



# Primary Lung Tumors in Children and Adolescents: 29 Years of Experience at a Single Institution

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## Abstract

**Purpose:** Primary lung tumors in children are rare and comprise a broad range of histopathologic types. The incidence and outcome of these lesions are still largely unknown. We investigated the relative incidence of different primary lung tumors and their outcomes in children and adolescents at a single pediatric institution.

**Methods:** All patients diagnosed with primary lung tumors from 1984 through 2013 were retrospectively reviewed. Data were collected from medical records after approval was obtained from our Institutional Review Board.

**Results:** Seventeen-patients (8 boys, 9 girls) were identified with a mean age of 9.3 years (range: newborn to 18 years). Seven distinct histopathologic tumor types were identified: inflammatory myofibroblastic tumor (4), pleuropulmonary blastoma (4), carcinoid (n=3), mucoepidermoid carcinoma (2), synovial sarcoma (1), pulmonary hamartoma (2), and infantile fibrosarcoma (1). Chemotherapy was used in 37.5% (n=6) and radiation in 25% (4) of patients. The mortality rate was 25% (n=4), but only two deaths (12.5%) were directly related to the lung tumors. Of the 12 survivors, median duration of follow-up was 8.75 years (range, 0.5-20.4 years). One patient was lost to follow-up.

**Conclusions:** Our experience substantiates the rarity and histopathological diversity of primary lung tumors in pediatric patients. Although complete resection remains the standard of care for most lung tumors, the role of adjuvant therapy is dependent on the histopathologic tumor type.

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## Introduction

Primary pulmonary neoplasms are rare in children and are far more likely to be metastatic disease or inflammatory/congenital in nature. The ratio of primary to metastatic to inflammatory/congenital tumors is reported to be 1:5:60 [1]. The various pediatric pulmonary tumors differ in their prevalence and outcome. Another complicating factor is the evolution of the histopathologic classification system. The current World Health Organization (WHO) system differs substantially from many historical classification systems, as new tumors have been described (Pleuropulmonary Blastoma [PPB]), other tumors have been reclassified from benign to malignant (Inflammatory Myofibroblastic Tumor [IMT]), and still other tumors are more rare than once believed (rhabdomyosarcoma) [2-4]. In 1982, Hartman and Shochat reviewed 230 cases of primary pediatric pulmonary tumors described in the English-language literature [5]. Since that publication there have been several large, single-institution series reported [1,6-11]. The purpose of this article is to review and describe our experience over a 50-year period.

## Methods

A single-institution retrospective chart review was performed with the approval of the St. Jude Children's Research Hospital Institutional Review Board (IRB). Medical records of all patients diagnosed with a primary, non-hematologic pulmonary neoplasm were reviewed from 1962 through 2013.

## Results

### Demographics

Between 1962 and 1983 there were no patients identified with a primary lung tumor. From

**Table 1:** Patient demographic and clinical characteristics by histopathologic tumor type.

Tumor type	Number	Age <sup>a</sup> (Range, years)	Sex (no. F:M)	Laterality (no. L:R) <sup>b</sup>
Carcinoid	3	13.3 (12-15)	3:0	1:2
Mucoepidermoid carcinoma	2	11.9 (6.8-17)	0:2	0:2
Pleuropulmonary blastoma	4	1.7 (0-2.9)	2:2	1:3
Inflammatory myofibroblastic tumor	4	9.2 (5-14)	3:1	2:2
Synovial sarcoma	1	15.3	0:1	0:1
Infantile fibrosarcoma	1	0.1	1:0	0:1
Hamartoma	2	17.7 (17.5-18)	0:2	1:1

<sup>a</sup>Mean age<sup>b</sup>R= Right, L= left**Table 2:** Treatment by histologic tumor type.

Tumor	Surgical Resection (no.)			Laser ablation	Chemotherapy	Radiation
	Wedge	Lobectomy	Pneumonectomy			
Carcinoid <sup>a</sup>		2		1		
Mucoepidermoid carcinoma		1				
Pleuropulmonary blastoma	2 <sup>b</sup>	2	1		3	2
Inflammatory myofibroblastic tumor	2	2			1	
Synovial sarcoma			1		1	1
Infantile fibrosarcoma		1	1 <sup>c</sup>		1	
Hamartoma	2					

<sup>a</sup>Chemotherapy and radiotherapy data unavailable for one patient<sup>b</sup>One Patient had wedge resection and subsequently underwent lobectomy for positive margins<sup>c</sup>Patient had lobectomy initially and then underwent pneumonectomy for recurrence

1984-2013 seventeen-patients were identified (8 boys, 9 girls) with a mean age at diagnosis of 9.3 years (range: newborn to 18 years). Table 1 summarizes the demographic and clinical data. A total of seven distinct histopathologic pulmonary tumor types were identified. Tables 2 and 3 describe treatment and outcome data, respectively.

