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Bronchial carcinoid tumors in children and adolescents – A report and management considerations from the German MET studies

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ABSTRACT

Objectives: Bronchial carcinoid tumors (BC) are exceptionally rare in childhood, with an incidence of <0.2/1,000,000 per year. Typical low-grade BCs are distinguished from atypical, intermediate-grade BCs. Little is known about BCs in pediatric patients and management guidelines are missing. In this study, we explored characteristics and outcome of pediatric patients with BC prospectively registered with the Malignant Endocrine Tumor studies.

Material and methods: We performed a retrospective multicenter study in children, adolescents, and young adults (aged 0–20 years) with BC reported to the German MET registry between January 1997 and December 2022. Data were last updated on 28 of February 2023.

Results: Thirty-two patients were diagnosed at a median age of 15.0 years (range, 9.8–19.2). Atypical BCs (23.3%) were less frequent than typical, but more common than in adulthood. Lymph node metastases were present in 14.3% of cases (atypical BC: 28.6%, typical BC: 10.5%), distant metastases in one (3.1%) patient with atypical BC. 92.6% of patients were in complete remission after surgical resection (median follow-up: 2.7 years). The patient with metastatic spread and one patient with atypical BC and multiple recurrences were on treatment at last follow-up. 5-year event-free survival of typical BC was 100% and 83.3% in atypical BC.

Conclusions: Completely resected localized BCs in pediatric patients have a favorable outcome also with lung tissue sparing surgery. Atypical BC with risk of metastatic spread and recurrence occurred more frequently compared to adults. Interdisciplinary management and collaborative efforts are needed to improve our understanding and the management of pediatric BC.

1. Introduction

Bronchial carcinoids are among the rarest pediatric tumors, accounting for <0.1% of all malignant tumors in childhood [1]. They have a crude annual incidence rate of 0.18/1,000,000 in children and adolescents 0–18 years of age [2]. While bronchial carcinoids represent

Abbreviations: CR, Complete Remission; CT, Computed Tomography; EFS, Event-Free Survival; ESMO, European Society for Medical Oncology; EXPeRT, European Cooperative Study Group for Pediatric Rare Tumors; [^{18}F]FDG, [^{18}F]Fluorodeoxyglucose; FU, Follow-Up; GPOH, German Society for Pediatric Oncology and Hematology; MEN 1, Multiple Endocrine Neoplasia Type 1; MET, German Registry for Malignant Endocrine Tumors; MRI, Magnetic Resonance Imaging; PDGFR, Platelet-Derived Growth Factor Receptor; PET, Positron Emission Tomography; R_0, Resection without Microscopic Residue; SSTR, Somatostatin Receptor; UICC, Union for International Cancer Control.

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only 1–2% of lung malignancies in adults, they account for 42–63% of all primary lung malignancies in the pediatric population [1–5]. Within the heterogeneous group of neuroendocrine tumors in children, bronchial carcinoids account for 11% (adults: 20–30%) [5,6].

The etiology of bronchial carcinoids in childhood is largely unexplained. The significance of cancer predisposition syndromes has yet not been explored [7]. In adults, somatic mutations in *MEN1* are reported in 11–13% of cases [8,9]. However, to the best of our knowledge, bronchial carcinoids associated with multiple endocrine neoplasia type 1 (MEN 1) have not been reported in childhood so far. About 3–13% of patients with MEN 1 develop bronchial (mostly typical) carcinoids, but usually not until adulthood [10–14]. Adult bronchial carcinoids are characterized by low PD-L1 expression and driver mutations in genes regulating histone modification and chromatin remodeling [15]. Pediatric bronchial carcinoids have yet not been characterized by molecular genetics.

Bronchial carcinoids are classified as typical, low-grade carcinoids (<2 mitoses/2 mm^2, absence of necrosis) and atypical, intermediate-grade carcinoids (2–10 mitoses/2 mm^2 and/or foci of punctate necrosis), with the latter more commonly exhibiting metastatic behavior [16,17]. The role of Ki-67 proliferative index in predicting survival in adults is limited. Atypical carcinoids are more likely in tumors with a Ki-67 index of > 5%, but no cut-off value has been established [18,19].

