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Research Article

Carcinoid lung tumors: long-term results from 111 resections

Langzeitergebnisse nach 111 Resektionen wegen Bronchuskarzinoid

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Abstract

Objective: Carcinoids are rare neuroendocrine tumors of the bronchial system. Only recently, the histological classification was standardized, and there are varying opinions about the extent of surgical resection. This research reports on the long-term results of 111 consecutive patients, who underwent surgery in a department for thoracic surgery.
Methods: Between 1/1988 and 2/2001, 111 consecutive pulmonary resections were conducted in patients with bronchial carcinoids. Retrospectively, researchers obtained clinical and surgical data and re-classified all histological specimen according to the WHO classification of 1999. Information regarding long-term results was obtained by using data obtained during follow-up visits and by talking to the patient on the phone.
Results: 97 patients with typical and 14 with atypical carcinoids were identified. The preoperative diagnosis of typical or atypical carcinoid had been correct in 56 patients (50.5%). Surgical procedures included 79 lobectomies, 16 bilobectomies, 8 pneumonectomies, 5 segmental resections, 2 sleeve resections of the main bronchus without parenchymal resection and one exploratory thoracotomy. Mediastinal lymphadenectomies were performed on 105 patients (94.6%). Post-operative staging revealed 91 patients (81.2%) in UICC stage I, 12 (10.8%) in stage II, 7 in stage III and one in stage IV. 97 (87.4%) typical and 14 (12.6%) atypical carcinoids were classified. 30-day mortality was 1.8% (n=2). Mean follow-up was 73.4 months. The total cohort showed a 5-year survival rate of 94% and a 10-year survival rate of 82%. In patients with typical and atypical carcinoids, the 5-year survival rates were 94% and 82%, respectively (n.s.), and the 10-year survival rates were 92% and 62%, respectively ($p<0.01$). The 5- (10-) year survival rate without lymph node involvement was 96% (85%), with N1 involvement 88% (65%), with N2 involvement 67% (no 10-year survival).
Conclusions: Patients with bronchial carcinoids who underwent a radical oncological resection with mediastinal lymphadenectomy have very good survival chances. There are no prospective randomized studies evaluating the surgical procedures as they relate to the classification. Since a preoperative diagnosis cannot clearly determine if the lymph nodes are involved and what histology type the physician dealing with, a limited resections without lymphadenectomy is insufficient. It is absolutely necessary to conduct retrospective and multi-center studies on the prognostic importance of lymph node involvement and on the impact of adjuvant therapies.

Keywords: bronchial carcinoid, neuroendocrine tumors, resection, histological classification

Zusammenfassung

Fragestellung: Das Karzinoid zählt zu den seltenen neuroendokrinen Tumoren des Bronchialsystems. Die histologische Klassifikation wurde erst jüngst vereinheitlicht, und über das Ausmaß der chirurgischen Resektion existieren unterschiedliche Ansichten. Wir berichten über den

