Clinical and pathological analysis of pediatric patients with primary pulmonary tumors at a single center

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Abstract. Primary pulmonary tumors in pediatric patients are rare; however, they are frequently malignant, posing significant diagnostic challenges. Therefore, the present study aimed to systematically investigate the clinical, imaging and pathological characteristics of primary pulmonary tumors in children. A total of 36 pediatric patients diagnosed with primary pulmonary tumors were included. Clinical data were collected, including clinical manifestations, imaging findings, pathological analysis, diagnosis and therapy. Among 36 pediatric patients with primary pulmonary tumors, 19 were girls and 17 were boys. The age at diagnosis was 2.0-9.8 years with a median of 4 years. A total of 11 histopathologic tumor types were identified, with pleuropulmonary blastoma (PPB) being the most prevalent. The clinical manifestations were nonspecific, primarily presenting as respiratory symptoms, including cough and fever. These symptoms were frequently associated with complications, including pleural effusion and atelectasis. The maximum tumor diameter ranged from 2.0 to 7.0 cm (median: 4.0 cm), with a predominance of unilateral and unifocal lesions. Furthermore, younger age at diagnosis, solitary lesions and larger non-cystic tumors are indicative of a higher likelihood of PPB. The surgical treatment of thirty-five patients was primarily comprised of open thoracotomy and thoracoscopic surgery. Chemotherapy was administered to 16 patients, while two received a combination of chemotherapy and radiotherapy. Follow-up data were available for 33 patients, with a median follow-up time of 15.0 months and three patients experienced tumor recurrence. The clinical manifestations of primary pulmonary tumors in children are not specific. Imaging and pathological characteristics are valuable in the differential diagnosis of benign and malignant tumors. Younger age at diagnosis, solitary lesions and larger non-cystic tumors are indicative of a higher likelihood of PPB. Integrating molecular diagnostics is an important direction for future research to improve early detection and treatment outcomes.

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Abbreviations: PPB, pleuropulmonary blastoma; p53, tumor protein p53; TTF-1, thyroid transcription factor-1; CT, computed tomography; SD, standard deviation

Key words: pulmonary tumors, primary, pathology, differential diagnosis, children

Introduction

Primary pulmonary tumors are extremely rare in children, with an annual incidence of <2 per million (1). The ratio of primary to metastatic to inflammatory/congenital tumors is reported to be 1:5:60 (2-4). The pathological spectrum of primary pulmonary tumors is complex and diverse (5). According to the histological origin, there are five main categories: Mesenchymal tumors (rhabdomyosarcoma and inflammatory myofibroblastic tumor), epithelial tumors (alveolar carcinoma), lymphoid tumors (Langerhans cell histiocytosis and lymphoma), embryonic tumors (hamartoma and pleuropulmonary blastoma) and neuroendocrine tumors (small cell carcinoma and large cell neuroendocrine carcinoma).

The clinical manifestations often present with nonspecific symptoms, including fever, persistent coughing, dyspnea, chest pain and recurrent pulmonary infections, depending on the type of tumor (6-7). Some cases are asymptomatic and detected incidentally on imaging studies (4,8). Due to the lack of characteristic clinical features, these conditions are frequently misdiagnosed as asthma, foreign body aspiration,

infectious diseases, or reactive airway disorders, leading to diagnostic delays (9).

Despite the rarity, ~65-76% of these tumors are malignant (7,10). The overall mortality rate for primary malignant tumors is ~30%, while the mortality rate for primary benign pulmonary tumors in children is 8.7% (4). However, they continue to have an improved prognosis compared with those encountered in adulthood. Early diagnosis and prompt treatment are critical for optimal outcomes in children with primary pulmonary tumors (9). The differential diagnosis of primary pulmonary tumors in children is complex, as it requires the differentiation of these tumors from both metastatic pulmonary lesions and more prevalent non-tumorous conditions. The prognosis and treatment approaches of these three conditions are markedly different.

In the medical literature, the incidence data on primary pulmonary tumors in children are limited due to the predominance of individual case reports and diagnosis-specific case series. The present study analyzed the clinical and pathological data of pediatric patients diagnosed with primary pulmonary tumors by the Pathology Department of the Children's Hospital of Zhejiang University School of Medicine between January 2016 and October 2024. The objective was to investigate the clinical and pathological characteristics, diagnosis and therapy of primary pulmonary tumors in children, to highlight the diagnosis and therapy of primary pulmonary tumors.

Materials and methods

Study population. A retrospective case series review was conducted. Clinical and pathological data were collected from 36 pediatric patients diagnosed with primary pulmonary tumors by the Pathology Department at the Children's Hospital of Zhejiang University School of Medicine between January 2016 and October 2024. The age, sex, signs and symptoms on admission, tumor localization, imaging findings, pathology, surgical procedure, complications and postoperative follow-up were recorded for each patient.

The present study was approved by the Ethics Committee of Children's Hospital of Zhejiang University School of Medicine (approval no. 2024-IRB-0397-P-01).

