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ORIGINAL ARTICLE

Clinical prognostic factors and outcome of surgical treatment in patients with early-stage bronchial carcinoid tumors

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Summary

Purpose: *Surgical resection is the treatment of choice for bronchial carcinoids (BC). The primary endpoint of this study was to look at the survival of patients with BC after the surgical treatment and to identify some clinicopathological prognostic factors influencing survival.*

Methods: *The analysis included 57 patients with early-stage BC submitted to surgical treatment in the period 2000-2008. Major inclusion criteria were: pathologically confirmed BC, ECOG performance status 0-2, and surgical resection of the tumor.*

Results: *No significant difference in survival in relation to gender was registered. N0, N1 and N2 status was registered in 39, 9 and 2 patients, respectively. There were statistically significant differences in survival according to N status (p=0.032). Twenty-two patients had T1N0 stage, 21 T2N0, and 4 T1N1. There was a trend for significant differences in survival according to TN stage (p=0.063). Also, analysis revealed significant differences in survival depending on tumor size (p=0.000), as well as on the type of the tumor (typical vs. atypical) (p=0.010).*

Conclusion: *Nodal status and TN stage affect patients' survival. Tumor size and typical/atypical tumor are also significant prognostic factors for survival of surgically treated patients.*

Key words: bronchial carcinoid, interventional pulmonology, lung cancer, neuroendocrine tumors, TNM, surgical treatment

Introduction

BC tumors are rare malignancies of the lung, making about 1-2% of all invasive lung cancer types. It is known that - besides the common lung cancer symptoms - the symptoms of BC usually include paraneoplastic features, Cushing's syndrome, and acromegaly. There are no gender predilections or association with smoking in BC. The treatment of choice in patients with BC is surgery. It has been established that the patients with typical BC have better prognosis than the ones with atypical forms of the tumor [1-5]. BCs are often localized in the bronchial tree as a polypoid, centrally located formations and therefore are accessible for interventional pulmonology treatment [6-9]. There are reports of successful treatment with laser resection, electrocautery or argon plasma coagulation [10,11]. Nodal involvement in carcinoid tumors, especially the typical ones, is not so frequent, registered in only 5-10% of the cases. When compared to the typical BC, atypical forms are usually larger in size, have a higher rate of metastases and poor prognosis. The major distinguishing feature between typical and atypical BC is the rate of mitoses and the presence of central necrosis. The typical BC shows a low mitotic rate (<2 mitoses per 10 high-power fields [HPF]), and absence of necrosis. A mitotic rate of 2-10 mitoses and the presence of necrosis characterize atypical carcinoids.

The major aim of this study was to examine the survival rate of surgically treated patients with early-stage BC in relation with clinical factors that could possibly influence survival. We postulated that the survival of patients with typical BC who were surgically treated would be improved. We were also interested in finding

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out whether there existed any correlations between the patients' gender, nodal involvement, TNM stage and tumor size with survival.

Methods

This study was partially prospective and partially retrospective analysis of patients with early-stage BC, who were surgically treated at the Institute of Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia, in the period 2000-2008. The relevant data were obtained from patients` medical records, surgery reports, definitive pathological findings from surgically obtained samples, as well as patients' oncology charts with data from the postoperative follow-up period.

Inclusion criteria

The inclusion criteria were: histologically confirmed BC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2, fitness for surgery, patient compliance, disease stage I-IIIA, and absence of known or suspected metastases.

Exclusion criteria

The exclusion criteria were: non-BC tumors, inoperability or non-resectability, disease stage > IIIB, presence of metastases, and ECOG PS ≥3.

Survival

Survival was measured from 2000 to 2008.

Statistical analysis

The analysis included clinicopathological characteristics such as gender, size of the tumor (stratified in mm as: < 20, 21-30, 31-40, 41-50, and >51), nodal involvement, and carcinoid type. These characteristics were studied and analyzed for possible impact on survival.

All statistical computations were done using SPSS for Windows v 11 (Chicago, IL, USA). The statistical data analysis included discriminative analysis and Roy's test. Chi-square test, and for multivariate analysis MANOVA test were used. A p-value < 0.05 was considered to indicate statistical significance. Kaplan-Meier method was used to generate survival curves.

