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Significance of the resection margin in bronchopulmonary carcinoids

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ABSTRACT

Background: Complete surgical resection is the treatment of choice in bronchopulmonary carcinoids. Previously published data showed no inferiority of sublobar *versus* lobar resection. Data on the length of resection margins are lacking; thus, we aimed to analyze resection margins in pulmonary carcinoids and correlated them with survival and recurrence.

Methods: We retrospectively analyzed 85 patients who underwent surgery for atypical (AC) or typical (TC) pulmonary carcinoids. Patient charts were reviewed, and clinicopathologic and survival data were collected. Pathology reports were reviewed for length of resection margins.

Results: The median follow-up period was 42.3 mo (range, 0.3–172.2). There was no statistically significant difference in disease-free survival (DFS) when comparing resection margins $\leq$2 mm to >2 mm ($P = 0.93$, hazard ratio = 1.7). When looking at AC alone, a worse DFS can be seen if the resection margin was smaller than 2 mm ($P = 0.06$, hazard ratio = 15.8). In AC, likelihood of recurrence was higher when the resection margin was $\leq$1 cm (odds ratio = 5.1, $P = 0.28$). In TC, this tendency was not present (odds ratio = 1.2, $P = 1$).

Conclusions: There is a trend toward a worse prognosis and higher likelihood of recurrence in smaller resection margins in AC in contrast to TC. Owing to low sample size, no definitive statements can be made based on this study; however, respective data on these rare tumors cannot be drawn from tumor databases. The resection margin is one of the critical issues for the treating surgeon, and any information on this topic is of highest importance to the field.

1. Introduction

Pulmonary carcinoids are rare and account for approximately 1%–3% of primary lung tumors. They belong to the heterogeneous group of neuroendocrine neoplasias that include in the lung small-cell, large-cell neuroendocrine and carcinoid tumors. Based on their histopathologic and immunohistochemical features, they are separated into typical (TCs) and atypical (ACs) carcinoids [1–3]. ACs have a worse prognosis and generally show a higher rate of lymph node and distant metastasis as well as recurrence. Nonetheless, pulmonary carcinoids have a favorable prognosis showing 5-y survival rates of 92% in TC and 66% in AC, respectively [4]. According to the NCCN guidelines, standard treatment in localized

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bronchopulmonary carcinoids is the anatomic resection and mediastinal lymph node dissection or sampling. The only exceptions are peripheral TCs, in which a margin negative wedge resection is considered sufficient [5]. Current recommendations for the extent of surgery are mostly based on single-institution retrospective analyses with limited patient numbers. Previous studies have shown a noninferiority of sublobar *versus* lobar resection in pulmonary carcinoids [5,6]. However, these studies did not specifically address the length of the resection margin being one of the critical issues for the surgeon. In addition, recently published analyses from multi-institutional databases with large patient numbers lack pathologic details, such as the length of resection margin [6–8]. In this retrospective, single-institution analysis from a high-volume center, we aimed to analyze the impact of the resection margin on survival and recurrence in pulmonary carcinoids.

2. Material and methods

In this retrospective single institution analysis, we studied 85 patients with histologically proven ACs or TCs which were consecutively resected in our center between 2006 and 2014. Typical and atypical carcinoids were distinguished according to the World Health Organization criteria [3]. A typical carcinoid was considered in tumors with carcinoid morphology and <2 mitoses per 2 mm^2 (10 HPF) which lack necrosis. Atypical carcinoids were differentiated by mitosis count (2–10 mitoses per 2 mm^2) or presence of necrosis. Patient charts were reviewed, and clinicopathologic and survival data were collected from our database and augmented by telephone interview when possible. Pathology reports were analyzed to assess resection margins. The study was approved by our local ethics committee and registered in the German Registry for Clinical Trials (DRKS-ID: 00006164).

Data were recorded in a database designed in Microsoft Office Excel (Microsoft, Redmond, WA), and GraphPad Prism 6.03 (GraphPad Software Inc., La Jolla, CA) was used for statistical analysis. For evaluation of survival data, the Kaplan–Maier estimator was used, and the log-rank test was used for comparison of survival curves. Multivariate analysis was not performed as there was only one factor statistically significant in univariate analysis. To analyze the impact of certain resection margins on the likelihood of recurrence Fisher's exact test was used.

Results were considered statistically significant if the *P* value was <0.05. A trend was considered when the *P* value was between 0.05–0.1.

Overall survival (OS) was defined by the time interval from surgery to death by any cause. Disease-free survival (DFS) was defined as the time interval from surgery to tumor recurrence or death by any cause.

3. Results

3.1. Demographics

The mean age at the time of surgery was 56.4 (±16) years, and there were 45 (53%) women in the study cohort. In 22 (26%) cases, a sublobar resection was performed of which in 18 (82%) cases a wedge and in 4 (18%) cases a segmental resection was performed. Lobectomy was carried out in 33 (39%), and bronchoangioplastic resection was performed in 29 (34%) cases; pneumonectomy was necessary in one patient only. Histologic and immunohistochemical analysis verified TC in 64 (75%) and AC in 21 (25%) of the resected specimen. The mean resection margin was 7.3 mm (±9) in TC and 10.0 mm (±12) in AC (Fig. 1). Lymphadenectomy was carried out in 74 (88%) cases. Mean lymph node count resected in TC was 14 (±9) and 18 (±11) in AC, respectively. Tumor cells were verified in the resection margin (R1) in two cases of TC and in two cases of AC. The latter received adjuvant radiation. None of the other patients received adjuvant treatment. Recurrence occurred in six (7%) patients of which five (6%) showed local recurrence (four ACs and two TCs), and all of them were completely resected (R0) in the initial surgery. Lymph node metastases were detected in 14 (17%) cases (eight ACs and six TCs). None of the patients included in the study showed distant metastasis at the time of diagnosis, but four (5%) patients at the time of recurrence. Demographic and clinical characteristics are summarized in Table 1.

3.2. Survival

Median follow-up was 42.3 mo (range, 0.3–172.2). OS at 2 and 5 y was 94% and 92%, respectively. DFS at 2 and 5 years was 94% and 89%, respectively (Fig. 2). DFS in AC was also excellent in our cohort with a survival rate of 90% at 2 y and 85% at 5 y. Survival in TC was 94% at 2 y and 91% at 5 y.

The effect of the resection margin on DFS and OS was evaluated for the different groups according to the different lengths of resection margins. Cutoffs for the resection margins were chosen at 2 mm and 1 cm to create representative and comparable groups for close and wide margins. Analysis was also performed using cutoffs at 1 mm and 2 cm (data not shown) but comparison did not create representative results

Table 1 – Demographic and clinical characteristics of pulmonary carcinoids.

Characteristics	
Age (y)	56.4 (±16)
Female gender, *n* (%)	45 (53)
Histology, *n* (%)	
Typical carcinoids	64 (75)
Atypical carcinoids	21 (25)
Surgery type performed, *n* (%)	
Sublobar wedge	18 (21)
Sublobar anatomic	4 (5)
Lobectomy	33 (39)
Bronchoangioplasty	29 (34)
Pneumonectomy	1 (1)
Resection margin	
TC	7.3 (±9)
AC	10.0 (±12)
Lymphadenectomy performed, *n* (%)	74 (88)
TC (lymph nodes resected)	14 (±9)
AC (lymph nodes resected)	18 (±11)

If not stated results are presented as mean with standard deviation.