Published in final edited form as:

J Pediatr Hematol Oncol. 2019 January ; 41(1): 67–70. doi:10.1097/MPH.0000000000001100.

Pediatric Bronchial Carcinoid Tumors: A Case Series and Review of the Literature

Samara L. Potter, M.D., M.B.A.¹, Josephine HaDuong, M.D.², Fatih Okcu, M.D., M.P.H.¹, Hao Wu, M.D.³, Murali Chintagumpala, M.D.¹, and Rajkumar Venkatramani, M.D., M.S.¹

¹Texas Children's Cancer Center, Department of Pediatrics, Baylor College of Medicine, Houston, Texas

²Division of Oncology, Hyundai Cancer Center, Children's Hospital of Orange County, Orange, California

³Department of Pathology and Immunology, Texas Children's Hospital and Baylor College of Medicine, Houston, Texas

Abstract

Bronchial carcinoid tumor, while rare, remains the most common primary malignant lung tumor in children. We present a retrospective analysis of seven patients with typical bronchial carcinoid tumors diagnosed at two pediatric tertiary care referral centers between 1990 and 2014. The most common presenting symptom was pneumonia, followed by respiratory distress. Somatostatin scans were performed in selected patients. All patients had negative resection margin following surgery and were alive without disease at last follow-up. Typical carcinoid tumors have a good prognosis following definitive surgical resection. A review of published literature on pediatric bronchial carcinoid tumors is provided.

Keywords

bronchial carcinoid; neuroendocrine tumor; endobronchial

Introduction

Bronchial carcinoid tumors are the most common primary malignant lung tumors in children, comprising between 63-80% of all cases.¹ These tumors arise from bronchial mucosal neuroendocrine cells which have the ability to secrete amines and peptides. The term "carcinoid" distinguishes these well-differentiated neuroendocrine tumors from their poorly differentiated counterparts, which include large-cell neuroendocrine carcinomas (LCNECs) and small-cell lung cancer (SCLC).

Corresponding author contact information: Dr. Rajkumar Venkatramani, Texas Children's Hospital, 6701 Fannin Street, Suite 1510, Houston, TX 77030, Phone: 832-824-2511, Fax: 832-825-4039, venkatra@bcm.edu.

Conflicts of Interest and Source of Funding: For the authors none were declared.

Bronchial carcinoids are further subdivided based on malignancy potential, with a majority of pediatric patients presenting with typical carcinoids (TCs) which have low malignant potential. Atypical carcinoids (ACs) are less common in the pediatric population and have an intermediate malignancy potential. Unlike their poorly differentiated counterparts, bronchial carcinoids in children have a good prognosis when appropriately treated. Recent data from the National Cancer Database showed a 5 year overall survival of 95%.¹

Given the relative rarity of malignant pulmonary tumors in children, the majority of information about bronchial carcinoid tumors comes from adult literature. Here we present a retrospective analysis of a cohort of pediatric patients with bronchial carcinoids from two institutions over a 25-year period and review the published literature.

Materials and Methods

All patients less than 21 years of age diagnosed with bronchial carcinoid between 1990 and 2014 at Texas Children's Hospital and Children's Hospital Los Angeles were identified from the pathology database. Their presenting symptoms, clinical features, treatment, and outcome were obtained by review of medical records. The institutional review boards at both institutions approved the conduct of the study.

Results

A total of seven pediatric patients with bronchial carcinoids were identified. The patients ranged in age from 9-16 years with a mean age of 12.7 years (Table 1). Three patients were male and four were female. The most common presenting symptom was pneumonia in three patients. Two patients exhibited respiratory distress (tachypnea, wheezing, or difficulty breathing), and one presented with hemoptysis. Only one patient presented with symptoms of Cushing syndrome due to ectopic adrenocorticotrophic hormone (ACTH) production by the tumor. Of note, Patient 1 was diagnosed with multiple episodes of wheezing over two years prior to receiving her diagnosis, and Patient 3 was treated for persistent cough and pneumonia for a month prior to diagnosis. Three patients were noted to have decreased breath sounds on one side during physical examination.

