, non randomized. We evaluated the clinical presentation, smoking habits, radiographic findings, treatment and survival of 21 patients with BAC treated at our Institute from 2000-2004.

Results: Registered were 16 (76.2%) male and 5 (23.8%) female patients, most of them in the 6th and 7th decade of life. Among younger patients females prevailed. Most common symptoms were dyspnoea 15 (71.4%), cough 14 (66.6%) and bronchial hypersecretion 9 (42.8%). There were 5 (23.8%) smokers, 6 (28.6%) ex-smokers and 10 (47.6%) nonsmokers. Main radiographic findings were lung consolidation (9; 42.8%), diffuse interstitial infiltrates (6; 28.6%), solitary (4;

19.0%) and multiple pulmonary lesions (2; 9.5%). Surgery was performed in 8 (38.0%) patients and 5 of them received adjuvant radio- and chemotherapy, while the remaining received chemotherapy alone (9; 42.8%) and symptomatic treatment (4; 19.0%). The median survival was 25 months and 1-year survival 70%, regardless of stage. In the group of patients treated surgically 1- and 2-year survival rate was 100% and the median survival 33 months. In non-operated patients the median survival was 18 months and 1- and 2-year survival 55% and 25%, respectively.

Conclusion: BAC is a special clinical and pathological form of adenocarcinoma of the lung. Surgical treatment is the best option for selected BAC patients. Survival is associated with the treatment modality. Larger scale studies are necessary to confirm these findings.

Key words: bronchioalveolar carcinoma, lung cancer, survival

Introduction

Bronchioalveolar carcinoma (Figure 1) is a subtype of bronchial adenocarcinoma and represents 2-

6% of all lung cancers. It is characterized by a nodular or multicentric growth pattern expressed by various radiological appearances. The very name of the tumor is associated with typical growth pattern of BAC cells - in line with alveolar areas and bronchioles. According to World Health Organization (WHO) definition from 1999, BAC is defined as a subtype of adenocarcinoma with pure bronchioalveolar growth pattern and no evidence of stromal, vascular or pleural invasion [1-5]. In relation to mucus production BAC is divided in 3 types: mucus, non-mucus and mixed. The mucus type usually grows multicentrically and is associated with bronchial hypersecretion. The non-mucus type shows a focal or central growth pattern and radiologically it appears as a peripheral nodular lesion.

In diagnosing BAC certain criteria must be taken into consideration: 1) absence of other primary adeno-

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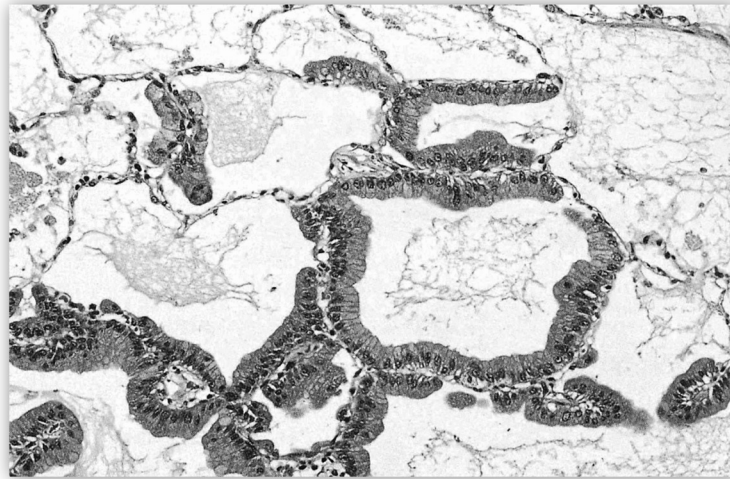


Figure 1. Bronchioloalveolar carcinoma (H&E ×200).

carcinoma; 2) absence of centrally located endobronchial lesions; and 3) typical growth pattern, in line with alveoli, bronchioles and lymphatic vessels (“lepidic pattern”).

The most important prognostic factor for survival of BAC patients is the stage of disease. It is reported that BAC occurs more often in younger female patients and that this type of lung cancer is less dependent on smoking than other lung cancer types [6-10].

