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Clinical Analysis of Primary Tracheobronchial Tumors in Children and Evaluation of the Predicting Models for Mucoepidermoid Carcinoma*

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[Abstract] Objective: To determine the clinical characteristics and prognosis of primary tracheobronchial tumors (PTTs) in children, and to explore the most common tumor identification methods. **Methods:** The medical records of children with PTTs who were hospitalized at the Children's Hospital of Chongqing Medical University from January 1995 to January 2020 were reviewed retrospectively. The clinical features, imaging, treatments, and outcomes of these patients were statistically analyzed. Machine learning techniques such as Gaussian naïve Bayes, support vector machine (SVM) and decision tree models were used to identify mucoepidermoid carcinoma (ME). **Results:** A total of 16 children were hospitalized with PTTs during the study period. This included 5 (31.3%) children with ME, 3 (18.8%) children with inflammatory myofibroblastic tumors (IMT), 2 children (12.5%) with sarcomas, 2 (12.5%) children with papillomatosis and 1 child (6.3%) each with carcinoid carcinoma, adenoid cystic carcinoma (ACC), hemangioma, and schwannoma, respectively. ME was the most common tumor type and amongst the 3 ME recognition methods, the SVM model showed the best performance. The main clinical symptoms of PPTs were cough (81.3%), breathlessness (50%), wheezing (43.8%), progressive dyspnea (37.5%), hemoptysis (37.5%), and fever (25%). Of the 16 patients, 7 were treated with surgery, 8 underwent bronchoscopic tumor resection, and 1 child died. Of the 11 other children, 3 experienced recurrence, and the last 8 remained disease-free. No deaths were observed during the follow-up period. **Conclusion:** PTT are very rare in children and the highest percentage of cases is due to ME. The SVM model was highly accurate in identifying ME. Chest CT and bronchoscopy can effectively diagnose PTTs. Surgery and bronchoscopic intervention can both achieve good clinical results and the prognosis of the 11 children that were followed up was good.
Key words: tracheobronchial tumors; children; bronchoscopy; clinical characteristics; support vector machine model

Primary tracheobronchial tumors (PTTs) are extremely rare and account for only 0.2% of all cancers in children, and therefore can be easily misdiagnosed[1]. Currently, few reports have described the characteristics of patients with these tumors, making their clinical presentation, treatment, and outcomes unclear.

In this study, we retrospectively reviewed the clinical data of children hospitalized with pathologically confirmed PTTs at the Children's Hospital of Chongqing Medical University from January 1995 to January 2020 who were then followed up by telephone in July 2020. We established machine learning models to predict the type of PTTs to assist with clinical decision-making and to help doctors develop effective treatment plans to reduce the pain of surgery in children. However, as the number of PTTs cases in children is small, we predicted the probability of the most common tumor types using three different models.

1 MATERIALS AND METHODS

The medical records of all children diagnosed with PTTs from January 1995 to January 2020 at the Respiratory Department, Thoracic Surgery Ward and the Ear-nose-throat (E.N.T) Department of the Children's Hospital of Chongqing Medical University were retrospectively reviewed. The data included demographic characteristics, clinical presentation, results of chest X-rays and computed tomography

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(CT) scans, pathological diagnosis, lesion location, treatment, follow-up, and clinical outcomes. The patients were included in the analysis if they were aged <18 years and had an intra-cavitary lesion of the trachea or large bronchus confirmed by chest CT and bronchoscopy, with pathology confirmed by biopsy[2, 3]. Patients with lung and laryngeal cancer or metastatic tracheobronchial tumors were excluded. The clinical manifestations and imaging characteristics of the patients were used to establish a database and construct an identification model for mucoepidermoid carcinoma (ME), the most common tracheobronchial tumor type. We used Gaussian naïve Bayes, support vector machine (SVM) and decision tree approaches to build the three models, respectively.

2 RESULTS

2.1 General Information

During the study period, 16 children (10 boys and 6 girls with a median age of 9.3 years; range 3–15 years) were diagnosed with PTTs. Of these patients, 5 (31.3%) exhibited ME, 3 (18.8%) inflammatory myofibroblastic tumors (IMT), 2 (12.5%) sarcomas, 2 (12.5%) papillomatosis, and 1 (6.3%) each with carcinoid carcinoma, adenoid cystic carcinoma (ACC), hemangioma, and schwannoma, respectively (table 1 and table 2). The personal and family history of the 16 children were unremarkable.

2.2 Clinical Manifestations

The main clinical manifestations in the 16 children were cough (81.3%), breathlessness (50%), wheezing (43.7%), progressive dyspnea (37.5%), hemoptysis (37.5%), and fever (25%) (table 3). Other rare manifestations included chest pain, weight loss, hoarseness, and dysphagia. The average delay between the appearance of symptoms and the initial diagnosis was 10 months (range, 7 days to 5 years). Tumors located in the trachea were more likely to present with dyspnea, hoarseness, dysphagia, or other neck compression symptoms.

