SCIE DOI: 10.14744/scie.2024.35556
South. Clin. Ist. Euras. 2024;35(4):400-404
Original Article

Evaluating Long-Term Survival Determinants in Bronchopulmonary Carcinoids Following Anatomical Resection: A Retrospective Analysis

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Submitted: 25.11.2024
Revised: 27.11.2024
Accepted: 28.11.2024

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Keywords: Carcinoid Tumor; Lobectomy; Thoracic Surgery; Video-Assisted.

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ABSTRACT

Objective: Bronchopulmonary carcinoid tumors (BCTs) are a rare type of lung cancer (1–2%). They are divided into two subtypes: typical (TK) and atypical (AK). Prognosis depends on various factors such as tumor type, size, spread, and Ki-67 (cell proliferation marker). This study aimed to identify these prognostic factors to improve treatment and survival rates in BCT patients. The main objective of this research was to retrospectively investigate the factors associated with long-term survival in patients with bronchopulmonary carcinoid tumors.

Methods: The data of 56 patients who underwent surgery at our center between February 2008 and March 2021 and were histopathologically diagnosed with bronchopulmonary carcinoid tumor were retrospectively analyzed.

Results: Most of the patients were female (60.7%) with a median age of 43. Lobectomy was the most common surgical procedure (60.7%). Prolonged air leak was the most common complication. Typical carcinoids were more common than atypical ones (69.6%–30.4%). Mediastinal lymph node metastasis was more common in atypical tumors. The findings of the study showed that tumor stage, lymph node metastasis, and Ki-67 index were prognostic factors associated with long-term prognosis in patients with bronchopulmonary carcinoid tumors. The 5-year survival rate was higher in typical carcinoids than in atypical ones (82.1%–64.7%). The recurrence rate was higher in atypical tumors (25%–2.4%).

Conclusion: These findings highlight the critical role of tumor characteristics in determining long-term outcomes in patients with bronchopulmonary carcinoid tumors. Considering factors such as tumor type, lymph node involvement, stage, and Ki-67 index, more personalized treatment strategies can be developed. Further research involving larger, multicenter patient groups may provide more robust data to improve prognostic models for this patient population and guide treatment decisions.

INTRODUCTION

Bronchopulmonary carcinoid neoplasms (BCNs) are a distinct category of lung cancers characterized by neuroendocrine features. While uncommon, they represent approximately 1% to 2% of all diagnosed lung carcinomas.[1,2] The initial histological description of a carcinoid tumor is credited to Theodor Langhans in 1867.[3] However, the first clinical cases documented were two patients with ileal carcinoid tumors discovered during autopsy by Otto Lubarsch in 1888.[4,5]

The incidence of BCNs has exhibited a significant rise over the past three decades.[6,7] This increase might not necessarily reflect a true surge in their prevalence but could be attributed to advancements in diagnostic techniques. The use of low-dose CT (Computerized Tomography) scans for lung cancer screening programs has likely played a role in identifying more incidental BCNs at an earlier stage.[8]

The 2015 IASLC classification system, established by Lee et al.,[9] categorizes BCNs into two main subtypes: typical carcinoid (TC) and atypical carcinoid (AC). TCs, constituting roughly 90% of all lung carcinoids, are generally indolent tumors with a slow growth rate and a favorable

prognosis.[10] They are typically associated with lower rates of metastasis and longer disease-free survival compared to Acs.[11] ACs, on the other hand, demonstrate a more aggressive biological behavior, exhibiting a higher propensity for local recurrence and distant metastasis.[12]

The cornerstone of treatment for patients with operable BCNs remains surgical resection.[13] Anatomical surgical resection, which aims to remove the entire tumor along with surrounding lymph nodes, offers the best chance for cure, particularly for patients with TC.[14] However, the prognosis for BCNs can vary depending on several factors. These factors can be broadly categorized into tumor-related characteristics, patient-related characteristics, and treatment-related factors. Tumor-related characteristics include histological subtype (TC vs. AC), tumor size, presence of lymph node involvement (stage), and markers of cell proliferation (Ki-67 index). Patient-related characteristics encompass age, gender, and underlying comorbidities. Treatment-related factors primarily focus on the extent of surgical resection (complete vs. incomplete) and the use of adjuvant therapies such as somatostatin analogs for patients with advanced or metastatic disease.

This study aims to investigate the prognostic factors that influence outcomes in patients undergoing anatomical lung resection for bronchial carcinoid tumors. By identifying these factors, we can potentially refine treatment strategies and improve patient survival rates. Understanding the interplay between these various factors will allow for a more personalized approach to BCN management, optimizing treatment efficacy and maximizing patient outcomes.