The purpose of this article was to analyze the clinical characteristics and patterns of appearance of BAC and also to evaluate the clinical course and treatment outcome in patients with this kind of lung cancer.

Patients and methods

The study was partially retrospective and partially prospective and was performed from January 2000 to December 2004. The study was approved by the ethical committee of our institution, and all of the patients of the prospective part of the study signed informed consent for participation in the investigation.

Twenty-one patients were enrolled onto study. Diagnosis was established either bronchoscopically or surgically. Parameters registered and analyzed included clinical presentation, smoking habits, radiological findings (chest X ray - CXR), disease stage, treatment modality, cumulative survival and survival in the group of surgically treated patients. Disease stage was the major factor for selecting patients for surgical treatment.

Results were statistically analyzed using Student's t-test and χ^2 test for determining statistical significance. Kaplan-Meier method was used for determining survival rates.

Results

In the analyzed series there were 16 (76.2%) male and 5 (23.8%) female patients. Most of them were in the 6th and 7th decade of life. Among younger patients the majority were females. Symptoms were present in all but one patient. The most common symptoms were dyspnoea (71.4%) and cough (66.6%). Clinical presentation – signs and symptoms of BAC are shown in Table 1.

Five (23.8%) patients were smokers. There were 6 (28.6%) ex-smokers with abstinence period of 15-30 years. Ten (47.6%) patients never smoked cigarettes.

Lung consolidation on CXR was present in 9 (42.8%) patients. In 6 (28.6%) patients CXR revealed interstitial infiltration. Solitary pulmonary nodule was visible in 4 (19%) patients and multiple pulmonary nodules in 2 (9.5%).

After complete diagnostic evaluation and TNM staging 5/21 (23.8%) patients had stage I, 1/21 (4.8%)

Table 1. Clinical presentation of bronchioloalveolar carcinoma

<i>Symptoms and signs</i>	<i>Patients, n</i>	<i>%</i>
Mucous expectoration	9	42.8
Dyspnoea	15	71.4
Cough	14	66.6
Thoracic pain	5	23.8
Fever	1	4.8
Loss of appetite	3	14.2
Body weight loss	5	23.8
Malaise	7	33.3
Haemoptysis	1	4.8
Hoarseness	2	9.5
Symptoms due to metastatic spread	4	19.0
Asymptomatic	1	4.8

stage II, 3/21 (14.2%) stage III and 12 patients (57.8%) stage IV.

Eight (38%) patients were selected for surgery. In 4 of them lobectomy was performed, in 2 bilobectomy and in another 2 pneumonectomy. After the operative treatment 3 patients received adjuvant chemotherapy (cisplatin 60 mg/m² day 1, plus etoposide 100 mg/m² days 1-3) and 2 chemoradiotherapy (same chemotherapy as above plus external beam radiation, split course, 40 Gy in 10 fractions). In the group of 13 non-operated patients 9 received chemotherapy (same as above) while the rest of them were treated symptomatically. Treatments applied are presented in Table 2.

Cumulative survival of patients, regardless of the disease stage, calculated with the Kaplan-Meier method showed median survival time of 23 months (Figure 2). In this series 1-year survival was 70%, and 2-year survival 45%.

In the group of stage I and II patients treated surgically 1- and 2-year survival was 100% and the median survival time 33 months. The median survival time in the group of non surgically treated patients (stage III) was 18 months. One-year survival in the group of non surgically treated patients was 55% and 2-year survival 25% ($p < 0.005$; Figure 3).

Table 2. Treatment modalities applied in the investigated bronchioloalveolar carcinoma patients

Treatment modality	Patients, n	%
Surgery	3	14.2
Surgery + chemotherapy	3	14.2
Surgery + chemotherapy + radiotherapy	2	9.5
Chemotherapy only	9	42.8
Symptomatic treatment	4	19.0