Five-year overall survivals of approximately 95% have been reported in pediatric patients with bronchial carcinoids in population-based data [3,4]. Thus, prognosis of pediatric patients seems to be superior compared to adults (10-year disease-specific survival with typical histology 90.3% and with atypical histology 65.0%) [5]. However, particularly in children and adolescents with atypical bronchial carcinoids and/or metastatic spread fatal outcomes and recurrences were reported [20–25]. Up to now, data on childhood bronchial carcinoids were derived from individual case reports and population-based data. Furthermore, there is no consensus on the management of patients [6,20,21,23,24,26,27].

In this study, we explore clinical characteristics and outcome in a cohort of children and adolescents with bronchial carcinoid tumors prospectively registered with the German Malignant Endocrine Tumor (MET) studies. Based on our and published data, we propose diagnostic and therapeutic strategies in children and adolescents with bronchial carcinoid tumors.

2. Materials and methods

This retrospective analysis included children, adolescents, and young adults aged <20 years (hereinafter termed pediatric) with diagnosis of a bronchial carcinoid tumor between 1997 and 2022 registered in the database of the German Registry for Malignant Endocrine Tumors (MET), which is a prospective clinical registry of the German Society for Pediatric Oncology and Hematology (GPOH). Pediatric patients with malignant endocrine tumors were reported to the MET registry by the treating physicians in Germany, Austria, and Switzerland upon informed consent of the legal guardians. We included patients who met diagnostic criteria as per the local pathologist's diagnosis. Patients and/or their legal guardians gave informed consent for data collection and analysis. The GPOH-MET registry was approved by the ethics committees of the University of Luebeck (Approval number 97125) and Otto-von-Guericke-University Magdeburg (Approval number 174/12 and 52/22), Germany, and the institutional review boards of the participating hospitals.

Data for patient-, tumor-, and treatment-related characteristics were collected using original source data. Frequencies were related to cases with recorded data. Staging was based on the TNM classification by the Union for International Cancer Control (UICC; Supplemental Material 1) [28,29]. The N stage was defined histopathologically, the M stage by imaging. Atypical bronchial carcinoids were defined by ≥2 mitotic figures per 2 mm^2 and/or presence of focal tumor necrosis [16,17].

Survival probabilities were estimated using the Kaplan-Meier method. Differences between groups were determined by a Student *t* test. A p value < 0.05 was considered significant. All data were analyzed with the IBM® SPSS® statistical package (version 28.0.0.0).

Details on the GPOH-MET 97 study protocol were provided elsewhere [30]. Briefly, lobectomy with concomitant lymphadenectomy and, if necessary, metastasectomy was recommended, given that complete resection of all tumor manifestations and, thus, a curative situation could be achieved. Induction therapy was advised for inoperable tumors or metastatic progression.

3. Results

We identified 32 patients with a median age at diagnosis of 15.0 years (range, 9.8–19.2) and a balanced sex distribution (male/female: 1.0). The median age of male patients was significantly higher than of female patients (male: 16.5, range, 9.8–16.8; female: 13.0, range, 12.1–19.2; p = 0.017). Clinical characteristics are given in Table 1. In 7 of 30 patients pre-existing conditions involving the lungs were reported including asthma (n = 4), recurrent pneumonia (n = 1), dust mite allergy (n = 1), and a bronchiocentric granulomatous lesion in the lower lobe (n = 1). The latter had been removed by lobectomy two years before diagnosis of the bronchial carcinoid in the ipsilateral middle lobe. In one patient, bronchial carcinoid was diagnosed as second malignancy two years after diagnosis and treatment of orbital rhabdomyosarcoma.

The median time from onset of symptoms to diagnosis was 7.3 months (range, 0–44). Tumor related symptoms were present in 27 of 30 patients, bronchial carcinoid was discovered incidentally in two patients. One of those patients underwent bronchoscopy due to suspected nut aspiration. In the other patient, bronchial carcinoid was detected during routine computed tomography (CT) in follow-up (FU) for rhabdomyosarcoma. In addition to cough, the most frequent symptoms were recurrent pneumonia (n = 12), hemoptysis (n = 11), dyspnea/stridor (n = 9), and pain (n = 5). One patient presented with concomitant pneumothorax and pleural effusion. Only one patient with localized disease suffered from loss of weight, fever, and night sweats. One further patient was diagnosed with hormone-related symptoms in terms of secondary amenorrhea due to ectopic ACTH production. Fourteen patients had received prior antibiotic treatment for a diagnosis of respiratory infection.