Pathology. All specimens were fixed with 10% formalin at room temperature for 12 h. After gross examination and sampling, tissues were placed in cassettes and processed in an automatic tissue processor for postfixation, dehydration, clearing, and paraffin infiltration as follows: Postfixation in neutral buffered formalin (pH 7.4) at room temperature for 4 h, rinsing under running tap water for 30 min, dehydration through graded ethanol at room temperature (80% ethanol for 30 min, 95% ethanol for 1 h x2, and 100% ethanol for 1 h x2), clearing in xylene at room temperature for 20 min x2, paraffin infiltration at 58-60˚C for 3 h, and embedding at 60-62˚C. Serial sections were cut at 3-4 μm, mounted onto slides, and baked in an oven at 60-62˚C for 2 h. The sections were then subjected to hematoxylin and eosin (H&E) staining and immunohistochemical staining, respectively. Images were captured under a light microscope (bright-field; Leica Microsystems GmbH).

H&E staining. Sections were dewaxed in xylene for 10 min x2, rehydrated through graded ethanol series (absolute ethanol for 3 min x2, 95% ethanol for 2 min x2, 80% ethanol for 2 min, and 70% ethanol for 2 min), and rinsed in running tap water. The sections were stained with Gill's hematoxylin for 10 min, rinsed under running tap water for 2 min, differentiated with 0.5% acid alcohol for several seconds under microscopic observation when necessary, rinsed under running water, and blued in warm water. After immersion in 95% ethanol for 1 min, the sections were stained with 0.5% alcoholic eosin for 1 min, briefly differentiated in 80% ethanol, dehydrated through 95% ethanol for 3 min x2 and 100% ethanol for 3 min x2, cleared in xylene for 5 min x2, and finally mounted with neutral balsam. All procedures were performed at room temperature.

Immunohistochemistry. Immunohistochemical analysis was performed on formalin-fixed paraffin-embedded tissue sections. The immunostaining was performed on a Leica Biosystems BOND3 instrument with a Bond Polymer Refine Detection kit (cat. no. DS9800; Leica Microsystems GmbH). Heat-mediated antigen retrieval was performed with Tris-EDTA buffer (pH 9.0; BOND Epitope Retrieval Solution 2; Leica Microsystems GmbH) at 100˚C for 20 min. Endogenous peroxidase activity was blocked using the kit-supplied Peroxide Block (3-4% hydrogen peroxide) at room temperature for 5 min. Primary antibodies were incubated for 15 min at room temperature. Detection was performed using the kit-supplied Post Primary reagent (mouse IgG linker, containing 10% animal serum) followed by the Polymer reagent (rabbit anti-Poly-HRP-IgG); both reagents are ready-to-use without dilution and were incubated at room temperature for 8 min each. Chromogenic visualization was achieved using Mixed DAB Refine at room temperature for 10 min. All sections were counterstained with the kit-supplied Hematoxylin (<0.1%) at room temperature for 5 min. The primary antibodies used in the present study are listed in Table SI.

Statistical analysis. Statistical analysis was conducted using the Statistical Package for the Social Sciences software (version 26.0; IBM Corp.). Normally distributed data are described by mean ± standard deviation (SD) and analyzed using the independent t-test. Non-normally distributed data are described by median and quartile ranges [medians, (P25, P75)] and analyzed using the Mann-Whitney test. Categorical data are expressed as frequencies (%) and were compared using the χ^2 test or Fisher's exact test. Graphics were generated through Microsoft Excel 2021 (Microsoft Corporation). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Among 36 pediatric patients with primary pulmonary tumors, 19 were girls and 17 were boys. The age at diagnosis ranged from 2.0 to 9.8 years, with a median age of 4.0 years. A total of 11 distinct histopathologic tumor types were identified. Pleuropulmonary blastoma (PPB) was the most prevalent tumor type, comprising 44.44% (16/36; 7 of type I, 6 of type II and 3 of type III). Pulmonary mucoepidermoid carcinoma and pulmonary sclerosing pneumocytoma each accounted for 11.11% (4/36; Table I). The remaining 12 patients exhibited

Table I. The clinical and pathological characteristics of all patients (n=36).

Characteristic	All patients
Demographics	
Age (year), [median, (P25, P75)]	4, (2, 9.75)
Sex (F:M)	19:17
Clinical manifestations	
Fever, n (%)	17 (47.22)
Cough, n (%)	25 (69.44)
Dyspnea, n (%)	6 (16.67)
Chest pain, n (%)	6 (16.67)
Hemoptysis, n (%)	2 (5.56)
Swollen lymph nodes, n (%)	1 (2.78)
Localization	
Tracheal, n (%)	6 (16.67)
Multiplicity, n (%)	7 (19.44)
Imaging features	
Maximum diameter (cm), [median, (P25, P75)]	4, (2, 7)
Atelectasis, n (%)	7 (19.44)
Pleural effusion, n (%)	8 (22.22)
Pneumothorax, n (%)	1 (2.78)
Pathological Features	
Morphological characteristics[a], n (%)	15 (41.67)
Hemorrhage necrosis/Calcification, n (%)	18 (50)
Ki-67 index (%), [median, (P25, P75)]	25, (5.88, 60)
Treatments	
Surgery, n (%)	35 (97.22)
Chemotherapy, n (%)	18 (50)
Radiation, n (%)	2 (5.56)
Outcomes	
Follow up time (years), [median, (P25, P75)]	1.25, (0.71, 3.00)
Metastasis, n (%)	2 (5.56)
Recurrence, n (%)	3 (8.33)

[a]Morphological characteristics: With marked atypia and/or mitotic figures.