Langzeitverlauf von 111 konsekutiven Patienten die in einer thoraxchirurgischen Abteilung operiert wurden.
Patienten und Methode: Von 1/1988 bis 2/2001 erfolgten 111 Lungenresektionen wegen Bronchuskarzinoid. Retrospektiv wurden anamnestische, klinische und operationsbezogene Daten erhoben. Die histologischen Präparate aller operierten Patienten mit der Diagnose „Bronchuskarzinoid“ wurden überprüft und nach den Kriterien der WHO Klassifikation von 1999 reklassifiziert. Angaben zum Langzeitverlauf wurden durch Tumornachsorgedokumentation und telefonische Befragung 8/2004 erfasst.
Ergebnisse: 97 typische und 14 atypische Karzinoide wurden klassifiziert. Die Diagnose „Karzinoid“ und der Differenzierungsgrad waren präoperativ bei 56 Patienten (50,5%) richtig festgelegt worden. Operiert wurden: 79 Lobektomien, 16 Bilobektomien, 8 Pneumonektomien, 5 Segmentresektionen, 2 Manschettenresektionen des Hauptbronchus ohne Parenchymresektion und eine Probethorakotomie. Mediastinale Lymphadenektomien erfolgten bei 105 Patienten (94,6%). Die postoperative Stadieneinteilung ergab: 91 x (81,2%) UICC Stadium I, 12 x (10,8%) Stadium II, 7 x Stadium III und einmal Stadium IV. 97 (87,4%) typische und 14 (12,6%) atypische Karzinoide wurden klassifiziert. Die 30-Tage-Mortalität betrug 1,8% (n=2). Der Nachbeobachtungszeitraum betrug im Durchschnitt 73,4 Monate. Für die gesamte Kohorte wurde ein 5-Jahresüberleben von 94% und ein 10-Jahresüberleben von 82% ermittelt; bei Patienten mit typischem bzw. atypischem Karzinoid waren es nach 5 Jahren 94% bzw. 82% (n.s.) und nach 10 Jahren 92% bzw. 62% ($p<0,01$). Das 5- (10-) Jahresüberleben ohne Lymphknotenbefall (N0) betrug 96% (85%), bei N1 Befall 88% (65%), bei N2 Befall 67% (10-Jahresüberleben nicht erreicht).
Folgerungen: Nach onkologisch radikaler Resektion mit mediastinaler Lymphadenektomie haben Patienten mit Bronchuskarzinoid eine sehr gute Prognose. Prospektiv randomisierte Untersuchungen zur Evaluation verschiedener Operationsverfahren in Abhängigkeit vom Differenzierungsgrad existieren nicht. Weil die präoperative Diagnostik nicht sicher Lymphknotenbefall und ungünstigeren Histologietyp ermitteln kann, halten wir limitierte Resektionen ohne Lymphadenektomie nicht für ausreichend. Prospektive und multizentrische Untersuchungen zur prognostischen Bedeutung des Lymphknotenbefalls und zum Wert adjuvanter Therapien sind unumgänglich.

Introduction

Bronchial carcinoids are rare neuroendocrine tumors; age-adjusted incidences are between 0.38/100,000 for men and 0.49/100,000 for women [1]. According to the current WHO classification, the bronchial carcinoid is classified as a neuroendocrine lung tumor, as are the small cell bronchial carcinoma and the large cell neuroendocrine bronchial carcinoma [2], [3]. Typical and atypical carcinoids are a subgroup of this segment; criteria to differentiate between the typical and atypical carcinoid and small cell neuroendocrine bronchial carcinoma are defined in a very precise manner [3], [4]. The classification takes into account the different prognoses for neuroendocrine lung tumors, as survival rates differ significantly between typical and atypical carcinoids, and between atypical carcinoid and large cell neuroendocrine bronchial carcinoma [2].
The prognoses for bronchial carcinoids are reported to be very good, particularly after surgical resection [1], [5], [6], [7], [8], [9], [10], [11]. Since its description by Arrigoni, the atypical carcinoid is regarded as a variation with a less favorable prognosis [2], [12]. During the past two decades, surgical interest has mainly focused on the question whether less radical resections are adequate for the prognostically favorable typical carcinoid compared to the atypical form. This question is still the subject of many controversial discussions [1], [5], [6], [7], [9], [10], [13], [14], [15]. Furthermore, it is not clear whether lymph node involvement can be recognized as an independent prognostic factor [5], [7], [9], [11], [16], [17], [18]. In addition, there is no clear consensus on whether a radical mediastinal lymphadenectomy should be recommended [5], [15], [18]. There is no information regarding the usefulness of adjuvant therapies during advanced tumor stages [15], [16], [17], [19].
This retrospective analysis analyzes the long-term results of patients who have undergone curative surgery for a bronchial carcinoid. After the histological specimen had been classified according to the WHO classification of

1999, the carcinoids were divided into a "typical" and an "atypical" group [3]. We compared our own findings with recent relevant publications in detail.

Patients and methods

Between 1/1988 and 2/2001, 124 consecutive patients underwent therapy for a bronchial carcinoid. Because of confirmed distant metastases or poor general health, 7 patients were unable to undergo surgical therapy, but had a palliative endobronchial laser resection instead. One of the researchers (S.M.) checked the paraffin blocks of the remaining 117 patients who had been diagnosed with "bronchial carcinoid" and who had undergone surgery during the period of this study and re-classified them according to the criteria of the WHO classification of 1999 [3]. The data of 6 patients with neuroendocrine non-small cell bronchial carcinoma was excluded from further analysis. Staging of the 111 remaining confirmed cases of bronchial carcinoids was conducted in accordance with the TNM classification of 2002 for non-small cell lung cancer.

