

Pulmonary carcinoids – analysis of early and long-term surgical treatment outcomes in a group of 90 patients



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Abstract

Introduction: Over the years, pulmonary carcinoids have been treated as locally malignant tumors because of the favorable prognosis. It is currently known that the clinical course of the disease is mainly dependent on the carcinoid subtype.

Aim: To analyze the early and long-term surgical treatment outcomes for typical and atypical carcinoids.

Material and methods: A total of 90 patients were treated surgically for pulmonary carcinoid tumors in the years 2007–2015. Typical carcinoids were diagnosed in 69 (77%) cases, while atypical carcinoids – in 21 (23%); 67 patients underwent lobectomy, 3 – sleeve lobectomy, 9 – bilobectomy, 2 – pneumonectomy, 1 – segmentectomy, and 8 – wedge resection.

Results: None of the patients died in the postoperative period. Complications occurred in 14.4% of patients. The most common complications included: arrhythmias (5.6%), prolonged air leak (3.3%), and residual pneumothorax (3.3%). Among the 21 patients with atypical carcinoids, N1 metastasis was found in 1 (4.8%) patient, while N2 – in 5 (23.8%) patients. In the group of 69 patients with typical carcinoids, N1 metastasis was revealed in 7 (10.1%) patients and N2 metastases – in 2 (2.9%) patients. The probability of 5-year survival in patients with typical and atypical carcinoids was 96% and 83%, respectively. During the follow-up period 7 (7.8%) patients, including 6 with atypical carcinoids, experienced local recurrence; distant metastasis occurred in 8 (8.9%) cases, including 6 with atypical carcinoids.

Conclusions: Although radical surgical treatment provides excellent long-term outcomes, it should be noted that patients with pulmonary carcinoids (especially with the atypical subtype) may experience local recurrence and distant metastases even many years after surgery.

Key words: typical carcinoid, atypical carcinoid, surgical treatment.

Streszczenie

Wstęp: Ze względu na dobre rokowania rakowiaki płuc były przez lata uznawane za nowotwory miejscowo złośliwe. Obecnie wiadomo, że przebieg kliniczny tej choroby zależy głównie od podtypu rakowiaka.

Cel: Analiza wczesnych i odległych wyników leczenia chirurgicznego rakowiaków typowych i atypowych.

Materiał i metody: W latach 2007–2015 z powodu rakowiaka płuca leczono operacyjnie 90 pacjentów. Rakowiak typowy został zdiagnozowany w 69 (77%) przypadkach, natomiast rakowiak atypowy – w 21 (23%); u 67 pacjentów wykonano lobektomię, u 3 – lobektomię mankietową, u 9 – bilobektomię, u 2 – pneumonektomię, u 1 – segmentektomię oraz u 8 – resekcję klinową.

Wyniki: W okresie okotooperacyjnym nie stwierdzono zgonów. Powikłania pooperacyjne wystąpiły u 14,4% pacjentów. Najczęstszymi powikłaniami były: zaburzenia rytmu serca (5,6%), przedłużony przeciek powietrza (3,3%) i resztkowa komora odmowa (3,3%). Spośród 21 chorych z rakowiakiem atypowym u 1 (4,8%) potwierdzono cechę N1, aż u 5 (23,8%) – cechę N2. W grupie 69 chorych z rakowiakiem typowym cechę N1 potwierdzono u 7 (10,1%) pacjentów, natomiast cechę N2 – u 2 (2,9%). Prawdopodobieństwo 5-letniego przeżycia u chorych z rakowiakiem typowym i atypowym wyniosło odpowiednio 96% i 83%. U 7 (7,8%) chorych, w tym u 6 z rakowiakiem atypowym, w czasie obserwacji stwierdzono wznowę miejscową; przerzuty odległe wystąpiły w 8 (8,9%) przypadkach, w tym u 6 pacjentów z rakowiakiem atypowym.

Wnioski: U chorych z rakowiakiem płuca radykalne leczenie operacyjne zapewnia bardzo dobre wyniki odległe, należy jednak pamiętać o możliwości wznowy miejscowej i przerzutów odległych (zwłaszcza w rakowiakach atypowych) nawet wiele lat po operacji.