Five tumors occurred in the right bronchi and two in the left. Four patients underwent pre-operative computed tomography (CT) scans, none of which showed evidence of mediastinal lymphadenopathy. Three patients underwent somatostatin scans which showed uptake in all three. Distal bronchopathy due to obstruction was common in this series and included two patients with hyperinflation and air trapping, two with atelectasis, and one with pneumothorax and pneumomediastinum. Endobronchial biopsy was performed in four cases prior to definitive surgery. All patients were treated by surgical resection. Pathological examination revealed typical carcinoid tumors in all patients. Lymph nodes were sampled in six patients, three of whom had a positive lymph node. The majority of patients had negative margins after surgery, with the exception of one patient with minimal residual disease, and one whose data was unavailable. Genetic testing for *MEN1* gene mutation performed in two patients was negative. Bronchial stenosis requiring balloon dilatation developed in one

patient. All patients were alive without disease at last follow-up (median 49 months, range 3-67 months.)

Discussion

Bronchial carcinoid is the most common primary malignant lung tumor in children; however, it remains a rare diagnosis due to the low incidence of childhood lung malignancies. Published literature of pediatric bronchial carcinoid is summarized in Table 2. Children typically present with respiratory symptoms including cough, chest pain, wheezing, hemoptysis, and difficulty breathing.^{5,8,9} Similar to Patient 1 in our series, misdiagnosis as asthma is common given the nonspecific and persistent respiratory symptoms. Endobronchial obstruction by the tumor can lead to a unilateral lobar consolidation on chest radiograph, commonly interpreted as pneumonia; the presence of a tumor may only become apparent after investigations for these recurrent episodes. Rarely, children can present with Cushing syndrome due to ectopic ACTH secretion, as noted in patient 4.¹⁸ Carcinoid syndrome, caused by the release of systemic vasoactive substances that cause symptoms including wheezing, flushing, palpitations, and diarrhea, is rare in the absence of metastases. The most common site of metastasis is the intrathoracic lymph nodes, although liver and skeletal metastases have been described in children.¹²

Bronchial carcinoid is usually detected as a mass on chest imaging performed for respiratory symptoms.^{16,19} Typical carcinoids tend to be more centrally located, whereas atypical carcinoids tend to be located peripherally. Diagnosis is generally confirmed by histopathological examination following endobronchial biopsy. When there is concern for metastasis, an octreotide scan may be used to identify metastatic lesions. MIBG scans and PET scans are options for patients with negative octreotide scans, although recent adult data found low MIBG sensitivity for detecting pulmonary carcinoids, suggesting PET may be preferable.¹⁹ Testing for multiple endocrine neoplasia type I (MEN-1) should be considered, as bronchial carcinoid occurs in 5% of these patients.²⁰

Morphologically, typical carcinoid is characterized by highly organized architecture and <2 mitoses per 10 high-power fields (HPFs) and the absence of necrosis. Atypical carcinoid, by contrast, has greater mitotic activity (2–10 mitoses/10 HPF), and/or the presence of necrosis. Both tumor types may be positive for neuroendocrine markers such as chromogranin A and synaptophysin. Ki-67 index may help differentiate high grade and low grade tumors, and has been shown to be associated with length of overall survival in adults.¹⁹

For localized tumors, complete surgical resection is the treatment of choice. Lymph node resection is recommended for atypical carcinoid given its increased malignancy potential. The effect of lymph node resection on overall survival for typical bronchial carcinoid in pediatrics has not been clearly defined; however, multiple series have shown that lymphatic spread occurs in up to 20% of pediatric patients of both histologies.^{1,5,9,17} Given this information, we believe that lymph node resection should be performed for all enlarged nodes and lymph node sampling should be considered in other patients.