First suspicion of a tumor was raised by computed tomography (CT; n = 14), plain radiography (n = 7), bronchoscopy (n = 7), and magnetic resonance imaging (MRI; n = 1); information was missing in 3 cases. Various diagnostic modalities were used for staging including ultrasound, MRI, bone scintigraphy, [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography (PET)/CT, as well as somatostatin receptor (SSTR)-directed imaging including [^{68}Ga]Ga-DOTA-TATE-PET/CT, and octreotide scan. Tumors were diagnosed by radiography (7/23), cross-sectional imaging (28/29), bronchoscopy (25/25), conventional SSTR scintigraphy (3/6), and [^{68}Ga]Ga-DOTA-TATE-PET/CT (8/8). One patient was diagnosed with extensive metastatic disease including the spleen, liver, ovary, and brain. Hormones, metabolites, and neuroendocrine markers were abnormal in 1/10 (serotonin), 2/14 (5-hydroxyindoleacetic acid), and 4/15 (chromogranin-A) patients, respectively. Chromogranin-A was elevated in one patient with an atypical bronchial carcinoid tumor (ID 3 in Table 2), the other abnormal parameters were reported in patients with typical bronchial carcinoid tumors.

In 22 of 32 cases, bronchoscopic (n = 18) or thoracoscopic (n = 4) biopsy of the tumor was performed prior to surgical resection. In four of those patients, bronchoalveolar lavage was additionally done, which was positive in one case and negative in three including the patient with distant metastases. Noteworthy, diagnosis on the biopsy specimen was subsequently revised by histopathological review of the completely resected tumor in 4 patients including one atypical carcinoid (subsequently revised to a typical carcinoid), two typical carcinoids (subsequently revised to atypical carcinoids), and one leiomyomatous tumor (subsequently revised to a typical carcinoid). Taken together, diagnosis

Table 1
Characteristics and clinical features of patients with bronchial carcinoid tumors. Proportions are calculated based on cases with recorded data.

Characteristics	German Registry for Malignant Endocrine Tumors (MET) ($n = 32$)	
	Count	Proportion
Sex		
male	16	50.0%
female	16	50.0%
Age at diagnosis		
<10	1	3.1%
10–14	15	46.9%
15–19	16	50.0%
Median tumor size	2.6 cm (range, 0.5–7.5)	n.a.
Laterality of the tumor		
right lung	20	69.0%
left lung	9	31.0%
unknown/no data	3	n.a.
Localization of the tumor		
upper lobar bronchus	3	11.1%
middle lobar bronchus	5	18.5%
lower lobar bronchus	9	33.3%
intermediate bronchus	8	29.6%
main bronchus	2	7.4%
unknown/no data	5	n.a.
T stage		
1	13	54.2%
2	9	37.5%
3	1	4.2%
4	1	4.2%
no data	8	n.a.
N stage		
0	24	85.7%
1	4	14.3%
no data	4	n.a.
M stage		
0	31	96.9%
1	1	3.1%
Disease stage		
I A1-3/B	17	73.9%
II A/B	5	21.7%
III A/B/C	0	0%
IV A/B	1	4.3%
unknown/no data	9	n.a.
Type of carcinoid		
typical	23	76.7%
atypical	7	23.3%
unknown/no data	2	n.a.
Modality of diagnosis of a bronchial carcinoid tumor		
bronchoscopic biopsy	17 *	53.1%
thoracoscopic biopsy	4 **	12.5%
tumor resection	11 (+validation of diagnosis: 18)	34.4%

Abbreviation: n.a., not applicable; * in one case each, diagnosis was changed from typical to atypical bronchial carcinoid tumor and vice versa after resection; ** in one case, diagnosis was changed from typical to atypical bronchial carcinoid tumor after resection.

of bronchial carcinoid tumor was established in 21 patients on biopsy specimen.