Słowa kluczowe: rakowiak typowy, rakowiak atypowy, leczenie operacyjne.

Introduction

Lung carcinoids are a relatively rare type of neuroendocrine neoplasms, constituting 2.5% of all lung tumors.

Because of the very favorable prognosis, they were considered benign or locally malignant neoplasms for many years [1]. Surgical treatment was, therefore, often limited

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to wedge resection or segmentectomy, while, in the case of minor endobronchial lesions, bronchoscopic endoresection was conducted with good long-term outcomes [2, 3]. It has since been established that neuroendocrine lung tumors are a very diversified group, including mature typical carcinoids with favorable prognoses as well as aggressive neuroendocrine large-cell and small-cell lung carcinomas [4, 5]. In 1999, based on the new histological criteria presented by Travis *et al.*, the WHO and IASLC finally accepted the division of carcinoids into typical and atypical [6]. Because of the differences in their clinical course and ability to metastasize via lymphatic or hematogenous spread, there are still ongoing discussions concerning the therapeutic management strategies for typical and atypical carcinoids. There are still doubts concerning both the extent of resection as well as indications for adjuvant treatment.

Aim

The aim of this study was to assess the early and long-term outcomes for the surgical treatment of lung carcinoids, with special consideration to their histological subtypes.

Material and methods

A total of 90 patients were treated surgically for lung carcinoids in the years 2007–2015. The study group included 59 women and 31 men. The age of the patients ranged from 21 to 79 years, 59 on average. Preoperative diagnostics included basic laboratory blood tests, chest computed tomography (CT), abdominal ultrasound or CT scan, and bronchofiberscopy; in some patients positron emission tomography/computed tomography (PET/CT), head CT, and transthoracic tumor biopsy were also conducted. When assessing respiratory function, the results of capillary blood gas and spirometry as well as diffusing capacity of the lungs for carbon monoxide (DLCO) were analyzed; some patients underwent a 6-min walk test or a stair climbing test. In cases of uncertainty, the predicted postoperative forced expiratory volume in 1 s (ppoFEV₁) and the predicted postoperative diffusing capacity of the lungs for carbon monoxide (ppoDLCO) were calculated. Circulatory assessment was conducted on the basis of electrocardiography (ECG) and echocardiography. In cases of enlarged mediastinal lymph nodes on CT, endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) or mediastinoscopy was conducted before lung tumor resection. In 2 patients rigid bronchoscopy with endoscopic removal of the part of the tumor protruding into the main bronchus was conducted before the planned operation to assess the possibility of lobectomy. Patients with adequate respiratory and circulatory function and locally operable tumors (as assessed with CT and bronchofiberscopy) were qualified for surgical treatment after the exclusion of distant metastases (PET/CT, abdominal CT or ultrasound, head CT) and metastases to mediastinal lymph nodes (PET/CT, EBUS, mediastinoscopy).

The procedure was conducted under general intravenous anesthesia with a double lumen bronchial intubation via anterolateral thoracotomy (70 patients) or video-as-

sisted thoracoscopic surgery (VATS) (20 patients). Mediastinal lymphadenectomy was performed in each patient. After obtaining the results of postoperative histopathological tests, the stage of the cancer was classified according to the 7th edition of the TNM classification of 2009. Every patient was consulted with an oncologist and (depending on the TNM stage, the patient's general condition, and the presence of coexisting diseases) was qualified for adjuvant treatment (chemo- and/or radiation therapy).

Clinical data was obtained from the medical documentation of the thoracic surgery and oncology department, while postoperative patient outcomes were established on the basis of phone conversations with the patients or their families and information acquired from the thoracic surgery and oncology outpatient clinic.

Statistical analysis

Statistical analysis was conducted with the use of the Statistica 12.5 software. The Mann-Whitney test was used; survival function was estimated using the Kaplan-Meier method.