Follow-up in our department was conducted 2-4 times per year with annual bronchoscopic testing until the 5th postoperative year. Patient information for the time period after the conclusion of the follow-up visits was obtained calling the patients themselves or their family physicians in 8/2004.

Survival and recurrence rates were calculated by using the Kaplan-Meier method, differences in survival by using the log-rank test. The study was approved by the ethics committee on human research of the University of Tubingen/Germany.

Results

59 men and 52 women between the ages of 16 and 78 (median 51 years) underwent surgery. The median age of patients with atypical carcinoids was higher than that of patients with typical carcinoids (55 vs. 51 years, n.s.). Preoperatively, 71.2% (n=79) of all patients had clinical symptoms: cough (n=33, 29.7%), dyspnea (n=14, 12.6%), pneumonia (n=14, 12.6%), fever (n=12, 10.8%), chest pain (n=10, 9%), hemoptysis (n=7, 6.3%), and recurrent pneumonias (n=3, 2.7%). One patient had increased ACTH production, and in one case, the carcinoid occurred within the context of a MEN I syndrome; there were no clinical signs for increased serotonin production. In 28.8% of patients (n=32) the tumor was an incidental finding on chest X-ray. 47 patients (42.3%) were smokers; median cigarette consumption was 15 pack years (range 1-100). The percentage of smokers was higher in patients with atypical carcinoids (57.1%) than in those with typical carcinoids (40.2%).

Preoperative diagnostics included thoracic CTs for all 111 patients, bronchoscopy for 110 patients, sonography or abdominal CT for 82 patients, skeletal scintigraphy for 70 patients, cranial CT or MRI for 25 patients, and mediastinoscopy for 2 patients who preoperatively were suspected to have a small-cell bronchial carcinoma. Due to the risk of tumor cell dissemination, transthoracic small needle aspiration was not performed in surgical patients. Preoperative pulmonary function testing was conducted for 110/111 patients by doing a whole body plethysmography. 67 tumors (60.4%) were in a central location, i.e. they were visible on the bronchoscopy. In 56 patients (50.5%), the preoperative diagnosis "carcinoid" and the attribution "typical" or "atypical" were confirmed by the postoperative results. 2 patients had preoperatively been diagnosed with a small-cell bronchial carcinoma, and 6 patients had been diagnosed with a non-small cell bronchial carcinoma (7.2%); both patients with suspected small-cell bronchial carcinoma underwent preoperative chemotherapy.

The surgical procedures performed consisted of 79 (71%) lobectomies (2 of them with bronchial sleeve resection), 16 (14%) bilobectomies, 8 (7.2%) pneumonectomies, 5 (4.5%) segmental resections, 2 sleeve resections of the main bronchus without parenchymal resection and one explorative thoracotomy (termination due to pleural carcinosis). Mediastinal lymphadenectomies were performed in 105 patients (94.6%). 18 patients suffered from postoperative complications (16.2%), with the following severe complications: bleeding in 4 patients, pneumothorax in 3 patients, fatal right heart failure in 2 patients (1.8%) and one bronchial stump insufficiency.

Histopathological follow-up revealed 97 (87.4%) typical (TC) and 14 (12.6%) atypical carcinoids (AC) with 91 (81.2%) patients in stage I, 12 (10.8%) in stage II, 7 (6.3%) in stage III and one in stage IV. 12 patients (10.8%) had lymph node involvement in N1 or N2 positions (Table 1).

10 patients with typical carcinoids had lymph node involvement (9.7%), 5 of them with ipsilateral hilar (N1) and 5 with mediastinal lymph node metastases (N2). 3 patients with atypical carcinoid proved to have lymph node involvement (21.4%), 2 of them with ipsilateral hilar (N1) and 1 with mediastinal (N2) nodal deposits. In 5 patients with mediastinal lymph node involvement (pN2), the mediastinal lymph drainage was postoperatively irradiated with 60 Gy percutaneously; three of these patients had no recurrence, two patients had distant metastases, and one patient died.