Surgical resection of the tumor was reported in 29 of 32 patients. Resection was performed by thoracotomy (n = 23), thoracoscopy (n = 4), and bronchoscopic resection (n = 1). The method of surgical resection was not reported in one case. Resection was conducted as lobectomy (n = 20), bi-lobectomy (n = 6), and segmentectomy (n = 1) and was performed as sleeve resection in 8 cases. Resection without microscopic residue (R_0) was achieved in 20 cases. Microscopic and macroscopic residues were determined in three and one patient, respectively. No resection status was reported in five patients. Concomitant lymphadenectomy was done in 25 cases, in four of those regional lymph node involvement was diagnosed. One patient with metastatic spread additionally underwent metastasectomy in the liver and right ovary.

The median tumor diameter was 2.6 cm (range, 0.5–7.5). The tumor was located in the right lung in 20 patients and with regard to bronchial tree localization in the lobar bronchi in 17 patients.

Pathological evaluation determined 13 of 24 tumors as T1 stage, 9 as T2 stage, one as T3 stage, and one as T4 stage. Seven bronchial carcinoids were classified as atypical carcinoids (details on these patients are given in Table 2) including the patient with distant metastases. Twenty-three tumors were considered typical carcinoids, data were missing in two cases. Immunohistochemical testing of neuroendocrine markers was positive for chromogranin-A in 23/23 cases, for synaptophysin in 22/22, for CD56 in 10/10, and for neuron-specific enolase in 5/6. Expression of somatostatin receptors was rarely analyzed (SSTR2a 3/3, SSTR5 1/1). In one patient, platelet-derived growth factor receptor (PDGFR)-alpha expression was detected. Concomitant pneumonitis and atelectasis were present in 18 and 14 cases, respectively. Reference pathology evaluation confirmed the diagnosis in 22 cases. In no case diagnosis was revised by the reference pathologist.

Following tumor resection by lobectomy and metastasectomy, the patient with metastatic spread was on treatment at last follow-up (3 months after diagnosis). Treatment comprised temozolomide and radiotherapy to bone metastases. One patient with an atypical carcinoid tumor (ID 4, Table 2) experienced a local relapse three months after microscopic incomplete tumor resection by segmentectomy. Relapse was diagnosed on routine SSTR-directed PET/CT and tumor resection was performed by lobectomy with lymphadenectomy. Histopathological review determined one affected local lymph node. Twenty-five months later, a second ipsilateral recurrence was diagnosed. Resection was accomplished by pneumonectomy of the remaining left lung along with lymphadenectomy revealing lymphangiosis carcinomatosa. Adjuvant radiotherapy was recommended but rejected by the patient's family. A third recurrence in the contralateral lung was detected 20 months later by [^{68}Ga]Ga-DOTA-TATE-PET/CT. Due to the substantially reduced vital capacity of the remaining lung, surgical resection was not feasible and instead treatment with everolimus was initiated. Thirty-six months later, the patient showed stable disease on continued everolimus therapy.

After a median FU of 2.7 years (range, 0–9.5), 25 patients were in complete remission (CR). In five patients including one patient with microscopic incomplete resection, FU data were not reported. Five-year event-free survival (EFS) in patients with typical bronchial carcinoid tumor was 100% and in patients with atypical bronchial carcinoid tumor 83.3% (Fig. 1).

4. Discussion

To the best of our knowledge, this is the largest series reporting on children and adolescents with bronchial carcinoid tumors so far. In line with previous population-based reports, outcome of patients with completely resected tumors was favorable [3,4].

Sex distribution was balanced in our cohort. A predominance of the male sex is inconsistently reported in pediatric patients (female/male ratio 0.5–1.1), while in adults 67% of patients are female [2,3,5,21].

In pediatric patients, bronchial carcinoids are usually diagnosed between a mean age of 11.6 and 13.8 years but may occur as early as at 3 years of age [2,6,23,27,31]. There is a substantial delay in diagnosing bronchial carcinoids in children and adolescents due to unspecific symptoms at disease onset. This is reflected by the median time from onset of symptoms to diagnosis in our cohort (7.3 months) and published data (8.5 months) [20]. The predominant symptoms of bronchial carcinoids are cough, dyspnea and stridor. These resemble the typic symptoms of respiratory infections and pneumonia in childhood which may be accompanied with bronchial obstruction and atelectasis. The endobronchial growth of bronchial carcinoids mimicking bronchial obstruction often leads to an initial misdiagnosis of asthma only [27]. However, asthma could also be part of a carcinoid syndrome. Recurrent

Table 2
Details on patients with atypical bronchial carcinoid tumors.