Results

Among the 90 patients undergoing surgery, 69 (77%) were diagnosed with typical carcinoids in the final histopathological examination, while the remaining 21 (23%) patients were diagnosed with atypical carcinoids. Lobectomy was performed in 67 patients, sleeve lobectomy – in 3 patients, bilobectomy – in 9 patients, pneumonectomy – in 2 patients, segmentectomy – in one patient, and wedge resection – in 8 patients. On average, the procedures lasted 120 min (50–240 min), while the average intraoperative blood loss was 240 ml (50–800 ml). Pleural drainage was maintained for 1–10 days (avg 3 days). Hospital stay time was 4–23 days (avg. 7 days). No perioperative mortality was reported. Postoperative complications occurred in 13 (14.4%) patients. The most frequent complications included: atrial fibrillation (5 patients), prolonged air leak (3 patients), and residual pneumothorax (3 patients). The types and percentages of individual complications are presented in Table I. In 75 (83.3%) patients, postoperative histopathological examination did not reveal any metastases to local lymph nodes; N1 metastases were confirmed in 8 (8.9%) patients, while N2 lymph node metastases were found in 7 (7.8%) patients. Among the 21 patients with atypical carcinoids, N1 metastasis was revealed in 1 (4.8%) patient, while N2 – in 5 (23.8%) patients. In the group of 69 patients with typical carcinoids, metastases to N1 lymph nodes were found in 7 (10.1%) patients, while N2 disease was observed in 2 (2.9%) patients. Patients with stages I (76.7%) and II (14.4%) constituted the majority (Tab. I). A total of 2 (2.2%) patients with atypical carcinoids underwent preoperative chemotherapy – remission was achieved in both cases. None of the patients were treated with preoperative radiation therapy. In 89 (98.9%) patients, the procedure was oncologically complete (R0). In 1 (1.1%) case, neoplastic infiltration was observed in the bronchial resection margin (R1). A total of 7 (7.8%) patients

underwent postoperative chemotherapy, 2 (2.2%) – postoperative radiation therapy, and 5 (5.6%) – postoperative chemoradiotherapy.

The follow-up period lasted from 18 months to 10 years. In the group of patients with typical carcinoids, the probability of 1-, 2-, and 5-year survival was, respectively: 100%, 98%, and 96%, while in the group of patients with atypical carcinoids: 100%, 83%, and 83% (Fig. 1). In patients with atypical carcinoids, the probability of 2- and 5-year survival was lower in comparison to patients with typical carcinoids, but the difference was not statistically significant. The average time from surgery to death was 26 months. In 7 (7.8%) patients, including 6 patients with atypical carcinoids, local recurrence was found during the follow-up period (in the area of the operated lung or regional lymph nodes); distant metastases occurred in 8 (8.9%) patients, including 6 patients with atypical carcinoids. The time from surgery to the diagnosis of local recurrence ranged from 2 months to 33 months, while the period from surgery to the occurrence of distant metastasis was from 5 months to 48 months. The distant metastases were revealed in the liver (4 cases), the brain (2 cases), bones (2 cases), and an adrenal gland (1 case). Patients with disease recurrence received chemotherapy or therapy with somatostatin analogs labeled with a technetium isotope. Age, sex, extent of resection, surgical approach (VATS vs. thoracotomy), intraoperative blood loss, presence of postoperative complications, hospital stay, T stage, N stage, and disease stage according to the TNM classification had no statistically significant influence on the probability of survival; the small number of deaths and the relatively small number of patients with atypical carcinoids constituted a limitation of the statistical analysis.