### Inflammatory myofibroblastic tumor

Four patients (23.5%) had IMF. The first patient had been treated for Hodgkin lymphoma 2 years before the diagnosis of IMF. Pulmonary wedge resection was performed without any additional therapy, and remained disease-free at 20.4 years. The second patient had a history of being treated for peripheral neuroectodermal tumor also underwent pulmonary wedge resection. Unfortunately the patient was also found to have myelodysplastic syndrome/AML which proved fatal. The third patient had bi-lobectomy and is disease free at 10.2 years. The fourth patient underwent lobectomy but developed recurrence and subsequently received chemotherapy. The patient remains disease free at 2.8 years.

### Pleuropulmonary blastoma

Four patients (23.5%) had PPB. The first patient underwent lobectomy, and was disease-free at 6.1 years of follow-up. The second patient underwent pneumonectomy in addition to chemotherapy and radiation, and remained disease-free at 19.9 years. Long-term complications included scoliosis from the thoracotomy and restrictive pulmonary disease due to radiation therapy. The third patient underwent pulmonary wedge resection at a different institution with gross spillage of tumor during surgery. The patient developed recurrence after one year which was treated with surgery, chemotherapy, and radiation. Despite these efforts the patient died within 2 years from initial diagnosis. The fourth patient had a lobectomy followed by chemotherapy and radiation, and was disease

free at 17.7 years. Unfortunately the patient developed scoliosis, sternal and chest wall hypoplasia due to radiation.

### Carcinoid tumor

Three patients (17.6%) had carcinoid tumors. Two patients underwent lobectomy and one patient had bronchoscopic laser ablations. The patient who underwent multiple bronchoscopic laser ablations, remained disease free after five years since last ablation. The bronchial surgical margins of one patient was positive after bi-lobectomy, however, the decision was made to perform scheduled clinical follow-up and imaging in addition to bronchoscopy as the positive margins were at bifurcation of bronchus. The patient remains disease-free after 0.5 year. One patient was lost to follow-up.

### Mucoepidermoid carcinoma

Two patients (11.7%) had mucoepidermoid carcinoma. One patient underwent lung biopsy and died within one month of diagnosis. The second patient had lobectomy and did not require adjuvant therapy. The patient remains disease-free at 7.3 years of follow-up.

### Pulmonary hamartoma

Two patients (11.7%) had a pulmonary hamartoma, and both underwent pulmonary wedge resections. The first patient had metastatic osteosarcoma, and during thoracotomy for metastatectomy, one nodule was identified as hamartoma. This patient died due to the initial disease. The second patient had a primary diagnosis of craniopharyngioma with subsequently development of osteosarcoma and myelodysplastic syndrome. An evaluation for bone marrow transplantation revealed a pulmonary nodule that was resected (wedge) and a hamartoma was found. This patient was disease-free

**Table 3:** Outcome and follow-up data by histopathologic tumor type.

Tumor type	Number	Mortality (n, %)	Follow-up median <sup>a</sup> (range)
Carcinoid <sup>b</sup>	3	0, 0	3.4(0.5-6.3)
Mucoepidermoid carcinoma	2	1, 50	7.3
Pleuropulmonary blastoma	4	1, 25	17.7(6.1-19.9)
Inflammatory myofibroblastic tumor	4	1 <sup>c</sup> , 25	10.2(2.8-20.4)
Synovial sarcoma	1	0, 0	13.5
Infantile fibrosarcoma	1	0, 0	19.2
Hamartoma	2	1 <sup>d</sup> , 50	3

<sup>a</sup>Years<sup>b</sup>One patient was lost to follow-up<sup>c</sup>Patient died of myelodysplastic syndrome that progressed to acute myelocytic leukemia<sup>d</sup>Patient died of the initial tumor (osteosarcoma)

at 3 years.

### Synovial sarcoma

One patient (5.8%) had a pleural-based synovial sarcoma. The patient underwent pneumonectomy and received adjuvant chemotherapy and radiation. The patient remains disease-free at 13.5 years.

### Infantile fibrosarcoma

One patient (5.8%) had a lung mass at birth and underwent lobectomy. He was diagnosed as infantile fibrosarcoma. The patient developed recurrence after 2 years and underwent pneumonectomy and chemotherapy. The patient developed scoliosis secondary to pneumonectomy, however, remains disease-free at 19.2 years. The overall mortality rate was 25% (n=4) in our series, however, only 2 deaths (12.5%) were attributable to the primary lung tumors. Chemotherapy was used in 37.5% cases (n=6) and radiation in 25% (n=4). Of the 12 survivors, the median duration of follow-up was 8.75 years (mean: 10.5 years; range: 0.5-20.4 years) at the time of this review. One patient was lost to follow-up.