2.3 Radiological Examinations

Most of these children underwent chest CT with enhancement and airway reconstruction. The chest CT usually showed bronchial luminal obstruction in the lesion with soft tissue shadowing, with or without bronchiectasis, atelectasis, or compensatory emphysema (fig. 1). The most common complications were atelectasis (9/16, 56.3%), followed by bronchiectasis (4/16, 25%) and emphysema (2/16, 12.5%). The maximum tumor diameters ranged from 5 to 40 mm. A total of 7 tumors were located in the left main bronchus, 3 in the right main bronchus, and 6 in the trachea. PET/CT scanning of 1 patient with ME (moderately malignant) and carcinoid carcinoma revealed an standard uptake value (SUV) in the primary lesion that was significantly higher than the SUV in the surrounding tissue. These findings were consistent with the manifestations of a malignant tumor[4].

2.4 Treatments

There were 16 patients. One child died during hospitalization due to the sudden onset of extreme dyspnea. Bronchoscopy revealed complete obstruction of the left main bronchus and 2/3 of the right bronchus by the tumor. An autopsy confirmed the diagnosis of rhabdomyosarcoma. A total of 15 children underwent bronchoscopy (fig. 2) and biopsy. Seven children were treated with surgery. Three (19%) underwent sleeve lobectomy, 2 of which involved left upper sleeve lobectomies and 1 involved a right middle sleeve lobectomy. One (6%) patient underwent a right middle and lower lobectomy, and 3 (19%) underwent tracheal sleeve lobectomies with end-to-end anastomosis, including 1 patient who also underwent partial thyroidectomy. The remaining 8 children underwent local tumor resection via bronchoscopy, 5 (31%) of which underwent tumor resection alone, and 2 (13%) underwent tumor resection followed by chemotherapy. Surgery was successful in all 15 patients.

2.5 Follow-Up and Patient Outcomes

Of the 15 children, 4 cases were not followed up, and 2 patients were lost to follow-up after 5 and 60 months. The remaining 9 children were successfully contacted by telephone in July 2020. The average duration of follow-up was 46 months (range 5–182 months). One child (patient No. 3) experienced tumor recurrence within 2 months after tracheal sleeve resection. This patient underwent 2 operations for local tumor resection with no recurrence after 18 months. However, this patient still reported episodes of wheezing after strenuous activity. Two children with intratracheal papillomatosis (patient No. 13 and 14) experienced tumor recurrences 6–8 times and underwent repeated local tumor resection. These patients had no new recurrences at the last follow-up, but both patients reported hoarseness. Two patients (patient No. 2 and 4) who underwent local tumor resection plus chemotherapy are still receiving chemotherapy. Patient No. 2 was still being treated with ifosfamide, etoposide, vindesine, methotrexate, and prednisone. The remaining children showed no evidence of disease recurrence and no deaths were reported during the follow-up period.

2.6 The Recognition Model of ME

ME carcinoma was the most common tracheobronchial tumor in children. A total of 16 characteristic parameters were selected to construct a database. These parameters included 10 clinical manifestations (cough, fever, progressive dyspnea, weight loss, wheezing, dysphagia, breathlessness, hemoptysis, chest pain, and hoarseness), 3 tumor locations (left bronchus, right bronchus, and trachea),

Table 1 The clinical profiles and outcomes of 16 patients with primary tracheobronchial tumors