MATERIALS AND METHODS

The study included all patients with histologically confirmed typical and atypical carcinoid tumors who underwent anatomical surgical resection at the Department of Istanbul University Istanbul School of Medicine Thoracic Surgery from February 2008 to March 2021. Patient informed consent was not required due to retrospective data analysis. This study was conducted in accordance with the Declaration of Helsinki and approved by the Istanbul University Istanbul School of Medicine Clinical Trials Ethical Board (2023/707).

It is based on demographic data (such as age at diagnosis, gender, race, marital status, life expectancy, and duration), tumor characteristics (site of onset, laterality, histological grade, histological type, primary tumor size, T, N, and M stage), Ki-67 index, and clinical data (surgery, radiology, and chemotherapy). Additional evaluations included medical history review, physical examination, blood hematology and biochemistry, respiratory function test, chest x-ray, and contrast-enhanced tomography (CT) of the chest and abdomen. Further evaluation of the disease included 2-deoxy-2-(18F) fluoro-D-glucose (FDG) positron emission tomography (PET)/CT and fiberoptic bronchoscopy (requires biopsy).

The main outcomes of this study were cancer-specific survival (CSS), time to cancer diagnosis, and incidence of cancer death. The Cox proportional hazards regression model was used to identify independent predictors of survival by calculating relative hazards and associated 95% confidence intervals. Variables found to be significant ($p<0.05$) in univariate Cox regression analysis were included in multivariate Cox regression analysis. Kaplan-Meier curves and logistic regression were used to compare and contrast the CSS of patients in different groups. The accuracy of survival prediction was also evaluated using the area under the receiver operating characteristic (ROC) curve. Two-sided $p<0.05$ indicates statistical significance.

This study was conducted with the ethical approval of the Istanbul University Istanbul School of Medicine Ethics Committee (approval number: 1737659, date: April 28, 2023). This ensures that the research adhered to ethical guidelines and participant safety was prioritized throughout the study. This approval process included the review and participant consent for all procedures involved in the study.

RESULTS

A total of 56 patients were included in the study, with a median age of 43 (range 15–57) years. There were 34 (60.7%) females and 22 (39.3%) males. Among them, lobectomy was performed in 34 (60.7%) patients, sleeve lobectomy in 10 (17.9%) patients, segmentectomy in 5 (8.9%) patients, and bi-lobectomy in 6 (10.7%) patients. The median hospital stay for all patients was 7±1.3 days. The most common complication affecting all patients was prolonged air leak, diagnosed in 8 patients. One patient who underwent sleeve right upper lobectomy required pneumonectomy afterward due to total atelectasis in the early postoperative period. Patients with any type of complications had a significantly longer duration of hospital stay, with a median of 18 days compared to 6.3 days for patients without complications ($p=0.001$). No 90-day mortality was observed.

Of the cases included in the study, 39 (69.6%) were typical carcinoid tumors and 17 (30.4%) were atypical carcinoid tumors. Although females tended to have typical carcinoid tumors more frequently, this difference was not statistically significant ($p=0.68$). Similarly, patients with atypical carcinoids tended to be younger, but this was also not significant ($p=0.06$). Among the typical carcinoid tumors, 3 (7.7%) had nodal invasion, while among the atypical carcinoid tumors, 3 (17.7%) had nodal invasion. One patient with an atypical carcinoid presented with subcarinal lymph node metastasis.

In terms of TNM 8 staging, 35 (62.5%) patients were staged for T stage as T1a, 7 (12.5%) as T1b, 5 (8.9%) as T2a, 4 (7.1%) as T2b, and 5 (8.9%) as T3a. The median Ki-67 index was 3.23% for typical carcinoids and 7.76% for atypical carcinoids ($p=0.002$). Compared to other patients, stage IA patients had lower Ki-67 values ($p=0.033$),

less necrosis (p=0.016), a significantly lower rate of mitosis (p=0.004), and were more likely to have typical carcinoid tumors (p=0.007).

The median follow-up period was 87 months. Median follow-up for typical and atypical carcinoid tumors was 102 and 70 months, respectively. Table 1 summarizes patient characteristics and prognostic factors. The 5-year survival rates for typical and atypical carcinoid tumors were 82.1% and 64.7% (p=0.02). Also, early postoperative complications (p=0.905), tumor necrosis (p=0.9), significant mitosis presence (p=0.981), and gender (p=0.206) showed no survival difference. The 5-year survival rates were significantly different for tumor status (T) (p=0.001), lymph node status (N) (p=0.005), and pathologic tumor-node-metastasis (TNM) stage (p=0.0001). Overall survival rates according to T stage, based on the TNM 8 classification, are detailed in Figure 1.