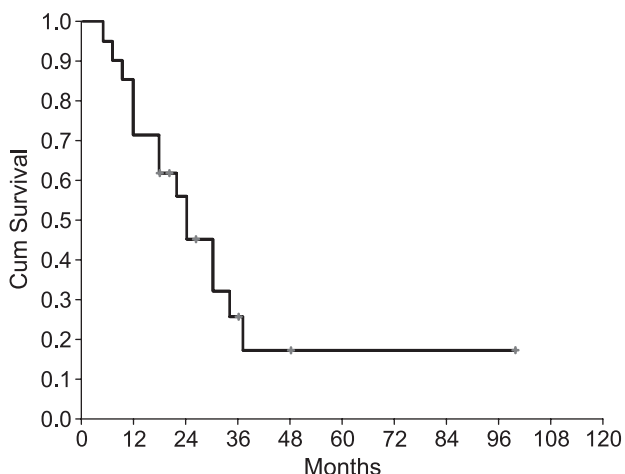


Figure 2. Survival in bronchioloalveolar carcinoma patients (all stages included).

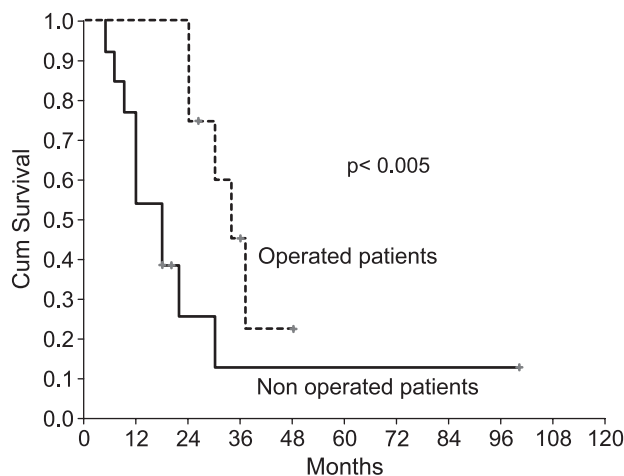


Figure 3. Comparison of survival in operated (stage I and II) and non operated (stage III) bronchioloalveolar carcinoma patients.

Discussion

In the last two decades the worldwide incidence of lung adenocarcinoma is increasing and in some regions already exceeds the incidence of squamous cell carcinoma. This is partially due to an increase in histological diagnosis of BAC. In the 1980s the incidence of BAC diagnosis was around 5-10% of all adenocarcinomas, but in 1990s this incidence increased to 20-24% [9-12]. BAC is usually diagnosed in older patients (in the 6th or 7th decade of life). Sex-related studies have revealed that BAC is the more common type of lung adenocarcinoma in younger women, with better survival than in men. BAC seems to be less dependent on smoking; in a large number of studies more than 30% of the patients were non-smokers and BAC was usually diagnosed at an advanced stage. However, survival in this group of patients is better than in smokers, probably due to better cardiopulmonary status and less frequent relapse of the disease [12-14]. In our group of patients we found BAC to be more frequent in older males, while in women it was diagnosed at a younger age. The majority of the patients were non-smokers or ex-smokers with long periods of abstinence. These results are comparable with the findings of other authors.

At the time of diagnosis 40-60% of patients are asymptomatic. In these patients BAC is usually discovered on routine CXR and presents as a solitary pulmonary nodule. Some of the solitary bronchioloalveolar carcinomas are growing slowly over the years without signs of metastatic spread. Others can grow quickly and metastasize in a very short period of time. Symptoms and signs of BAC are similar to the clinical

presentation of other lung cancer types. Most frequent manifestations are cough, dyspnoea, thoracic pain and haemoptysis. Late manifestations of BAC include mucous expectoration, hypoxia and body weight loss. Intense mucous expectoration is a characteristic symptom of the mucus type of BAC and it is present in 10-50% of the patients with this histology. Symptoms of metastatic spread or paraneoplastic manifestations are rare in BAC [14-19].

In our study most frequent symptoms were cough (71.4%) and dyspnoea (66.6%). Mucous expectoration was present in 42.8% of the patients. Malaise was registered in 33.3% of the patients, while thoracic pain and body weight loss were reported in 23.8% of the patients each. Fever, haemoptysis and hoarseness were encountered less frequently. Symptoms of metastatic spread in our series were rarely seen; metastases were confirmed in 4 patients (skeleton, regional lymph nodes and pericardium). Similar results in the evaluation of BAC symptoms and signs were reported in a large number of studies [12-20].