## Discussion

The histopathologic diagnosis of primary pediatric lung tumors has evolved significantly during the past several decades. In their 1982 review of the literature, Hartman and Shochat [5] described 230 tumors comprising 16 histopathologic subtypes. In contrast, the current WHO histologic classification of lung tumors now consists of 41 distinct epithelial entities (31 malignant and 10 benign) [3], illustrating how the distinction of these tumors has advanced. For years, the proportions of malignant and benign primary lung lesions have been accepted as 66% and 34%, respectively. However, the most common "benign" tumor, IMT, has been reclassified as malignant [3]. With this change, the cohorts reviewed by Hartman and Shochat [5] and 10 years later by Hancock and colleagues [9] would have had a malignant tumor frequency of 85% to 90%, consistent with the 86% observed in our series.

Carcinoid tumors have been reported to account for 11% to 20% of all pediatric pulmonary tumors [5,9,11] which is consistent with 18.5% in our series. The outcome of carcinoid tumor is dependent on the extent of disease at presentation [12]. Five-year survival estimates for local, regional, and disseminated disease are 81%, 77%, and 26%, respectively [13]. Our one patient who was lost to follow-up had localized tumor, suggesting a good prognosis; the second patient also had localized disease and remained disease-free at last follow-up. Salivary gland tumors consist of mucoepidermoid, adenoid cystic,

epithelial-myoepithelial carcinomas, and in adults, these tumors represent less than 0.2% of primary lung tumors and are associated with a poor prognosis (39% survival at 5 years) [14]. In children, as many as 10% of primary pulmonary tumors are of the salivary gland histologic types, and the prognosis is favorable [8,11,15]. In our series there were 2 patients with mucoepidermoid carcinomas where one died within 1 month after diagnosis, and the second who underwent lobectomy remained disease-free at last follow-up. IMF, previously known as plasma cell granuloma and inflammatory pseudotumor, has traditionally been considered a benign entity. However, the WHO has recently recognized IMT as a low-grade mesenchymal malignancy. A significant proportion of IMTs have demonstrated ALK1 gene mutations, and the tumors are currently regarded as malignant neoplasms [16]. Treatment of pulmonary IMT is based on surgical resection, although these can rarely recur, have invasion of adjacent organs, and lead to death [17,18]. The two patients in our series underwent pulmonary wedge resection. One was disease-free at last follow-up (20.4 y), while the second died of acute myelogenous leukemia. The two patients who underwent lobectomy were both disease free at last follow-up. However, one patient had recurrence and ultimately received chemotherapy. Of the 7 cases reported by Yu et al. [11], 2 had wedge resection, 2 required lobectomy, and 3 had pneumonectomy. Two of the tumors recurred, and one patient died during anesthesia induction for resection of recurrent tumor. Chemotherapy, radiation, and anti-inflammatory medications have been proposed as adjuvant therapies, however, no single regimen is generally accepted. The term PPB was first used in 1988 by Manivel and colleagues. These blastemic pediatric pulmonary tumors had previously been grouped with adult pulmonary blastomas. Three subtypes of PPB have been described on the basis of gross features. Type I is cystic and lacks a solid component; conversely, type III is solid and lacks a cystic component, while type II is a mixture of solid and cystic. Outcomes were generally poor, with a 2-year survival estimate of 63% overall (type I, 80%; type II, 73%; type III, 48%). However, outcomes improved with time and in recent report from International Pleuropulmonary Blastoma Registry 5 year OS for type I is 91%, type II 71% and type III is 53% [19]. A germline mutation in DICER1 is the genetic cause in the majority of PPB cases. However, DICER 1 mutation was not related to outcome [19]. Treatment previously advocated by Parsons et al. [20] depends on aggressive surgery followed by chemoradiotherapy. Although the reported effectiveness of local radiotherapy varies, some studies suggest that it is helpful when resection is incomplete [21,22]. Our three cases of PPB had a disease-free follow-up of 6.1, 17.7 and 19.9 years, and two patients received radiation and chemotherapy. The fourth patient

underwent lobectomy, chemotherapy and radiation for recurrence, and died after 2 years from initial diagnosis. Pulmonary sarcomas are extremely rare, constituting only 0.1% of all primary lung malignancies. Their histogenesis is not well understood, but they are thought to arise from immature mesenchymal cells. The prognosis of pulmonary synovial sarcoma is poor, with a 5-year survival estimate of 50%. Our series included two patients, both of them were disease free till last follow up.

## Conclusions

Our experience substantiates the rarity and histopathological diversity of primary lung tumors in pediatric patients. Although complete resection remains the standard of care for most tumors, the role of adjuvant therapy is dependent on the histopathologic tumor type.

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