Table II. Pathological types of primary pulmonary tumors in the present study.

A, Benign (n)	
Pulmonary sclerosing pneumocytoma	4
Hamartoma	3
Langerhans cell histiocytosis	2
Mature teratoma	1
Total	10 (27.78%)
B, Malignant (n)	
Pleuropulmonary blastoma	
Type I	7
Type II	6
Type III	3
Pulmonary mucoepidermoid carcinoma	4
Pulmonary blastoma	2
Hodgkin's lymphoma	1
Carcinoid tumor	1
Alveolar soft part sarcoma	1
Ewing's sarcoma	1
Total	26 (72.22%)

eight separate morphologies, including pulmonary hamartoma, Langerhans cell histiocytosis, pulmonary blastoma, mature teratoma, Hodgkin's lymphoma, carcinoid, pulmonary alveolar soft tissue sarcoma and Ewing's sarcoma (Fig. 1).

The most prevalent symptoms at the time of diagnosis were respiratory symptoms, including 25 (69.44%) patients with cough, six (16.67%) with dyspnea and two (5.56%) with hemoptysis. Other symptoms included fever in 17 (47.22%) and chest pain in six (16.67%). The imaging findings at the time of diagnosis included associated complications, including pleural effusion in 8 (22.22%), atelectasis in seven (19.44%) and pneumothorax in one (2.78%; Table I).

The maximum diameter of tumors ranged from 2.0-7.0 cm with a median of 4.0 cm. The imaging findings indicated that 32 (88.89%) patients had unilateral lesions, with 19 (59.38%) in the left lung and 13 (40.62%) in the right lung. The other three patients exhibited bilateral involvement and one presented with a lesion located in the mid-trachea. In total, tumors in 29 (80.56%) patients were solitary, with 11 located in the upper lobe of the left lung, eight in the lower lobe of the left lung, two in the upper lobe of the right lung, four in the middle lobe of the right lung, three in the lower lobe of the right lung and one in the mid-trachea. Other tumors in seven (19.44%) patients were multiple, including three bilateral and four unilateral. There were 11 (30.56%) patients with cystic lesions, 10 (27.78%) with cystic-solid lesions and 15 (41.67%) with solid lesions. Furthermore, six patients presented with intratracheal tumors and two had metastases to other sites (Fig. 1).

The immunohistochemical results were as follows: Desmin was positive in 66.67% (16/24), vimentin in 100% (14/14), Myogenic Differentiation 1 in 55.56% (10/18), myogenin in 76.92% (10/13), smooth muscle actins in 44.44% (4/9), epithelial membrane antigen in 75.0% (15/20), integrase interactor 1 in 100% (14/14), S-100 in 36.36% (8/22), chromogranin A in 44.44% (4/9), synaptophysin in 35.71% (5/14), CD34 in 100% (11/11), CD99 in 90.91% (10/11), tumor protein p53 (p53) in 100% (2/2) and thyroid transcription factor-1 (TTF-1) in 100% (2/2).

According to the classification of tumor malignancy, 10 were benign tumors and 26 were malignant tumors (Table II). A comparison of the clinical and pathological characteristics between benign and malignant tumors is presented in Table III.

The results indicated that there were no statistically significant differences (P>0.05) between benign and malignant pulmonary tumors in terms of demographic characteristics, clinical manifestations and tumor locations. However, regarding