Table 1. Clinicopathologic features of the patients with broncopulmonary carcinoid tumors

Feature	Mean±SD	Percentage (%)
Age	43.25±14.6	
Sex		
Female	33	60.7
Male	22	39.4
Smoking history (pack-year)	18±22.3	
Tumor localization		
Right upper lobe	7	12.5
Right middle lobe	8	14.3
Right lower lobe	15	26.8
Left upper lobe	12	21.4
Left lower lobe	14	25
Resection Type		
Lobectomy	34	60.7
Bi-lobectomy	6	10.7
Sleeve Resection	10	17.9
Segmentectomy	5	8.9
Pneumonectomy	1	1.8
Operation Preference		
Minimaly Invasive	29	51.8
Open thoracotomy	27	48.2
Complications		
Cardiovascular Complications	1	1.8
Chylothorax	1	1.8
Prolonged Air Leak	8	14.3
Pneumonia	3	5.4
Hystopathological Features		
Typical Carcinoid Type	39	69.6
Atipical Carcinoid Type	17	30.4
Staging		
Ia	35	62.5
Ib	7	12.5
2a	5	8.9
2b	4	7.1
3a	5	8.9
Pathological Structural Invasion		
Lymphovascular	16	28.1
Spread through air spaces	1	1.8
Perineural	1	1.8
Vascular	1	1.8

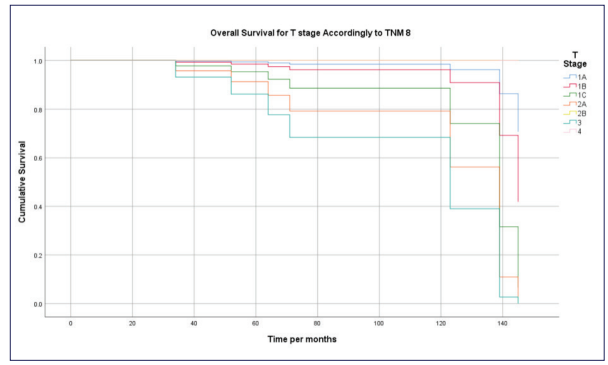

Figure 1. Stage-Specific Overall Survival Based on TNM 8 Classification.

A Ki-67 index greater than 3 was associated with a worse overall prognosis (p=0.03). During this time, 5 (2.4%) patients with typical carcinoid tumors and 7 (25%) patients with atypical carcinoid tumors experienced recurrences. Among the typical carcinoid tumors, 2 recurrences resulted in locoregional metastases, all occurring in N0 patients. Among the atypical carcinoid tumors, 5 recurrences were locoregional and 2 were distant metastases. Four of the locoregional recurrences were in N0 patients, while three were in N1/N2 patients, with one case of distant metastasis in each group. All recurrences were diagnosed during follow-up SRI PET/CT (somatostatin receptor positron emission tomography) or SPECT (Single-photon emission computed tomography) scans in asymptomatic patients.

DISCUSSION

Carcinoid tumors exhibit features similar to large cell neuroendocrine tumors and small cell carcinomas in terms of structure, morphology, and immunohistochemistry. However, their biological behavior differs considerably.[7] Studies suggest a relatively favorable prognosis for carcinoid tumors following surgery compared to other non-small-cell lung carcinomas (NSCLCs), even with tissue-sparing resection.[8]

While Lee et al.[9] reported no significant sex disparity, Soldath et al.[10] observed a female predominance in their cohort of 171 patients (71.3%). Conversely, larger studies have shown a male majority ranging from 54% to 63%.[11,12]

Our findings on five-year survival rates are consistent with previous literature. Kasprzyk et al.[13] reported a 65% rate in their study of 65 patients, while Rea et al.[14] observed a significantly higher 98% rate over the same period for

210 patients with typical carcinoids. Additionally, several studies, including ours, have identified the Ki-67 proliferation index as another significant prognostic factor in pulmonary carcinoid tumors,[14-16] which was also consistent with our research.

Anatomical resection is often chosen for bronchopulmonary carcinoids due to its effectiveness in achieving complete tumor removal and addressing potential lymphatic spread. Studies suggest that non-anatomical resections may leave behind microscopic disease or miss lymphatic involvement, which can increase recurrence risk. Anatomical resection also includes removal of regional lymph nodes, which is important in cases of atypical carcinoids that have higher rates of lymph node involvement.[16] This approach addresses possible spread through lymphovascular or perineural invasion, thereby helping to reduce locoregional recurrence. For typical carcinoids, anatomical resection supports long-term disease-free survival by ensuring thorough removal of the tumor and surrounding structures. Overall, anatomical resection remains a preferred approach for bronchopulmonary carcinoids, particularly in addressing lymphatic involvement and tumor spread. Even though small, centrally located tumors often have a favorable prognosis and positive long-term outcomes, their location can necessitate more extensive surgical resections. Therefore, close and frequent follow-up is essential during the monitoring period to ensure timely detection of any potential recurrence. A center specializing in thoracic oncology, staffed by experienced pulmonary oncologists, chest physicians, and thoracic surgeons, is critical for optimal follow-up care. Our study reaffirms the importance of the Ki-67 proliferation index as a significant prognostic factor, aligning with previous literature. Despite the generally positive prognosis for small, centrally located tumors, the necessity for extensive surgical resections and the risk of recurrence underscore the importance of meticulous, ongoing follow-up. Optimal patient outcomes are best achieved through comprehensive care provided by specialized thoracic oncology centers equipped with experienced multidisciplinary teams.