Mean follow-up was 73.4 months. 11 patients of the study cohort died, 2 of them postoperatively; 4 deaths were tumor-related, 5 not tumor-related. 11 patients suffered recurrences: local (n=1, AC), liver metastases (n=4, 2 TC/2 AC), multiple metastases (n=2, TC), bone metastases (n=1, TC), and pulmonary metastases (n=1, TC). 7 patients underwent limited or parenchymal sparing resections (5 segmental resections and 2 sleeve resections of the main bronchus without parenchymal resections, 2 sleeve lobectomies); none of these patients had local recurrences or distant metastases. The 5-year survival rate for the entire group was 94% and the 10-year survival rate was 82%. In patients with typical carcinoid,

Table 1: Postsurgical staging

Typical Carcinoid n = 97			Atypical Carcinoid n = 14		
Stage	Patients	TNM	Stage	Patients	TNM
IA	60	T1N0	IA	8	T1N0
IB	21	T2N0	IB	2	T2N0
IIA	4	T1N1	IIA	1	T1N1
IIB	1/5	T2N1/T3N0	IIB	1	T2N1
IIIA	3	T2N2	IIIA	1	T3N2
IIIB	1/1	T4N0/T4N2	IIIB	1	T4N0
IV	1	T4N2M1	IV	-	

5- and 10-year survival rates were 94% and 82%, respectively, and in atypical carcinoid 92% and 62%, respectively (5-year survival n. s., 10-year survival $p<0.01$). 5- (10-) year survival without lymph node involvement was 95% (85%), with N1 involvement 88% (65%), with N2 involvement 67% (no 10-year survival). Although patients with lymph node involvement tended to have worse results, differences were not statistically significant in a univariate Cox regression analysis.

Discussion

The revised WHO classification of 1999 clearly places bronchial carcinoids among the neuroendocrine pulmonary tumors; the spectrum ranges from typical carcinoids with low-grade malignancy and atypical carcinoids with moderate malignancy to highly malignant neuroendocrine pulmonary tumors, i.e. the large cell neuroendocrine carcinoma and small cell bronchial carcinoma. In contrast to the 1981 classification, the differentiating criteria are precisely defined: typical carcinoids have less than 2 mitoses per mm^2 and no tumor necroses. If tumor necroses or 2-10 mitoses per mm^2 are visible, the carcinoid is atypical, and the large cell neuroendocrine carcinoma is characterized by more than 10 mitoses per mm^2 [3]. These criteria help identify the large cell neuroendocrine carcinoma, a kind of tumor which undoubtedly has been included in several earlier studies on bronchial carcinomas [3], [11]. For this reason, all histological specimen were re-classified – similarly to the approach chosen by other authors – to exclude all other neuroendocrine tumors [9], [11].

Epidemiology

The two histologically different tumor entities described by the term bronchial carcinoid possibly differ in terms of epidemiology as well. Several studies have addressed the question whether the disease occurs more frequently in men or in women. Although some authors report that the disease occurs more frequently in women [1], [6], [8], our group and other researchers were not able to determine any differences between men and women [7], [9], [13]. Patients with bronchial carcinoids are on average 10 years younger than patients with other malignant pulmonary tumors [1]. 42.3% of our patients were smokers. Whether smoking has an impact on the development of a bronchial carcinoid, has yet to be determined [5], [6], [7], [9], [13]. According to the results of other investigators, the atypical carcinoid was found more frequently in smokers than in patients with the typical carcinoid [7], [8], [9], [13].

Diagnosis

The histological results of the preoperative bronchoscopy is of utmost importance for therapeutic decisions [9], [15]. According to some authors, the extent of pulmonary resection and sometimes the extent of the lymphadenectomy is dependent on whether the patient has a typical or an atypical carcinoid (Table 2) [6], [7], [9], [10], [15]. Our own results have shown that it may be difficult to preoperatively confirm the diagnosis or to differentiate between the two types of carcinoid. Only in 50.5% (n=56) of the patients, preoperative bronchoscopy resulted in the same classification as the postoperative analysis; in 7.2% of the cases, a small cell or non-small cell carcinoma was diagnosed preoperatively. The preoperatively correct histologies reported in the literature range between 47% and 83% [7], [8], [9], [10], [13], [15]. Surgical approaches selected with regard to the different prognoses of typical and atypical carcinoids require clear-cut criteria of differentiation. However, the reproducibility of differentiation between typical and atypical carcinoids by the pathologist has repeatedly been questioned [6] , [8], [13]. This is due to the fact that the criteria of differentiation are not applied as stringently as necessary [2], [20]; in addition, the characteristic mitosis rate and tumor necrosis in