Results

The study included 57 patients (25 males, 32 females, mean age 52.3 years, mean males age 53.9, mean females age 50.9). No significant survival differences were found in relation to patients' gender (p=0.128). At the conclusion of the study 6 patients had died (3 males and 3 females).

Thirty-nine patients had no metastases in the regional lymph nodes (N0). N1 involvement existed in 9 and N2 in 2 patients. No data on N status existed in 7 patients. N0 patients had a median survival of 50.3 months, while the median survival of N1 patients was 47.8 months (p=0.032, Figure 1).

Twenty-two (46.8%) patients had T1N0, 21 (44.7%) T2N0, and 4 (8.5%) T1N1 disease stage. Two patients with N2 disease and 7 patients without valid data on lymph node involvement were not included in this analysis.

The median survival of T1N1 patients was 37.75 months which was shorter than the survival of T1N0 (49.55 months) and T2N0 (57.95 months) (p=0.063). Figure 2 shows the TN stage-related survival of the 47 patients.

Fifty-five out of 57 patients had measurable tumors. Statistically significant survival differences were found in tumors >31 mm (p= 0.000).

The longest survival was registered in patients with tumor size 21-30 mm (68.64 months), followed by those with tumor size 31-40 mm (49.11 months) and < 20 mm (42.5 months). The shortest survival was registered in patients with tumor size > 51 mm (23.75 months). Most carcinoids (23 out of 57, 42%) were <20 mm in diameter. The median patient survival according to tumor size is shown in Figure 3.

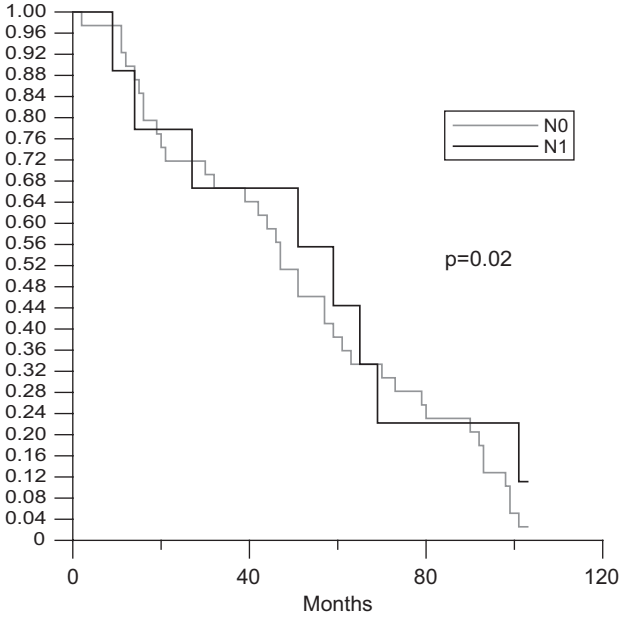

Figure 1. Survival according to N0 and N1 status.

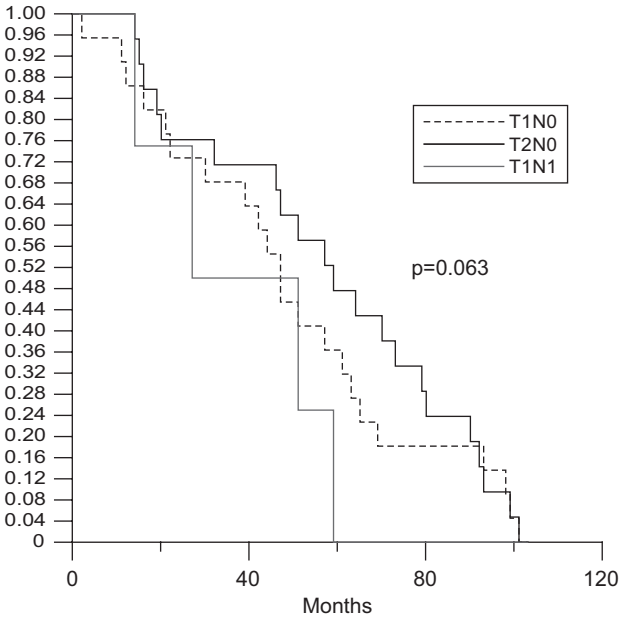

Figure 2. Survival according to TN stage.