ID	Sex	Age at diagnosis (years)	Primary site	TNM	Stage	Surgery of primary tumor	Lymph node resection	Further clinical course	Status at last FU	Time since diagnosis (years)
1	f	13.7	Right middle lobar bronchus	TxN0M0	unclear	Sleeve lobectomy	yes	Remained in complete clinical remission	Alive off therapy	1.9
2	f	12.9	Left lower lobar bronchus	T4N1M1c	IV	Lobectomy	yes	Primary tumor and metastases (liver, right ovary) resected; temozolomide treatment and radiotherapy of bone metastases	Alive under treatment	0.3
3	m	14.5	Right intermediate bronchus	T1bN1M0	IIB	Bi-lobectomy	yes	Remained in complete clinical remission	Alive off therapy	6.0
4	m	11.2	Left lower lobar bronchus	T1bN0M0	IA2	Sleeve segmentectomy	yes	1st local recurrence after 3 months: lobectomy (T1aN1M0). 2nd local recurrence with lymphangiosis carcinomatosa 28 months later: pneumonectomy. 3rd recurrence in the contralateral lung 20 months later: everolimus therapy → stable disease at last follow-up after another 36 months	Alive under treatment	7.8
5	f	14.8	Right lung, not further specified	T1bN0M0	IA2	Endoscopic resection	no	Tumor resected with microscopic residue	Alive off therapy	0.1
6	m	13.6	Right middle lobar bronchus	T2aN0M0	IB	Lobectomy	no	Remained in complete clinical remission	Alive off therapy	3.5
7	m	11.4	Left lung, not further specified	T1aN0M0	IA1	Partial lobectomy	no	Remained in complete clinical remission	Alive off therapy	2.8

Abbreviation: f, female; m, male; FU, follow-up; n.a., not applicable.

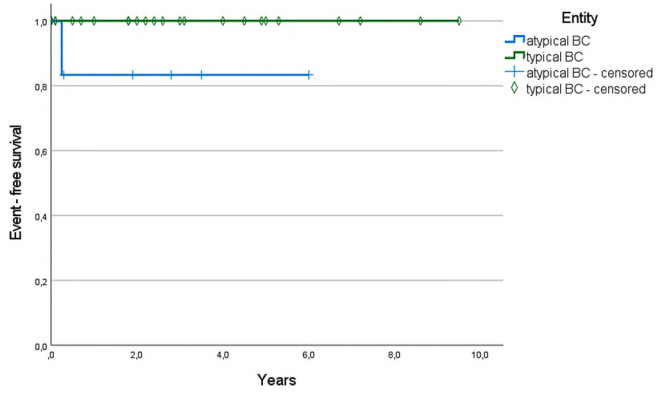

Fig. 1. Event-free survival of patients with bronchial carcinoid tumors (BC).

need of antibiotic treatment, unusual clinical presentation, and the lack of treatment success should prompt further diagnostics. In patients presenting with hemoptysis, the bronchial tumor was more timely diagnosed (median time 1.9 months).

In contrast to other neuroendocrine tumors, bronchial carcinoids rarely present with carcinoid syndrome. By totalizing our patient cohort with seven other published case series of pediatric patients with bronchial carcinoid tumors, a carcinoid syndrome was reported in only 3 of 92 patients [6,20,21,23,24,26,27]. Noteworthy, while carcinoid syndrome was reported in 2–5% of adult patients with lung carcinoid, this was mostly present in patients with liver metastases [16]. In our patient cohort, one patient had a functionally active bronchial carcinoid with ectopic ACTH production leading to increased insulin production and secondary amenorrhea. There are individual case reports of Cushing's syndrome due to ectopic ACTH production in pediatric patients [20,27,32]. Cushing's syndrome occurs in 3.3% of adult patients suggesting a similar frequency in children and adults [33].