At this time, there is no curative treatment for metastatic disease. Somatostatin analogues and interferon alpha have been used in advanced disease in adults without significant benefit. Temozolomide monotherapy achieved partial responses in 14% and stable disease in 52% of 31 adult patients with progressive metastatic bronchial carcinoid.²¹ Median progression free survival was 5.3 months and median overall survival was 23.2 months from the start of temozolomide.

Prognosis for patients with typical carcinoid is excellent, with > 90% survival.²² There is a paucity of data on atypical carcinoid in children, but 2 out of 8 patients died in a reported series.¹² A study of 247 adults with atypical carcinoid found that tumor size, lymph nodal metastatic involvement, pathological staging, mitotic index and Ki-67 (MIB-1) were all significant in the univariate analysis as prognostic factors; lymph node metastasis was significant in the multivariate analysis.²³

No follow-up is necessary for node negative localized completely resected typical carcinoid tumors.^{24,25} For others, computed tomography scan of the neck and chest every 6-12 months is appropriate given the indolent nature of these tumors. Recent data suggests that unlike their adult counterparts, pediatric patients with carcinoid tumors are not at increased risk for second primary malignancies, although this warrants further investigation.²⁶ In summary, pediatric typical bronchial carcinoid has an excellent prognosis following complete surgical resection. Delay in diagnosis may occur when concurrent pneumonia develops due to obstruction. Bronchial carcinoid should be included in the differential diagnosis for pediatric patients who present with recurrent pneumonia or wheezing to ensure timely diagnosis and treatment.

Abbreviations key

LCNEC	Large cell neuroendocrine carcinomas
SCLC	Small cell lung cancer
TC	Typical carcinoid
AC	Atypical carcinoid
ACTH	Adrenocorticotrophic hormone
CT	Computed tomography
MEN1	Multiple endocrine neoplasia type I
MIBG	Metaiodobenzylguanidine
PET	Positron emission tomography
HPF	High power field
OS	Overall survival
MET	Metastases