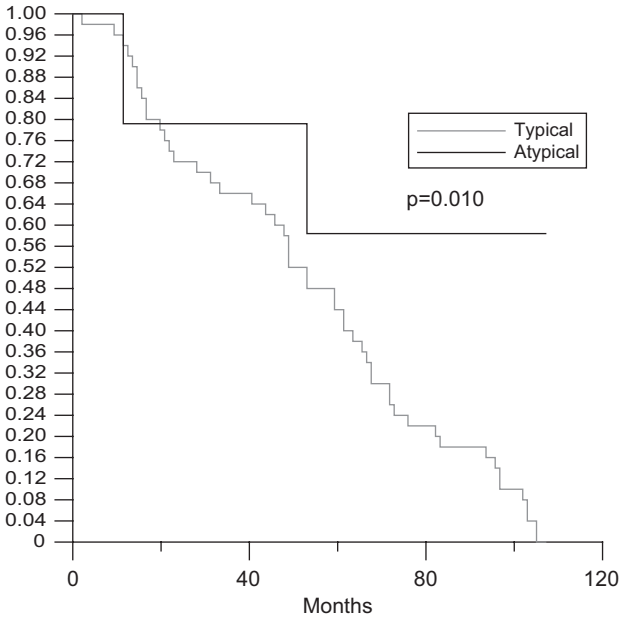

Figure 4. Survival according to the type of carcinoid.

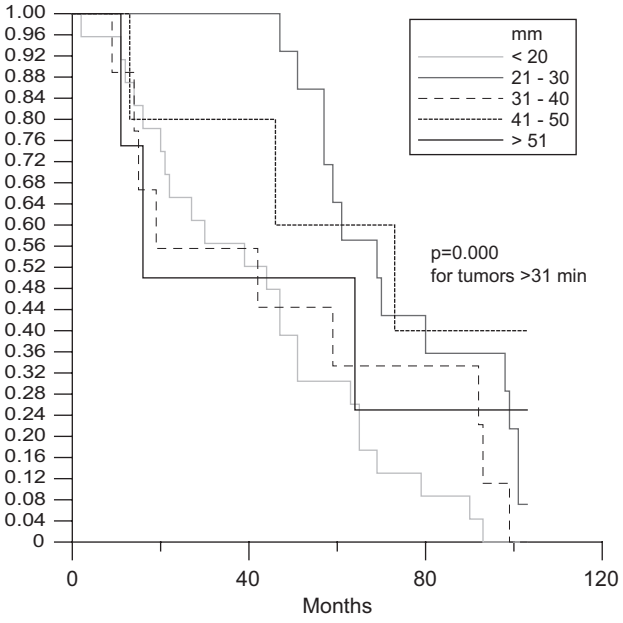

Figure 3. Survival according to tumor size.

In the examined series there were 52 patients with atypical and 5 with typical BC.

A median survival of 49.67 and 22.80 months was registered in patients with typical and atypical BC, respectively (p=0.010, Figure 4).

Discussion

BCs constitute 1-2% of all lung cancers and 25.3% of carcinoids of all localizations. They affect evenly both sexes, with a slight prevalence of women (women 55%, men 45%). All age groups (from 13 to 88 years) can be affected, but the disease is most commonly found in the middle age group (mean patient age 58 years) The incidence of atypical carcinoids is 4-5 times lower as compared to typical carcinoids. BCs originate from the neuroendocrine cells of the bronchial mucosa and they belong to the group of neuroendocrine lung tumors, including also small-cell lung cancer with its subtypes, and large-cell neuroendocrine carcinoma and its subtypes [1,2,5].

In this study, female patients were slightly more frequently affected than males. The affected females were usually middle-aged, but a little younger than the affected males. Among our patients, the youngest was 21, and the oldest 73 years old. No prognostic significance of sex in relation to survival was registered, in concordance with other authors' reports [12-14].

Approximately 75-80% of BCs have a central localization and clinical manifestations are usually cough, haemoptysis, wheezing, and recurring pneumonias distally from the location of BC. One half of the patients also report chest pain. Ectopic hormonal production which results in the carcinoid syndrome is observed in 1-5% of BC patients. Cushing's syndrome is noted in 1-2%, and acromegaly is a rare occurrence in these patients [15-17].