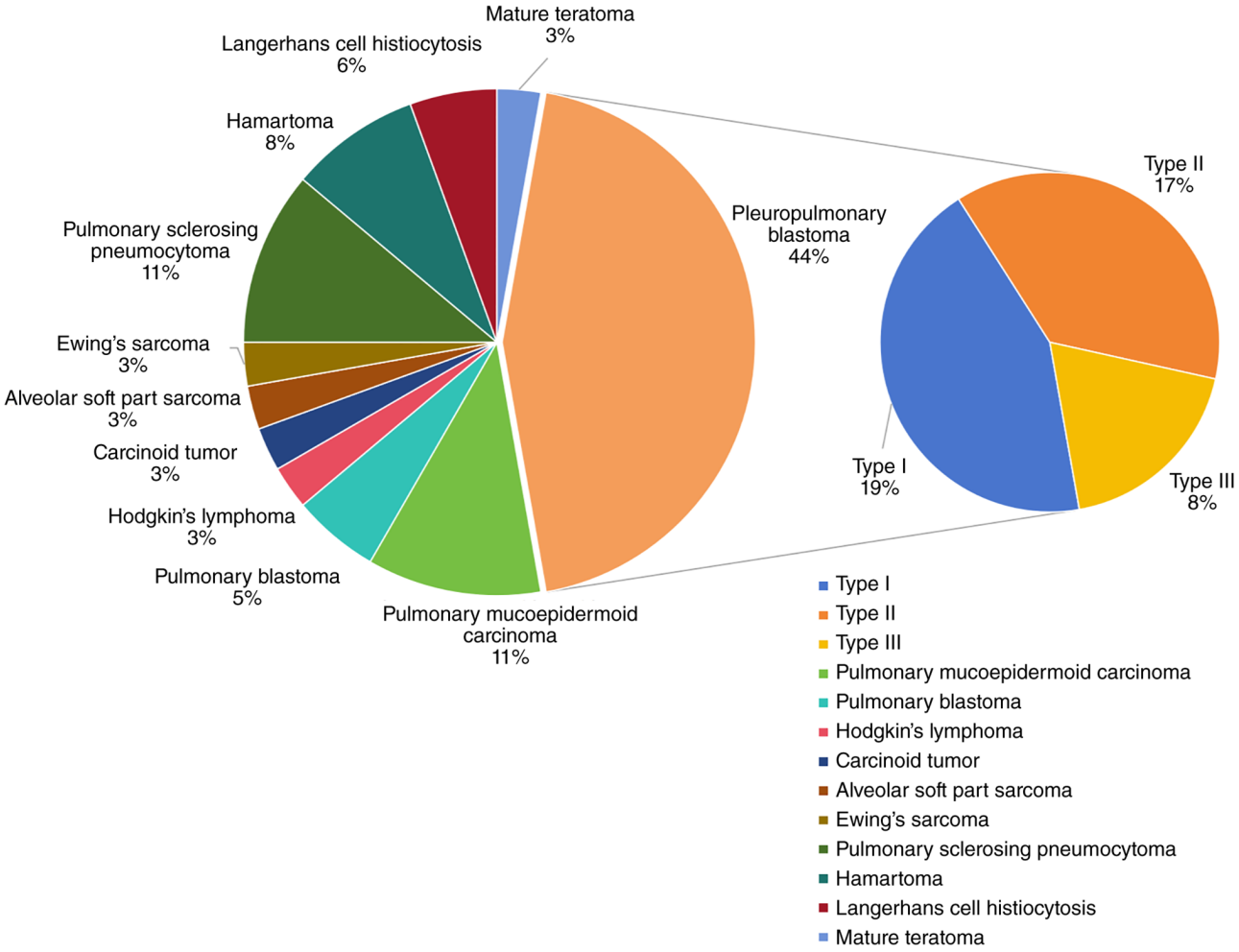

Figure 1. Pathological types of primary pulmonary tumors (n=36) identified in the present study.

imaging findings, the maximum diameter of malignant tumors ranged from 3.0-7.0 cm (median: 5.5 cm), which was markedly larger than that of benign tumors, with a range of 1.7-3.5 cm (median: 2.5 cm). The incidence of associated pleural effusion in malignant tumors was 30.77%, markedly higher than in benign tumors (0%). All eight patients with pleural effusion were diagnosed with malignant tumors, including six patients of PPB, one of pulmonary mucoepidermoid carcinoma and one of Ewing's sarcoma. Pathologically, 41.67% of malignant tumors exhibited significant cellular atypia or mitotic activity, compared to 0% in benign tumors. The Ki-67 index for malignant tumors (9.63-70.0%; median: 37.5%) was markedly higher than that of benign tumors (1.38-26.25%; median: 2.0%). The specific histological features and typical immunohistochemical results of benign and malignant tumors are presented in Figs. 2 and 3. Regarding treatment, 69.23% of patients with malignant tumors received chemotherapy, a proportion markedly higher than the 0% observed in patients with benign tumors. All differences were statistically significant ($P<0.05$).

PPB constituted the largest proportion in the present study. A comparative analysis of the clinical and pathological characteristics of type II and III (non-cystic) PPB vs. other malignant non-cystic pulmonary tumors is presented in Table IV. The age at diagnosis for pediatric patients with PPB (range: 2.0-4.0 years; median: 3.0 years) was markedly younger than that for patients with other malignant pulmonary tumors (range: 7.5-13.0 years; median: 10.0 years). The mean maximum tumor diameter in PPB was 7.86 cm (SD: 2.19), which was markedly larger than that of other malignant pulmonary tumors (mean: 2.44 cm, SD: 1.76). The proportion of multiple lesions was lower in PPB (0% vs. 62.50%). PPB exhibited a markedly higher Ki-67 index (mean: 66.67%, SD: 17.50) compared to other malignant pulmonary tumors (mean: 13.88%; SD: 12.88). Furthermore, PPB had a markedly higher chemotherapy rate (88.89% vs. 37.50%). All differences were statistically significant ($P<0.05$).

A patient with Hodgkin's lymphoma was confirmed by ultrasound-guided biopsy and chemotherapy was administered. Another 35 patients underwent surgical intervention. Among them, 18 (51.43%) patients were treated with thoracoscopy and 11 (31.43%) with thoracotomy. Notably, six (17.14%) patients were initially treated with fiberoptic bronchoscopy and four of them subsequently required thoracotomy, while one required thoracoscopy. A total of 34 lobectomy or segmentectomy specimens, six bronchoscopy biopsy specimens (five of which were accompanied by lobectomy or segmentectomy specimens) and one specimen from an ultrasound-guided biopsy were obtained. Chemotherapy was administered to 16 (44.44%) patients, while two (5.56%) patients received a combination of chemotherapy and radiotherapy.