Discussion

Primary lung carcinoids constitute 25% of all carcinoids and 0.4–3% of all lung cancers treated surgically [4]. As a re-

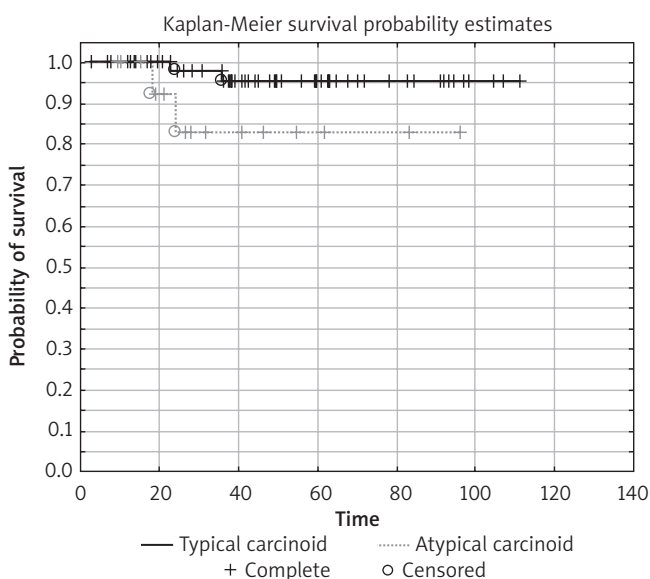


Fig. 1. The probability of survival depending on the histological type of the carcinoid

Tab. I. Clinical data of the study group

Parameter	Value
Age [years]	21–79 (avg. 59)
Sex, M/F n (%)	31 (34%)/59 (66%)
Histological type, n (%):	
Typical carcinoid	69 (77)
Atypical carcinoid	21 (23)
Surgical approach, n (%):	
Thoracotomy	70 (77.8)
VATS	20 (22.2)
Type of surgery, n (%):	
Lobectomy	67 (74.4)
Sleeve lobectomy	3 (3.3)
Bilobectomy	9 (10)
Pneumonectomy	2 (2.2)
Segmentectomy	1 (1.1)
Wedge resection	8 (8.9)
pN parameter, n (%):	
pN0	75 (83.3)
pN1	8 (8.9)
pN2	7 (7.8)
pTNM, n (%):	
IA	47 (52.2)
IB	22 (24.4)
IIA	10 (11.1)
IIB	3 (3.3)
IIIA	6 (6.7)
IV	1 (1.1)
Hospitalization time [days]	4–23 (avg. 7)
Drainage time [days]	1–10 (avg. 3)
Postoperative complications, n (%):	
Atrial fibrillation	5 (5.6)
Prolonged air leak	3 (3.3)
Residual pneumothorax	3 (3.3)
Bleeding requiring reoperation	2 (2.2)
Atelectasis of the operated lung	2 (2.2)
Pneumonia	2 (2.2)
Pleural hematoma	1 (1.1)
Surgical site infection	1 (1.1)
Postoperative psychosis	1 (1.1)

sult of the natural course of the disease (which differs from other histological types) and favorable prognosis, many surgeons accept not so aggressive treatment in carcinoid patients [1, 3, 7]. On the other hand, it needs to be taken into account that all carcinoids are classified as malignant neoplasms according to the current WHO histological classification because, despite their benign clinical course, carcinoids may grow and infiltrate neighboring structures and metastasize via lymphatic or hematogenous spread. The TNM classification used for staging carcinoids is identical to the one used in other histological types of lung cancer. According to various authors, the percentage of typical carcinoids ranges from 70% to 90%, while the rate of 5-year survival after surgical treatment in this group falls between 89% and 98.6%; in turn, atypical carcinoids constitute 10–30%, with a 5-year survival of 70–77.7% [8–12]. Atypical carcinoids occur very infrequently in patients under the age of 30, while in persons over the age of 50 they account for 25% of all carcinoid cases [4]. The analysis of the long-term surgical treatment outcomes of both typical and atypical carcinoids presented in this study confirmed the very favorable prognosis in this group of patients. The probability of 5-year survival was 96% in the case of typical carcinoids and 83% in the case of atypical carcinoids, despite the fact that metastases to regional lymph nodes were found in 15 out of the 90 operated patients (16.7%). When compared to typical carcinoids, atypical carcinoids are undoubtedly characterized by higher potential malignancy and, consequently, a higher risk of metastasis to lymph nodes and distant organs; this decreases the probability of long-term survival, although it remains significantly higher than in the case of other histological types of lung cancer [4, 13]. Metastasis to N1 and/or N2 lymph nodes in this group occurs in 34.9% of patients, while distant metastasis – in 18.8%. These percentages are significantly lower for typical carcinoids – 2.6% and 9.5%, respectively [8, 12, 14]. In the analyzed group of patients with typical carcinoids, metastases to N1 lymph nodes were confirmed in 10.1%, while to N2 lymph nodes – in 2.9%. In patients with atypical carcinoids, N1 lymph nodes were involved in 4.8% of cases, while N2 lymph nodes – in as many as 23.8% of cases. Because of the varying clinical course, some authors recommend different therapeutic strategies depending on the histological subtype of carcinoid. In the case of typical carcinoids, some clinicians accept resections smaller than lobectomy (segmentectomy, wedge resection) and lymph node sampling, as lymphadenectomy has no influence on long-term survival [4, 8, 11]. Still, according to most authors, the extent of resection and the performance of lymphadenectomy should depend on the size and location of the tumor (central, peripheral) as well as the assessment of the cN parameter in imaging examinations [4]. In cases of small peripheral tumors staged as cN0, segmentectomy or wedge resection and lymph node sampling may be taken into consideration, while for larger tumors (> 3 cm) or tumors staged as cN1/N2, lobectomy with lymphadenectomy should be performed [8]. In cases of endobronchial tumors with the involvement of the lobar