According to Ferolla et al. [3], endocrinological studies show that 15% of BC patients have clinical or subclinical hypersecretion of a wide hormone range, such as ACTH, antidiuretic hormone, serotonin, histamine, gastrin, calcitonin, tachiquinine, chromogranin A,

beta HCG, NSE, bombezine, parathormone, etc. Chromogranin A (CgA) is the serum marker most often used for well defined neuroendocrine lung tumors such as BC, although this metabolite is not responsible for any specific disease symptom, nor does it have any prognostic value [18-21]. The measurement of CgA is considered the gold standard of chemical tests for confirming the diagnosis of carcinoid and neuroendocrine tumors and for the follow-up of their course.

The 6th revision of the TMN staging system is acceptable for all lung cancer types (including small-cell carcinoma) because it provides prognostic information for all disease stages. For BC, however, this staging is not functional, so the 7th revision of the TNM presented by IASLC (International Association for the Study of Lung Cancer) is expected to be more suitable for BCs. For that purpose, a multicentre international database of patients with BC has been formed in the period from 1990 to 2000. Of 513 BC cases, 392 had sufficient data for determining the TNM stage. According to those data, and having analyzed their survival rates, it has been concluded that most BC patients (82%) had stage I disease. T status was a significant prognosticator of survival, and N and M status had negative correlation with survival. The most frequent BC size was <1.0-1.5 cm. Patients with tumor > 7 cm in diameter had lower survival rate [7,8,12,13].

In our study, significant tumor size-related differences in survival were registered, but a complete correlation of survival and tumor size of 21-40 mm was not established. Patients with tumor size > 51 mm in diameter had the shortest survival, as expected. Univariate analysis in our study showed that the best survival was observed in patients with tumor sizes of 21-30 and 31-40 mm. Literature data shows that 5-year survival can be expected in up to 92% of BC patients with N0 disease stage, in 74% of patients with N1 stage, but in 0% of patients with N2 and N3 nodal involvement. Therefore, 5-year survival might be observed in 93% of stage I, 85% of stage II, 75% of stage III, and in 57% of stage IV patients [7,9,17].

Due to atypical BC resection in 7 of our patients, no information on nodal involvement was available. In other patients, N stage had no significant prognostic value for survival (T1N0 vs. T1N1 = 49.55 vs. 37.75 months, p=0.063). As the best survival was registered in the group of patients with T2N0 stage, we could argue that T status might have had greater prognostic value compared with N status.

The histological study of typical carcinoids shows organoid or trabecular structure with moderate cell polymorphism, with a nucleus with granular chromatin and eosinophilic cytoplasm. The architecture can rarely be paraganglioid, light-celled, spindle-celled or melaninocytic. The number of mitoses is < 2 and necrosis is absent. Immunohistochemical staining reveals positivity for CgA, synaptophysin and CD56. Atypical carcinoids differ from typical ones by the presence of necrosis in the form of small foci inside cells and 2-10 mitoses. They can show greater architectural disorganization and greater polymorphism. These characteristics are not by themselves sufficiently discriminative criteria to differentiate between typical and atypical carcinoids. Regional and distant metastases are much more common in atypical carcinoids. It is sometimes difficult to differentiate between the two carcinoid types, and in these cases biomarkers of the proliferation potential in neuroendocrine tumors can be used, including Ki67, CD44, and MM23 [16,18,20,21].

Unlike typical, atypical carcinoids have a peripheral localization in 50% of the cases, making up 10-30% of BCs. By their biological behavior, they belong to the intermediate type of neuroendocrine lung tumors. The 5-year survival is 56% for atypical carcinoids [15,16].

In our group of patients, 52 had typical and 5 atypical BCs. The tumor type had prognostic value, because the average survival of patients with typical BCs was significantly longer compared with patients suffering from atypical BCs (49.67 vs. 22.80 months, p=0.010).

Conclusions

In our group of operated BC patients females prevailed, while no gender-related survival differences were established. T1N1 disease stage had the worst survival rate. The possible greater prognostic significance of nodal involvement survival in T2N0 stage patients. A significantly better survival may be expected in operated patients with typical BC.

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