Table III. Comparison between benign and malignant tumors.

Characteristic	Benign (n=10)	Malign (n=26)	Z/χ^2	P-value
Demographic				
Age (year), [median, (P25, P75)]	6.5, (3.5, 10.5)	4, (2, 9.5)	1.193	0.241
Sex (F:M)	5:5	14:12	0	1
Clinical manifestation				
Fever, n (%)	4 (40)	13 (50)	0.027	0.868
Cough, n (%)	6 (60)	19 (73.08)	0.129	0.720
Dyspnea, n (%)	0 (0)	6 (23.08)	1.357	0.244
Chest pain, n (%)	1 (10)	5 (19.23)	0.028	0.868
Hemoptysis, n (%)	0 (0)	2 (7.69)		1
Swollen lymph nodes, n (%)	0 (0)	1 (3.85)		1
Localization				
Tracheal, n (%)	0 (0)	6 (23.08)	1.357	0.244
Multiplicity, n (%)	2 (20)	5 (19.23)	0	1
Imaging feature				
Maximum diameter (cm)	1.7 (2.5, 3.5)	5.5 (3, 7)	-2.26	0.022
Atelectasis, n (%)	1 (10)	6 (23.08)	0.175	0.676
Pleural effusion, n (%)	0 (0)	8 (30.77)	2.376	0.123
Pneumothorax, n (%)	1 (10)	0 (0)		0.278
Pathological feature				
Morphological characteristics[a], n (%)	0 (0)	15 (41.67)	7.659	0.006
Hemorrhage necrosis/Calcification, n (%)	4 (40)	14 (38.89)	0.554	0.457
Ki-67 index (%)	2 (1.38, 26.25)	37.5 (9.63, 70)	-2.466	0.012
Treatment				
Surgery, n (%)	10 (100)	25 (96.15)		1
Chemotherapy, n (%)	0 (0)	18 (69.23)	13.846	<0.001
Radiation, n (%)	0 (0)	2 (7.69)		1
Outcome				
Follow up time (years)	0.27 (1, 1.38)	1.5 (0.71, 3.04)	-1.243	0.220
Metastasis, n (%)	1 (10)	1 (3.85)		0.484
Recurrence, n (%)	0 (0)	3 (11.54)		0.545

[a]Morphological characteristics: with marked atypia and/or mitotic figures.

Follow-up data were available in 33 of the 36 patients, with a median follow-up duration of 15.0 months (range: 8.5-36 months). Three patients experienced recurrences, which occurred between 9 and 13 months following the initial diagnosis. The conditions of three patients with tumor recurrence were as follows: The first pediatric patient of Type III PPB was diagnosed 6 years and 8 months ago, with recurrence 5 years and 7 months later. After initial surgery and four cycles of chemotherapy, the patient underwent a second surgery followed by eight additional cycles of chemotherapy. Computed tomography (CT) follow-up scans indicated a growing solid lesion in the lower right lobe. The parents refused further surgery and the child remains under follow-up. The second pediatric patient with Ewing sarcoma with EWSR1-FLI1 gene fusion was diagnosed 17 months ago and experienced recurrence for eight months. The patient received preoperative cyclophosphamide, doxorubicin, vincristine chemotherapy, followed by alternating ifosfamide, etoposide/vincristine, doxorubicin, cyclophosphamide chemotherapy and surgery. The presence of new lesions on follow-up CT scans nine months after treatment suggests the possibility of metastasis. The third patient was diagnosed with pulmonary blastoma and experienced recurrence one year after the initial diagnosis. The patient received chemotherapy and subsequently lost to follow-up. No fatalities were found among the pediatric patients.

Discussion

Primary pulmonary tumors are rare in children and their diagnosis and treatment can be challenging due to their nonspecific symptoms at the time of presentation (10). Studies have reported that the most prevalent primary malignant pulmonary tumors in children are carcinoid tumors and PPB (4,11). However, the histologic distribution of tumors has been markedly altered since the previous analysis, with an increased proportion of patients exhibiting the blastoma