Conclusion

Anatomical resections remain the preferred surgical approach, ensuring complete tumor removal and addressing lymphatic spread, particularly in atypical carcinoids. Despite the favorable prognosis for small, centrally located tumors, the potential for recurrence necessitates vigilant long-term follow-up.

Ultimately, the integration of precise surgical techniques, close postoperative monitoring, and multidisciplinary collaboration in specialized thoracic oncology centers is essential for optimizing patient outcomes and minimizing recurrence risk. Future research focusing on long-term survival and advanced imaging techniques may further refine treatment strategies for bronchopulmonary carcinoid tumors.

Ethics Committee Approval

The study was approved by the Istanbul University Istanbul School of Medicine Clinical Trials Ethics Committee (Date: 28.04.2023, Decision No: 1737659).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.D., B.Ö.; Design: S.D., M.K.; Supervision: B.Ö., A.D., M.K., S.A.T.; Fundings: M.K., S.A.T.; Materials: S.D., A.S.; Data collection &/or processing: S.D., A.S.; Analysis and/or interpretation: A.S.; Literature search: B.Ö., S.A.T.; Writing: S.D., A.S.; Critical review: B.Ö., A.D., M.K., S.A.T.

Conflict of Interest

None declared.

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Bronkopulmoner Karsinoidlerde Anatomik Rezeksiyon Sonrası Uzun Dönem Sağkalım Belirleyicilerinin Değerlendirilmesi: Retrospektif Veri Analizi

Amaç: Bronkopulmoner karsinoid tümörler (BKT), akciğer kanserinin nadir bir türüdür (%1-2). Tipik (TK) ve atipik (AK) olmak üzere iki alt tipe ayrılırlar. Prognoz; tümör tipi, boyutu, yayılımı ve Ki-67 (hücre proliferasyon belirteci) gibi çeşitli faktörlere bağlıdır. Bu çalışma, BKT hastalarında tedavi ve sağkalım oranlarını iyileştirmek amacıyla bu prognostik faktörlerin belirlenmesini amaçlamıştır. Bu araştırmanın ana hedefi, bronkopulmoner karsinoid tümörlü hastalarda uzun dönem sağkalım ile ilişkili faktörlerin retrospektif olarak incelenmesidir.

Gereç ve Yöntem: Şubat 2008 ile Mart 2021 tarihleri arasında merkezimizde ameliyat edilen, histopatolojik olarak bronkopulmoner karsinoid tümör tanısı almış 56 hastanın verileri retrospektif olarak analiz edildi.

Bulgular: Hastaların çoğu kadın (%60.7) olup ortanca yaşları 43 idi. Lobektomi en sık yapılan cerrahi olarak saptandı (%60.7). Uzamış hava kaçağı en sık komplikasyon olarak izlendi. Tipik karsinoidler atipik olanlardan daha yaygındı (%69.6-%30.4). Atipik tümörlerde mediastinal lenf metastazı daha sık saptandı. Çalışmanın bulguları, bronkopulmoner karsinoid tümörlü hastalarda uzun dönem prognozu ile ilişkili prognostik faktörlerin tümör evresi, lenf nodu metastazı ve Ki-67 indeksi olduğunu göstermiştir. Tipik karsinoidlerde 5 yıllık sağkalım oranı atipik olanlara göre daha yüksekti (%82.1-%64.7). Atipik tümörlerde nüks oranı daha yüksek olarak saptandı (%25-%2.4).

Sonuç: Bu bulgular, bronkopulmoner karsinoid tümörlü hastalarda uzun dönem sonuçların belirlenmesinde tümör özelliklerinin kritik rolünü vurgulamaktadır. Tümör tipi, lenf nodu tutulumu, evre ve Ki-67 indeksi gibi faktörleri göz önünde bulundurarak daha kişiselleştirilmiş tedavi stratejileri geliştirilebilir. Daha büyük, çok merkezli hasta gruplarını içeren ileri araştırmalar, bu hasta popülasyonu için prognoz modellerini iyileştirmek ve tedavi kararlarına rehberlik etmek için daha sağlam veriler sağlayabilir.

Anahtar Sözcükler: Göğüs cerrahisi; karsinoid tümörler; lobektomi; video-yardımlı cerrahi.