Table 2: Recommendations about the extent of the resection in the literature

Author	Period	n	Extend of resection
El Jamal	1980–2000	95	Pneumonectomy only in cases of destroyed distal lung parenchyma, occasionally sleeve resection, no lymphadenectomy.
Ferguson	1980–1998	139	TC/AC peripheral: segmentectomy, central: sleeve resection without parenchymal resection or sleeve lobectomy, lymphadenectomy only for AC.
Filosso	1977–1999	126	TC central: sleeve resection, peripheral: lobectomy. AC: lobectomy or pneumonectomy + lymphadenectomy.
Kurul	1974–2000	83	Bronchotomy for polypoid tumors, sleeve resection for sessile tumors; lobectomy in case of lymphnode involvment., always lymphadenectomy.
Marty-Ane	1983–1993	79	TC peripheral: segmentectomy + LN Sampling, central: sleeve resection. AC: lobectomy or pneumonectomy + lymphadenectomy.
Mezetti	1980–2001	98	TC peripheral: segmentectomy + LN Sampling, central: sleeve resection. AC: lobectomy or pneumonectomy + lymphadenectomy.
Stamatis	1968–1988	227	TC/AC peripheral: segmentectomy, TC central: sleeve resection. AC: lobectomy or pneumonectomy + lymphadenectomy.

Table 3: Long-term survival after resection of bronchial carcinoid in the literature

Author	Year	Period	n	TC /AC	Age	Survival 5yr/10yr	Survival TC 5yr	Survival AC 5yr	Survival TC 10yr	Survival AC 10yr
Cardillo	2004	1990–2002	163	121/42	49.5	90%/?	98%	70%		
Ferguson	2000	1980–1998	139	110/26	56	86%/?	90%	70%		
Filosso	2002	1977–1999	126	82/44	47	89%/79%	97%	77%		
Fink	2001	1980–1999	142	128/14	52	87%/79%	89%	75%	82%	56%
Mezetti	2003	1980–2001	98	88/10	54.5	91%/90%	92%	71%	90%	60%
Our study	2005	1988–2001	111	97/14	51	94%/82%	94%	92%	84%	62%

smaller specimen cannot always be determined [10], [13], [15].

Prognosis

In general, the prognosis after surgery on the localized bronchial carcinoid is considered to be very good [1], [5], [6], [7], [8], [9], [10], [11], [18], [21]. Even metastatic non-operated bronchial carcinoids are reported to have a 5-year survival rate of 76.6% [1]. The only recognized independent prognostic factors at present are the classification typical or atypical and, to a lesser extent, the nodal status (Table 3) [6], [9].

When separately considering the course of disease for patients with typical and atypical carcinoids, the outcome for patients with an atypical carcinoid is only slightly worse after 5 years, but significantly worse after 10 years. Thus, our figures support the assumption that the classification of the bronchial carcinoid is a prognostic factor [2], [5], [6], [7], [8], [9], [12]. All considerations of independent prognostic factors are of limited value, however, due to the low number of recurrences in the collectives with bronchial carcinoids, which is also true for the present study [6].

Lymph nodes

It has not been ascertained if lymph node involvement can be considered an independent prognostic factor. Only a few authors have studied the prognostic importance of lymph node involvement (Table 4) [5], [7], [9], [11], [16], [17], [22].

This study found some evidence for a statistical correlation between lymph node involvement and an unfavorable prognosis, which, however, might also be due to the low number of patients with lymph node involvement. Filosso did not find an impact of lymph node involvement on the prognosis, and neither did Schreurs, who studied 93 patients with exclusive typical carcinoids [7], [22]. However, Garcia (the Spanish multicenter study) and Filosso found significant differences between lymph node involvement in typical and atypical carcinoids [7], [16]. Mezetti revealed lower survival rates in cases with lymph node involvement for both types of carcinoids. Independent of the histological type, McCaughan and Mezzetti found reduced disease-free intervals in patients with lymph node involvement [9], [18]. Cardillo reported on a significantly lower 5-year survival rate in patients with atypical carcinoid and N1 involvement than in patients

Table 4: Survival and lymph node involvement in the literature

Author	n	Extend of lymphadenctomy	Nodal involvement	N0: 5 yr survival	N1: 5 yr survival	N2: 5 yr survival
Cardillo	163	100% lymphadenectomy	25.1%	100%	84.2%	22.2%
Filosso	126	89.7% sampling	15.9%	92%	85%	85%
Mezetti	98	100% sampling, lymphadenectomy in case of macroscopic involvement	23.5%	100%	75%	50%
Our study	111	94.6% lymphadenectomy	10.8%	96%	88%	67%

with the typical carcinoid and N1 involvement; even the 5-year survival rate of patients with an atypical tumor type and N2 involvement was significantly lower in this study [5]. The fact that not every patent had a mediastinal lymphadenectomy complicates the analysis of the present results [5]. In order to guarantee an exact staging and adequate tumor management, it is necessary to perform a radical or systemic lymph node dissection on a routine basis independent of the degree of resection [5], [15], [18]. So far, there are only retrospective studies that evaluate the prognostic importance of lymph node involvement in bronchial carcinoids.