XRT

Radiation therapy

References

1. Rojas Y, Shi YX, Zhang W, et al. Primary malignant pulmonary tumors in children: a review of the national cancer data base. *J Pediatr Surg.* 2015; 50(6):1004–1008. [PubMed: 25812444]
2. Andrassy RJ, Feldtman RW, Stanford W. Bronchial carcinoid tumors in children and adolescents. *J Pediatr Surg.* 1977; 12(4):513–517. [PubMed: 197221]
3. Lack EE, Harris GB, Eraklis AJ, et al. Primary bronchial tumors in childhood. A clinicopathologic study of six cases *Cancer.* 1983; 51(3):492–497. [PubMed: 6295603]
4. Hancock BJ, Di Lorenzo M, Youssef S, et al. Childhood primary pulmonary neoplasms. *J Pediatr Surg.* 1993; 28(9):1133–1136. [PubMed: 8308677]
5. Wang LT, Wilkins EW Jr, Bode HH. Bronchial carcinoid tumors in pediatric patients. *Chest.* 1993; 103(5):1426–1428. [PubMed: 8387419]
6. Gaissert HA, Mathisen DJ, Grillo HC, et al. Tracheobronchial sleeve resection in children and adolescents. *J Pediatr Surg.* 1994; 29(2):192–197. [PubMed: 8176590]
7. Al-Qahtani AR, Di Lorenzo M, Yazbeck S. Endobronchial tumors in children: Institutional experience and literature review. *J Pediatr Surg.* 2003; 38(5):733–736. [PubMed: 12720182]
8. Fauroux B, Aynie V, Larroquet M, et al. Carcinoid and mucoepidermoid bronchial tumours in children. *Eur J Pediatr.* 2005; 164(12):748–752. [PubMed: 16133240]
9. Rizzardi G, Marulli G, Calabrese F, et al. Bronchial carcinoid tumours in children: surgical treatment and outcome in a single institution. *Eur J Pediatr Surg.* 2009; 19(4):228–231. [PubMed: 19513967]
10. Roby BB, Drehner D, Sidman JD. Pediatric tracheal and endobronchial tumors: an institutional experience. *Arch Otolaryngol Head Neck Surg.* 2011; 137(9):925–929. [PubMed: 21930983]
11. Yu Y, Song Z, Chen Z, et al. Chinese pediatric and adolescent primary tracheobronchial tumors: a hospital-based study. *Pediatr Surg Int.* 2011; 27(7):721–726. [PubMed: 21290133]
12. Geramizadeh B, Reza Foroutan H, Shokripour M, et al. Pulmonary atypical carcinoid tumor in a 15-year-old girl: a case report and review of the literature. *Rare Tumors.* 2013; 5(3):e45. [PubMed: 24179657]
13. Redlich A, Wechsung K, Boxberger N, et al. Extra-appendiceal neuroendocrine neoplasms in children - data from the GPOH-MET 97 Study. *Klin Padiatr.* 2013; 225(6):315–319. [PubMed: 24158887]
14. Madafferi S, Catania VD, Accinni A, et al. Endobronchial tumor in children: Unusual finding in recurrent pneumonia, report of three cases. *World J Clin Pediatr.* 2015; 4(2):30–34. [PubMed: 26015878]
15. Erginel B, Ozkan B, Gun Soysal F, et al. Sleeve resection for bronchial carcinoid tumour in two children under six years old. *World J Surg Oncol.* 2016; 14:108. [PubMed: 27080124]
16. Cogen JD, Swanson J, Ong T. Endobronchial Carcinoid and Concurrent Carcinoid Syndrome in an Adolescent Female. *Case Rep Pediatr.* 2016; 2016:2074970. [PubMed: 27895950]
17. Degnan AJ, Tocchio S, Kurtom W, et al. Pediatric neuroendocrine carcinoid tumors: Management, pathology, and imaging findings in a pediatric referral center. *Pediatric Blood & Cancer.* 2017; 64(9):e26477–n/a.
18. Wyszynska T, Cichocka E, Wieteska-Klimczak A, et al. A single pediatric center experience with 1025 children with hypertension. *Acta Paediatr.* 1992; 81(3):244–246. [PubMed: 1511199]
19. Pericleous M, Karpathakis A, Toumpanakis C, et al. Well-differentiated bronchial neuroendocrine tumors: Clinical management and outcomes in 105 patients. *Clin Respir J.* 2016; 00:1–10.
20. Sachithanandan N, Harle RA, Burgess JR. Bronchopulmonary carcinoid in multiple endocrine neoplasia type 1. *Cancer.* 2005; 103(3):509–515. [PubMed: 15611976]
21. Crona J, Fanola I, Lindholm DP, et al. Effect of temozolomide in patients with metastatic bronchial carcinoids. *Neuroendocrinology.* 2013; 98(2):151–155. [PubMed: 23969949]
22. Filosso PL, Guerrero F, Evangelista A, et al. Prognostic model of survival for typical bronchial carcinoid tumours: analysis of 1109 patients on behalf of the European Association of Thoracic

- Surgeons (ESTS) Neuroendocrine Tumours Working Group. *Eur J Cardiothorac Surg.* 2015; 48(3): 441–447. [PubMed: 25564217]
23. Daddi N, Schiavon M, Filosso PL, et al. Prognostic factors in a multicentre study of 247 atypical pulmonary carcinoids. *Eur J Cardiothorac Surg.* 2014; 45(4):677–686. [PubMed: 24099733]
24. Lou F, Huang J. Reply: To PMID 23915584. *Ann Thorac Surg.* 2014; 98(3):1144. [PubMed: 25193220]
25. Lou F, Sarkaria I, Pietanza C, et al. Recurrence of pulmonary carcinoid tumors after resection: implications for postoperative surveillance. *Ann Thorac Surg.* 2013; 96(4):1156–1162. [PubMed: 23915584]
26. Fernandez KS, Aldrink JH, Ranalli M, et al. Carcinoid tumors in children and adolescents: risk for second malignancies. *J Pediatr Hematol Oncol.* 2015; 37(2):150–153. [PubMed: 25374281]