For diagnostic purposes, conventional radiography is diagnostically less conclusive and rarely detect the tumor. As demonstrated by our data, plain radiographs mostly identified concomitant infiltrates and atelectasis. A CT scan of the chest is well established as the initial imaging method of the primary and poses little radiation exposure with adequate pediatric protocols. For staging purposes, CT of the abdomen is recommended in adults, while abdominal MRI is usually preferred in children to avoid radiation exposure [34]. Further imaging, however, is controversially discussed [16,34,35]. Somatostatin receptor scintigraphy is inferior to conventional CT in terms of sensitivity for the primary tumor as well as liver metastases according to our and published data [35]. [^{68}Ga]Ga-DOTA-TATE PET/CT has the highest sensitivity in detecting pulmonary carcinoids and is therefore recommended in the most recent European Society for Medical Oncology (ESMO) guideline for adult patients with bronchial carcinoid [16,34,36]. [^{18}F]FDG-PET/CT may be considered in specific clinical constellations, such as negative somatostatin receptor imaging [34]. It has a high sensitivity for detecting the primary tumor and may provide important clues to histology, as carcinoid tumors have a lower uptake on [^{18}F]FDG-PET/CT than other lung malignancies [37]. However, based on [^{18}F]FDG-PET/CT, typical and atypical carcinoids cannot be sufficiently distinguished and lymph node metastases of both subtypes are poorly detected [34,38]. In general, atypical carcinoids have a high uptake on [^{18}F]FDG-PET/CT but low uptake on SSTR-directed PET/CT due to low somatostatin receptor expression, whereas typical carcinoids have low uptake on [^{18}F]FDG- and intense uptake on [^{68}Ga]Ga-DOTA-TATE PET/CT [36]. The most recent ESMO clinical practice guideline on lung carcinoids includes recommendations for adult patients only [34]. Following these recommendations, we suggest contrast-enhanced cross-sectional conventional imaging including CT of the chest and abdominal MRI including liver late arterial phase as initial staging. At least in case of atypical bronchial carcinoid, (suspected) lymph node and/or distant metastases, additional imaging by [^{68}Ga]Ga-DOTA-TATE-PET should be performed. In all other cases, somatostatin receptor imaging must be discussed individually based on the latest recommendations.

For confirming diagnosis, bronchoscopic biopsy is recommended prior to definitive surgical resection [34]. It aims for excluding other lung malignancies and, thus, allows for determining the optimal therapeutic strategy. However, histopathological evaluation of small biopsies cannot reliably distinguish between typical and atypical bronchial carcinoid as proliferation rates may vary at different sites of the tumor [16]. Consistently, the subtype diagnosis was revised by

histopathological evaluation of the completely resected tumor in 3 cases in our study.

We found a higher frequency of atypical carcinoids (23.3%) compared to adults (8–15%) [39]. This corroborates previous reports (13–25%) on smaller pediatric case series [5,6,21,26]. However, Wang and colleagues reported only a single case of atypical carcinoid in a series of 17 pediatric patients [20].

According to population-based data, 91.4% of pediatric patients had a maximum tumor diameter of <5 cm [4]. Median tumor size in our patient cohort was 2.6 cm with an upper limit of 7.5 cm.

Our data confirm that bronchial carcinoids in children and adolescents are most likely located in the right lung [20,21,27]. Approximately 75% are located in lobar bronchi, 10–20% in the main bronchi, and a minor proportion in the lung periphery [3,40]. In adults, typical bronchial carcinoids tend to be more centrally located, whereas atypical bronchial carcinoids occur more peripherally [41]. None of the atypical carcinoids in our patient cohort was localized in a main bronchus and only one was localized in an intermediate bronchus.

Most patients in our study presented with localized disease (stage I 74%, stage II 22%), whereas metastatic disease was rare in this age group (stage IV 4%). Previous studies found similar stage-related proportions and locally advanced disease in up to 7 % of pediatric patients [21]. In a study of adult patients with an 8.4% proportion of atypical bronchial carcinoid tumors, 15% of patients had stage III and 8% stage IV disease [5].

Lymph node metastases were diagnosed in 4/28 of patients in our study and were reported to range from 15 to 30% up to 40% in smaller pediatric case series [2–4,6,21,23]. In adults, 10–21% of patients present with lymph node metastases [5,42,43]. In line with published data from adults, we demonstrated an approximately three times higher lymph node involvement in atypical carcinoids than in typical carcinoids [44].

Distant metastatic spread in children is very rare and has been only reported in individual cases. It is mainly associated with atypical carcinoid histology as in the single patient with distant metastases in our study. In addition, tumor invasion to surrounding tissue, such as the diaphragm and pericardium, was reported in children [23,26]. In adults, 60% of metastases were associated with atypical carcinoid histology [45]. Metastases were most frequently diagnosed in the liver (75%) and bone (42%) [45].