BAC shows several growth patterns. Most frequent forms are solitary pulmonary nodule, lobar or segmental consolidation, diffuse pulmonary infiltrates and multiple pulmonary nodules. In the majority of cases BAC is radiologically presented as a slow-growing peripheral solitary pulmonary nodule situated in the upper lobes, preferably on the right. Patients with that radiological presentation have usually better prognosis. Diffuse forms of BAC are in most cases presented as multiple bilateral nodular infiltrates. Lobar or segmental pulmonary infiltrates are present in 30% of the patients. These radiological forms can be accompanied by unilateral or bilateral pleural effusion and signs of pleural carcinomatosis [21-26]. In our study group the most frequent radiological presentation was lung consolidation (42.8%). Diffuse interstitial infiltrations were found in 28.6% and solitary pulmonary nodules in 19% of the patients. Multiple pulmonary nodules were observed in only 9.5% of the cases. This ratio of radiological findings is comparable with most BAC studies. The lower number of solitary pulmonary nodules in our group can be explained by the fact that more patients had locally advanced disease.

TNM classification is used for all non-small cell lung cancer types; however, it might be difficult to apply TNM when diffuse forms of tumors are considered. In these cases the proposed categorization is Tx. Most of the patients with localized BAC have resectable disease and therefore better prognosis than patients with diffuse BAC. When compared to non-BAC lung adenocarcinoma, BAC is more often diagnosed in a

resectable disease stage, with better survival and longer time to progression. Two-year survival in early-stage BAC is better than in squamous cell lung cancer, but after 2 years this difference in survival disappears. In the study published by Daly and coworkers [6] survival of BAC patients was evaluated in relation to the stage of disease. This study revealed that 5-year survival in T1N0 can reach 90%, while in T2N0 stage the expected survival can be up to 55%. Stage I BAC patients can have one-year survival up to 80%. Other studies reported that relapse of the disease is more frequent in patients with BAC in stage II and III, when compared to squamous cell carcinoma or non-BAC adenocarcinoma of the lung [2-6]. One- and 2-year survival in stage I and II after complete resection can be up to 100% and 84%, respectively. One of the studies [6] confirmed that 1-, 2- and 3-year survival of BAC patients after complete resection, regardless of disease stage, can be up to 84%, 64% and 47%, respectively. The median survival time in that study was 32 months.

BAC is a chemoresistant tumor. Some studies report good results with epidermal growth factor receptor (EGFR) blocking agents, such as erlotinib and gefitinib [27,28] as first-line therapeutic agents. However, more randomized trials are necessary to draw firm conclusions about the place of these drugs in the treatment of this tumor. Various radiotherapeutic regimens were used for BAC treatment, usually in combination with chemotherapy. There is, however, lack of randomized trials, thus preventing a consensus over the optimal treatment of BAC [18-22,29-32].

Advanced-stage patients have poor prognosis. According to several authors treatment options in advanced stage are limited to symptomatic therapy with median survival time 5 months and 1-, 2- and 3-year survival 43%, 18% and 9%, respectively [31-35].

In our study 1-, 2- and 3-year survival was 85%, 47% and 25% respectively, regardless of stage. The cumulative median survival time was 23 months. In the group of patients treated surgically 1- and 2-year survival was 100% and 72% respectively, with median survival time of 33 months. In the group of patients with advanced disease treated symptomatically 1- and 2-year survival was 55% and 25%, respectively, with median survival time around 11 months. These results are comparable with the majority of the published studies. However, our results must be interpreted with caution considering the small cohort of patients.

Conclusions

Bronchioloalveolar carcinoma is a unique clini-

cal and pathological entity with various clinical and radiological presentations. Histological characteristics are making this type of lung cancer different from other adenocarcinomas. We have observed that asymptomatic disease and the radiological form of solitary pulmonary nodule is not so frequent as in other published series; however, this may be the result of the rather small cohort of our patients. Surgical treatment improves survival of BAC patients. These results must be interpreted with caution because of the small number of patients included in the study. Therefore, larger scale studies are needed to confirm these results.

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