bronchial orifice, very good outcomes are associated with the use of sleeve lobectomy, provided that a 5-mm margin of healthy bronchial tissue is achieved; however, according to some authors, it is sufficient to exclude neoplastic infiltration in the bronchial resection margin [4, 15, 16]. In most centers, in the majority of patients undergoing surgical treatment for typical carcinoids, adjuvant chemo- or radiation therapy is not recommended in the presence of metastasis to N1 or N2 lymph nodes [4]. The treatment is more aggressive in patients with atypical carcinoids. Regardless of the size and location of the tumor, lobectomy and mandatory lymphadenectomy should be performed at the very minimum, while in pN1/N2 cases, postoperative chemotherapy should be used [4, 8, 11, 17]. In our group, the difference in the probability of 5-year survival between patients with typical and atypical carcinoids was not statistically significant, but the majority of authors emphasize that the histological type of the carcinoid is the most important prognostic factor (definitely more important than the N parameter), especially in long-term follow-up [13, 17, 18]. In a group of 123 patients undergoing surgery for carcinoid tumors, Ferolla *et al.* reported the following percentages of 5-, 10-, and 15-year survival, respectively: 97%, 90%, and 84% for typical carcinoids and 76%, 67%, and 24% for atypical carcinoids, with the carcinoid type as the only factor with a significant influence on survival [18]. In the group of 21 patients with atypical carcinoid tumors analyzed in our study, distant metastasis occurred in the follow-up period in as many as 6 (28.6%) patients. Disease recurrence was treated with chemotherapy or therapy with a somatostatin analog labeled with a technetium isotope. Despite the significant percentage of metastasis, the probability of 5-survival was 83%. A separate diagnostic and therapeutic problem is constituted by tumorlets, i.e., multifocal, small carcinoid foci, found in 7.3–24% of operated patients [18]. Their clinical significance is unclear; they are not treated as metastatic foci, but isolated reports list the presence of “tumorlets”, accidentally revealed in postoperative histopathological examinations, as an unfavorable prognostic factor, responsible for carcinoid recurrence even many years after surgery [18].

Conclusions

Lung carcinoids, regardless of their histological subtype, may metastasize to regional lymph nodes and distant organs. As opposed to other types of non-small-cell lung cancer, they are characterized by very favorable prognosis, with radical surgery as the primary condition for treatment effectiveness. Surgical treatment should be considered even in patients with metastases to regional lymph nodes, especially in cases of typical carcinoid tumors. Because of the relatively high risk of metastasis to mediastinal lymph nodes and distant organs in patients with atypical carcinoids, postoperative adjuvant therapy should also be considered.

Disclosure

Authors report no conflict of interest.

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