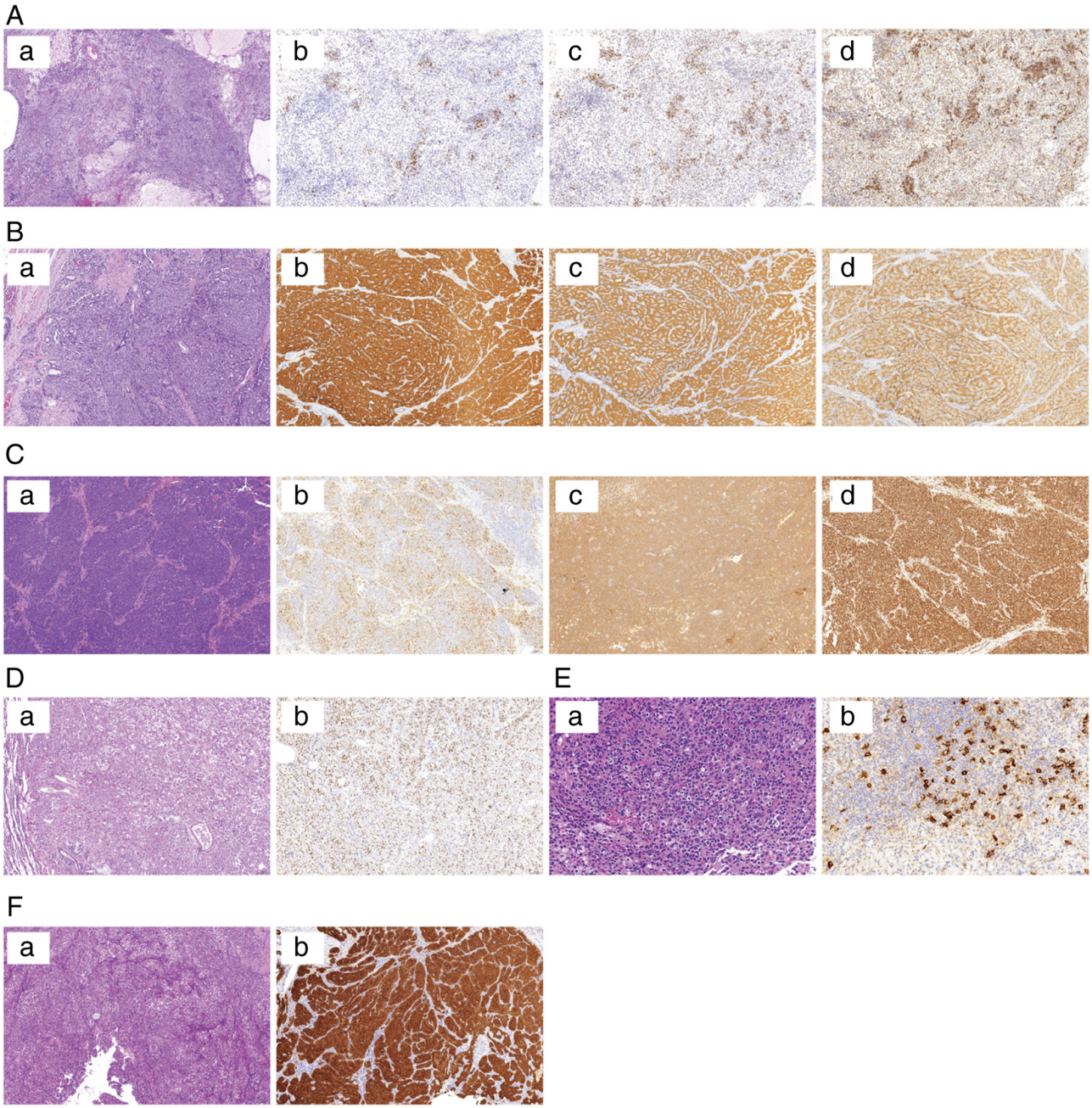

Figure 2. Six types of primary malignant pulmonary tumors and their typical immunohistochemical positive markers. (A) Pleuropulmonary blastoma. Tumor cells were diffusely distributed in oval and spindle shapes with significant atypia. Giant cells, mitotic figures, chondroid and striated muscle differentiation were observed. (Aa; magnification, x5) The stroma exhibited mucinous degeneration, hemorrhage and necrosis. Positive expression of (Ab; magnification, x10) myogenin, (Ac; magnification, x10) MyoD1 and (Ad; magnification, x10) desmin. (B) Carcinoid tumor. (Ba; magnification, x10) Tumor cells were arranged in a glandular pattern, with round nuclei and eosinophilic cytoplasm. (Bb; magnification, x10) Positive expression of synaptophysin, (Bc; magnification, x10) CK and (Bd; magnification, x10) chromogranin A. (C) Ewing's sarcoma. (Ca; magnification, x10) Tumor cells were round with deeply stained nuclei and certain cells exhibited pleomorphism. Multiple mitotic figures were observed. The cells were distributed in sheets, with some forming rosette-like clusters. Focal areas exhibited calcification and necrosis. Positive expression of (Cb; magnification, x10) NKX2-2, (Cc; magnification, x10) CD99 and (Cd; magnification, x10) FLI-1. (D) Alveolar soft part sarcoma. (Da; magnification, x10) Tumor cells were arranged in nests and acinar patterns, with abundant cytoplasm. Certain cells exhibited eosinophilic and clear cytoplasm. (Db; magnification, x10) Positive for TFE3. (E) Hodgkin's lymphoma. (Ea; magnification, x45) The tumor cells were round or oval, with some depicting binucleation. Nucleoli were prominent and the stroma exhibited significant eosinophilic granulocyte infiltration. (Eb; magnification, x30) Positive for CD30. (F) Pulmonary mucoepidermoid carcinoma. Tumor cells were arranged in nests or glandular patterns, with abundant cytoplasm. (Fa; magnification, x10) The regions were rich in mucin and mitotic bodies were readily observed. (Fb; magnification, x10) Positive for CK7. MyoD1, Myogenic Differentiation 1; CK Cytokeratin; NKX2-2, NK2 Homeobox 2; CD99, Cluster of differentiation 99; FLI-1, Friend leukemia integration 1; TFE3, Transcription Factor Enhancer 3.

and mucoepidermoid histological subtypes (12-13). The distribution of pathological types of primary pulmonary tumors in the present study was consistent with this trend, with PPB being the most prevalent, accounting for 44.44%, followed by mucoepidermoid carcinoma, which constitutes 11.11%.