Treatment of choice for localized bronchial carcinoids is complete anatomical resection without further adjuvant therapy [16,21,42]. This was achieved in 96.4% of patients in our study. Besides the goal of achieving tumor-free resection margins, surgery should also aim at conserving as much normal lung tissue as possible, for example by means of bronchial sleeve resection or sleeve lobectomy [16,21,42]. However, depending on age, the anatomic conditions in children may be considerably smaller. This surgical approach was employed in 30.8% of our patients and all of them remained in complete remission at last follow-up. Noteworthy, a recent analysis in adult bronchial carcinoid demonstrated no superiority of lobectomy compared to sublobar resection [46]. As the true extent of the tumor may be underestimated on bronchoscopy, bronchoscopic resection is reserved for patients who are not suitable for bronchopulmonary surgery [6,16,24]. In addition, systematic lymph node sampling or dissection with a minimum of six nodal stations (three hilar and three mediastinal stations, including the subcarinal station) is recommended in adults with bronchial carcinoids [34]. This holds also true for patients with unsuspicious preoperative imaging [16]. However, our data did not allow for analyzing the importance of lymph node sampling in children.

There is limited data on the efficacy of adjuvant treatment in adults with advanced and metastatic disease. As the probability of disease recurrence/progression is low in patients with microscopic residue and typical histology, the necessity of re-resection must be balanced against (re-)surgery-associated morbidity [47]. All 3 patients with microscopic residues in our study remained in remission after a median follow-up of 4.5 years. In patients with multiple primaries, metastatic spread, and recurrence, treatment options include targeted therapy with everolimus (FDA-approved for the treatment of unresectable bronchial carcinoid in adults) [15,48], cytotoxic chemotherapy (such as temozolomide-based regimens) [16,49–51], somatostatin analogs [16,52], and peptide receptor radionucleotide therapy [53]. Stable disease (up to now 36 months) was achieved with everolimus in the patient with several relapses in our study. It should not go unmentioned that multiple primaries may have been unrecognized in this patient and subsequently misdiagnosed as early ipsilateral relapse.

The FU in our study was very heterogeneous in terms of both diagnostics and interval (range: 3–24 months). Based on European recommendations for adult patients with bronchial carcinoids [16,34], we propose to perform routine FU including clinical evaluation and laboratory testing (especially for chromogranin-A) every 3 months for the first 2 years and every 6 months thereafter in patients with atypical bronchial carcinoids, with resected metastases, and after incomplete resection. This needs to be complemented by chest CT scans and MRI scans of the abdomen at 3, 6, and 12 months in the first year and every 6 months thereafter for a total of at least 2 years [27]. In patients with atypical bronchial carcinoids and/or resected metastases, [^{68}Ga]Ga-DOTA-TATE PET/CT should be considered at least once during FU [34]. In patients with completely resected, localized typical bronchial carcinoid, clinical and laboratory FU without any routine CT scans every 6 months for the first 2 years and every 12 months thereafter may be justified [27].

Our study has several limitations including its retrospective character, data availability, the various methods used for imaging, treatment that was not completely standardized, and incomplete follow-up data. Several modifications were made to the World Health Organization classification of bronchial carcinoid tumors during the period covered that could not be considered separately in this analysis. Most patients were diagnosed as adolescents. Subsequent transition to adult medicine hampered tracking of these patients and limited the period of follow-up and, thus, the possibility of capturing events. However, no disease-related fatalities - as reported in in adults with advanced disease - were reported within the first two years of follow-up in our patient cohort [5].

5. Conclusion

Completely resected localized bronchial carcinoids in children and adolescents seem to have a favorable outcome also with lung tissue sparing surgery. Compared to adults, atypical bronchial carcinoids occurred more frequently.

As pediatric patients with atypical bronchial carcinoids are at risk of metastatic spread and recurrence, thorough interdisciplinary staging, management, and follow-up are recommended.

Close collaboration of pediatric oncologists, pediatric surgeons, endocrine surgeons, radiologists, and nuclear medicine specialists is necessary for optimal treatment of these patients. Molecular studies including cancer predisposition analysis and collaborative efforts such as the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) are needed to improve our understanding of bronchial carcinoids in this age group.

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Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2023.107320.

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