Resection procedures

Numerous authors have addressed the extent of resection for patient with a carcinoid [1], [5], [6], [7], [9], [10], [13], [14], [15]. Because of the very good prognosis, especially for cases with a typical carcinoids, limited or parenchymal-sparing resections are generally considered sufficient, and it is particularly important to avoid unnecessary pneumonectomies [1], [6], [7], [9], [10], [13], [14], [15]. There are only retrospective analyses of patient cohorts, who were operated upon within long periods between 12 and 26 years, and it is not clear which criteria were applied to decide in favor of parenchymal sparing or anatomical resection [7], [13]. Marty-Ane correctly states that some authors who recommend limited resections have mainly performed extended anatomical resections on their patients, which might have been the deciding factor for their good results [13], [15]. In addition, recurrences have sometimes been attributed only to the histological type and the nodal status, but not to the resection procedure [7], or there was no meaningful statistical analysis due to low recurrence rates [7]. Another factor complicating matters is that authors differ on how they define the terms “parenchymal sparing” or “limited resection” (Table 2).

The patients of the present study underwent anatomical resections such as lobectomies, bilobectomies or pneumonectomies according to the same criteria of oncological radicality as in non-small cell bronchial carcinoma. We did not use this approach in 5 cases with restricted pulmonary function and did segmental resections instead, and in 2 patients with a typical carcinoid, we conducted sleeve resections of the main bronchus without a parenchymal resection; none of these 7 patients suffered a recurrence. Although the results reported in literature suggest parenchymal sparing resections for confirmed typical carcinoids, we adhered to the recommendations of those authors who, independent of the histological subtype and given a sufficient functional reserve, prefer anatomical resections with radical lymphadenectomy because of the unclear pre- and intraoperative differentiation and a seamless transitions between neuroendocrine carcinomas of different malignancies [5], [11], [18].

Adjuvant therapy

5 patients who participated in this study and who had mediastinal lymph node involvement (pN2) underwent postoperative percutaneous radiation therapy with 60 Gy at the mediastinal lymph drainage; three of these patients had no recurrence, two patients had distant metastases and one patient died. In some reports on the use of adjuvant radiation therapy for bronchial carcinoids a total between 2 and 9 patients had postoperative radiation therapy, mostly because of mediastinal lymph node involvement [15], [16], [17], [19]. In our opinion, the low number of cases and recurrences do not allow for a statement on adjuvant radiation therapy. There is no information on neoadjuvant studies or therapy protocols in the literature. Since bronchial carcinoids may over-express somatostatin receptors, they may be treated or investigated with somatostatin analogues (e.g. octreotide). Treatment with octreotide has so far been restricted to advanced tumor stages with distant metastases [7], [23]. So far, there are no results from controlled studies on the application of somatostatin analogues as an adjuvant in surgical therapy of bronchial carcinoids. Prospective multicenter studies are needed to evaluate adjuvant therapies [15], [19].

Conclusion

Due to their excellent prognoses, bronchial carcinoids have a distinct place among the neuroendocrine tumors

of the lung. The classification into typical and atypical carcinoids distinguishes between two tumor entities, which are different in terms of prognosis. Based on the current data, it is not possible to ascertain whether limited resections depending on the histological subtype can be recommended, whether the nodal status is an independent prognostic factor and which benefits adjuvant therapies may have. The low incidence of bronchial carcinoids makes multi-centre studies indispensable. Since there can be a seamless transition from one neuroendocrine pulmonary tumor to another with a different prognosis and since preoperative diagnosis is unable to exclude lymph node involvement and unfavorable type of histology in all cases, we consider limited resections without lymph node resection as insufficient.

Dedication

In honour of Prof. Dr. Heikki Toomes on the occasion of his 65th anniversary.

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