In this cohort of primary pulmonary tumors, malignant tumors accounted for 72.22%, consistent with the previously

Table IV. Comparison between type II and III (non-cystic) PPB and other malignant non-cystic pulmonary tumors.

	PPB type II and III (n=9)	Other tumors (n=8)	Total (n=17)	Z/χ^2	P-value
Demographic					
Age (year)	3 (2, 4)	10 (7.5, 13)	4 (2.5, 10)	-3.344	<0.001
Sex (F:M)	5:4	4:4	9:8	0	1
Clinical manifestation					
Fever, n (%)	5 (55.56)	4 (50)	9 (52.94)	0	1
Cough, n (%)	6 (66.67)	7	13 (76.47)	0.192	0.661
Dyspnea, n (%)	2(22.22)	1 (12.50)	3 (17.65)	0	1
Chest pain, n (%)	3 (33.33)	1 (12.50)	4 (23.53)	0.192	0.661
Hemoptysis, n (%)	0 (0)	2 (25)	2 (11.76)		0.206
Swollen lymph nodes, n (%)	0 (0)	1 (12.50)	1 (5.88)		0.471
Imaging feature					
Multiplicity, n (%)	0 (0)	5 (62.50)	5 (29.41)	5.243	0.022
Maximum diameter (cm)	7.86±2.19	2.44±1.76	5.15±3.40	0.597	<0.001
Pleural effusion, n (%)	4 (44.44)	2 (25)	6 (35.29)	0.108	0.742
Atelectasis, n (%)	1 (11.11)	4 (50)	5 (29.41)	1.496	0.221
Pathological feature					
Ki-67 index (%)	66.67±17.50	13.88±12.88	41.82±31.04	7.002	0
Treatment					
Surgery, n (%)	9 (100)	7	16 (94.12)		0.471
Chemotherapy, n (%)	8 (88.89)	3 (37.50)	11 (64.71)	2.906	0.088
Radiation, n (%)	0 (0)	2 (25)	2 (11.76)		0.206

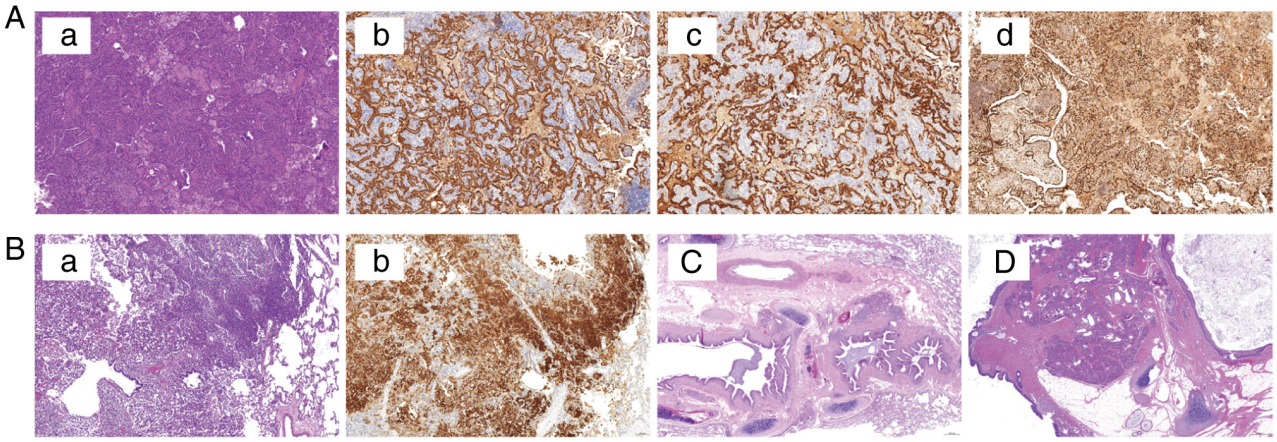

Figure 3. Four types of primary benign pulmonary tumors and their typical immunohistochemical positive markers. (A) Pulmonary sclerosing pneumocytoma. Tumor cells were arranged in a papillary pattern, covered by cuboidal epithelium. The stroma contained round and spindle-shaped cells, with certain cells exhibiting clear cytoplasm. (Aa; magnification, x10) Focal collagen degeneration was observed and foamy histiocytes were scattered in localized areas. Positive expression of (Ab; magnification, x10) CK, (Ac; magnification, x10) CK7 and (Ad; magnification, x10) TTF-1. (B) Langerhans cell histiocytosis. (Ba; magnification, x10) The tissue revealed sheets of eosinophilic cytoplasm, tumor cell proliferation with nuclear grooves and infiltration by numerous eosinophils, lymphocytes and histiocytes. Positive expression of (Bb; magnification, x10) CD1a. (C; magnification, x2.5) Hamartoma. Multiple dilated and distorted bronchi were observed, with mucus plugs inside. Surrounding structures included cartilage, bone-like tissue and adipose tissue. (D; magnification, x3.5) Mature teratoma. (D) Tissue components, including skin and its appendages, respiratory epithelium, pancreas and cartilage, were observed. CK Cytokeratin; TTF-1, Thyroid Transcription Factor-1; CD, Cluster of differentiation.