Table 1

Clinical features

Pt. No.	Age/Sex	Presenting symptom	Location	Tumor size (cm)	Surgery	Lymph Node Metastasis	Margins	Follow-up (months)
1	9/F	Respiratory distress, wheezing	Left main stem bronchus	1.9	Left upper lobe sleeve lobectomy	No	Negative	10
2	11/M	Hemoptysis	Right main stem bronchus	2.7	Resection and reconstruction of right upper lobe bronchus	No	Negative	63
3	13/F	Tachypnea, pneumonia	Left main stem bronchus	3	Left lower lobe sleeve lobectomy	Yes	Not specified	67
4	13/F	Facial acne, hirsutism, headaches, skin stretch marks	Superior segment right lower lobe	1.5	Wedge resection	Not assessed	Negative	49
5	15/F	Respiratory distress	Right bronchus intermedius	–	Right middle and lower lobectomy	No	Negative	53
6	16/M	Recurrent pneumonia	Right bronchus intermedius	–	–	Yes	Negative	3
7	12/M	Persistent pneumonia	Right lower lobe	2.4	–	Yes	MRD	13

Pt: patient; No: number; F: female; M: male; cm: centimeter; –: data unavailable; MRD: minimal residual disease.

Table 2

Summary of published pediatric data on bronchial carcinoid

Publication	Number of patients	Age range (years)	Treatment	Outcome	Pathology
1977 Andrassy ²	21 (8 cases + 13 from literature)	9-19	Surgery	3 died (2 of pneumonia 7 and 12 months post-op, respectively; one 2 months post-op with elevated 5HIAA)	–
1983 Lack ³	4 (1 with mets to choroid, bone, lungs, liver, adrenals, lymph nodes, and ovaries)	6-10	Surgery in 4, +chemotherapy and XRT in 1	1 died of disease	–
1993 Hancock ⁴	3	10-15	Surgery	All alive	–
1993 Wang ⁵	17 (including 1 patient with Cushing syndrome)	10-21	Surgery	All alive, 2 patients developed mets after surgery (one with right lung lymphovascular invasion requiring pneumonectomy)	All typical
1994 Gaisser ⁶	4	8-19	Surgery	All alive	–
2003 Al-Qahtani ⁷	5	10-15	Surgery, +laser ablation in 1	All alive	All typical
2005 Fauroux ⁸	11	9-15	Surgery	All alive	All typical
2009 Rizzardi ⁹	15 (3 patients with nodal mets, of which 2 were atypical)	8-18	Surgery	14 alive (2 late recurrence, both typical), 1 died in motor vehicle accident	13 typical, 2 atypical
2011 Roby ¹⁰	5	13-18	Surgery	All alive	–
2011 Yu ¹¹	2	15-17	Surgery	All alive	1 typical, 1 atypical
2013 Geramizadeh ¹²	8 (7 from literature, including Rizzardi ³ and Yu ²²)	10-21	Surgery in 6, +chemotherapy in 2, +XRT in 1; chemotherapy only in 1 (patient with bone met)	2 died (one with subcarinal lymph node met, another with skull bone met that did not undergo surgery)	All atypical
2013 Redlich ¹³	12	<18	Surgery	All alive	All typical
2015 Rojas ¹ (Retrospective review of National Cancer Database)	133	<18	Surgery 90%, chemotherapy 5%, XRT 2%	95% OS	–
2015 Madafferi ¹⁴	1	14	Surgery	Alive	Typical
2016 Erginel ¹⁵	2	4-6	Surgery	All alive	Both typical
2016 Cogen ¹⁶	1	14	Surgery	Alive	Typical
2017 Degnan ¹⁷	5 (2 with mets: one typical with mediastinal lymph nodes, one atypical with subcarinal mass + mediastinal lymph nodes)	7-17	Surgery in 4, laser resection in 1	All alive	4 typical, 1 atypical

OS: Overall survival; Mets: metastases; XRT: radiation therapy; –: data unavailable.