reported range of 65-76% (2). These primary tumors, which predominantly present as pulmonary nodules, pose a significant diagnostic challenge in children due to their diverse appearances and the absence of established criteria to distinguish benign from malignant lesions. The present study compared the demographic characteristics, clinical manifestations, imaging findings, pathological findings, treatment approaches and prognosis of benign and malignant primary pulmonary tumors in children. The results indicated that differentiating between benign and malignant tumors is challenging when based solely on demographic characteristics and clinical manifestations. However, imaging findings, including tumor

size and the presence of pleural effusion, can provide valuable diagnostic insights. Studies have demonstrated that pleural effusion is prevalent in pulmonary tumors and is frequently indicative of malignant spread to pleural membranes, which is associated with a poor prognosis (14-15). Therefore, in clinical practice, when pleural effusion is observed in association with pulmonary tumors, it should be closely monitored for potential malignant progression and given due clinical attention. Pathologically, tumors characterized by significant cellular atypia, prominent mitotic activity and a high Ki-67 index are strongly associated with a higher likelihood of malignancy.

In the present study, PPB was the most prevalent malignant pulmonary tumor; however, its misdiagnosis rate remains high in clinical practice. A study demonstrates that up to 51.2% of patients are initially misdiagnosed with non-tumorous conditions, with misdiagnosis rates of 100, 58.3 and 39.1% for type I, II and III PPB, respectively (16). Therefore, it is important to summarize and refine the differential diagnosis of PPB. The present study specifically compared type II and III PPB with other non-cystic malignant pulmonary tumors due to the substantial proportion of non-cystic malignant tumors. The findings revealed that a younger age at diagnosis (median: 36 months), solitary tumor presentation (100%), larger tumor diameter (7.857±2.193 cm) and higher Ki-67 index (66.67±17.5) are distinguishing features of PPB when compared to other non-cystic malignant pulmonary tumors. In a report involving 350 PPB patients, the median age at diagnosis for type II and III PPB was 37 months (17). Additionally, 62.76% of patients presented with tumors larger than 10.0 cm and 85.47% had unifocal type II or type III PPB. In the present study, all pediatric patients of PPB were unifocal, which can be attributed to the smaller sample size. Other findings were consistent with the results of the present study. Accordingly, it can be inferred that, prior to pathological diagnosis, in children suspected of having a non-cystic pulmonary tumor, a younger diagnostic age and a solitary larger-diameter tumor are more indicative of PPB.

Recent advances in molecular biology have markedly improved the diagnosis and classification of pulmonary tumors (18). The 2021 World Health Organization Classification of Lung Tumors underscored that while morphology remains the foundation of diagnosis, immunohistochemistry and molecular techniques are essential adjuncts (19). It highlighted the critical need to integrate molecular characteristics and genetic mutations with histopathology to improve diagnostic accuracy and prognostic evaluation. A study involving 74 patients with pulmonary tumors found that all patients exhibited genetic mutations, suggesting that these alterations play a key role in tumor progression (8). Furthermore, p53 expression varies across different types of pulmonary tumors, with high levels markedly associated with tumor progression and poor prognosis (20). Notably, in the present study, a Type III PPB case with recurrence exhibited strong p53 positivity (++); however, given that p53 immunohistochemistry was performed in only two cases (100% positive), no statistically significant correlation can be established between p53 expression and prognosis. Definitive assessment of TP53 mutational status requires sequencing confirmation, which was not available in the present study. Therefore, a multidisciplinary approach to personalized treatment and improved outcomes is necessary for the accurate diagnosis of pulmonary tumors, which includes the integration of molecular pathology in addition to clinical and imaging findings.

The present study had several limitations. First, the median follow-up period of 15 months (range: 8.5-36 months) is relatively short for pediatric oncology studies and long-term survival outcomes require further investigation. Second, the lack of comprehensive molecular diagnostics is a significant limitation of the present study. Future studies should incorporate DICER1 mutation analysis for all PPB cases and TP53 sequencing to correlate with p53 immunohistochemistry expression patterns.

In summary, primary pulmonary tumors in children lack specific clinical manifestations. Imaging and pathological characteristics are valuable in the differential diagnosis of benign and malignant tumors. Younger age at diagnosis, solitary lesions and larger non-cystic tumors are indicative of a higher likelihood of PPB. The integration of molecular diagnostics is an important direction for future research to improve early detection and treatment outcomes.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

LFT, WGZ and CY conceived and designed the study and reviewed the manuscript. YC drafted the initial manuscript. WZG, CY and TYY analyzed the data and improved the later revision of the article. YH, SJM, ML and XZW participated in the data collection. LFT, WZG and CY confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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