Patient no.	Age/ sex	Year of diagnosis	Symptoms	Symptom duration (months)*	Pathology	Location	Size (mm)	Imaging characteristics	Treatment methods	Follow-up (months)	Recurrence	Outcome
1	4/B	2016	Cough, fever, dyspnea, weight loss	0.4	IMT	LM	16.3×4	Atelectasis	Upper sleeve lobectomy	48	No	NED
2	5/B	2020	Cough, fever, wheezing	1	IMT	LM	26.8×10.2	Atelectasis, bronchiectasis	Tumor resection+ chemotherapy	6	No	NED
3	11/B	2018	Dyspnea, dysphagia	4	IMT (ALK positive)	T	18.4×16.5×14.5	Normal	Trachea sleeve resection	22	Yes	Wheezing after strenuous exercise
4	12/B	2019	Cough, wheezing, breathlessness	2	ME (moderate malignancy)	LM	25.4×13.2×12.8	Atelectasis, emphysema	Tumor resection+ chemotherapy	5	No	NED
5	10/G	2019	Cough, wheezing, breathlessness, hemoptysis	10	ME (low-grade malignancy)	RM	23.8×19.2×40.6	Emphysema	Tumor resection	16	No	NED
6	9/B	2016	Cough, fever, breathlessness, dyspnea	1	ME (low-grade malignancy)	LM	13×16×12	Atelectasis, bronchiectasis	Tumor resection	44	No	NED
7	14/B	2008	Cough, breathlessness, hemoptysis	60	ME (low-grade malignancy)	LUL	35×25	Atelectasis, emphysema, bronchiectasis	Upper sleeve lobectomy	Lost	NA	NA
8	9/B	2013	Cough, hemoptysis	5	ME	RIL	37.5×16.3×17.4	Atelectasis	Middle sleeve lobectomy	Lost	NA	NA
9	13/G	2018	Cough, wheezing, breathlessness, hemoptysis	24	Carcinoid	RIL	7.3×22.6	Atelectasis	Middle and lower lobectomy	19	No	NED
10	13/B	2016	Cough, fever, wheezing, breathlessness, dyspnea	1	ACC	T	13.2×11.5×24.7	Bronchiectasis	Trachea sleeve resection	Lost	NA	NA
11	15/B	2018	Cough, breathlessness, hemoptysis, chest pain	1	Schwannoma	T	12.7×8.2	Normal	Trachea sleeve resection+ right partial thyroidectomy	25	No	NED
12	8/G	2015	Cough, hemoptysis	0.2	Hemangioma	T	5×3.6	Normal	Tumor resection	76	No	NED
13	3/G	2002	Hoarseness, dyspnea	24	Papillomatosis	T	10×10×10	Normal	Tumor resection	60	Yes	Shortness of breath, hoarseness
14	4/B	2003	Wheezing, breathlessness	24	Papillomatosis	T	10×5	Atelectasis	Tumor resection	182	Yes	NED, hoarseness
15	6/G	1995	Cough, wheezing, breathlessness, dyspnea	1	Rhabdomyosarcoma	LM	20×18	Atelectasis	Dead	NA	NA	NA
16	13/G	2016	Cough, hemoptysis, chest pain	6	Synovial sarcoma	RM	7.7×16.6	Normal	Tumor resection	Lost	NA	NA

G: girl; B: boy; ME: mucoepidermoid tumor; ACC: adenoid cystic carcinoma; IMT: inflammatory myofibroblastic tumor; ALK: anaplastic lymphoma kinase; LM: left main stem bronchus; LUL: left upper lobe; RM: right main stem bronchus; RIL: right intermiddle lobe; T: trachea; NED: no evidence of disease; NA: not applicable. *Time from symptom appearance to initial diagnosis

Table 2 The characteristics of the various types of tracheobronchial tumors

Parameters	Malignant tumors				Benign tumors				Total
	ME	Sarcoma	ACC	Carcinoid	IMT	Papillomatosis	Schwannoma	Hemangioma	
n	5	2	1	1	3	2	1	1	16
Left bronchus /trachea/ right bronchus	3/0/2	1/0/1	0/1/0	0/0/1	2/1/0	0/2/0	0/1/0	0/1/0	7/6/3
Sex (B/G)	4/1	0/2	1/0	0/1	3/0	1/1	1/0	0/1	10/6
Average age (years)	10.8	9.5	13	13	6.7	3.5	15	8	9.3
Atelectasis	4	1	0	1	2	1	0	0	9
Death	0	1	0	0	0	0	0	0	1
Recurrence	0	0	0	0	1	2	0	0	3
Follow-up	3	0	0	1	3	2	1	1	11

ME: mucoepidermoid carcinoma; ACC: adenoid cystic carcinoma; IMT: inflammatory myofibroblastic tumor ; B: boy; G: girl

Table 3 The main symptoms reported in the 16 pediatric patients with tracheobronchial tumors

Symptoms	*n* (percentage)
Cough	13 (81.3%)
Breathlessness	8 (50%)
Wheezing	7 (43.8%)
Progressive dyspnea	6 (37.5%)
Hemoptysis	6 (37.5%)
Fever	4 (25%)
Chest pain	2 (12.5%)
Dysphagia	1 (6.3%)
Weight loss	1 (6.3%)
Hoarseness	1 (6.3%)
Asymptomatic	0

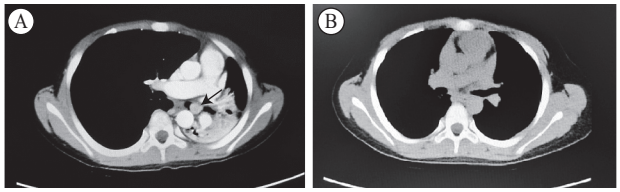

Fig. 1 Computed tomography (CT) scans of patient No. 6
The (A) image shows a lesion located in the left main stem bronchus (black arrow) that obstructed the distal bronchus and caused left upper lung atelectasis. The (B) image on the right shows airway patency and the disappearance of atelectasis 3 months after tumor resection.

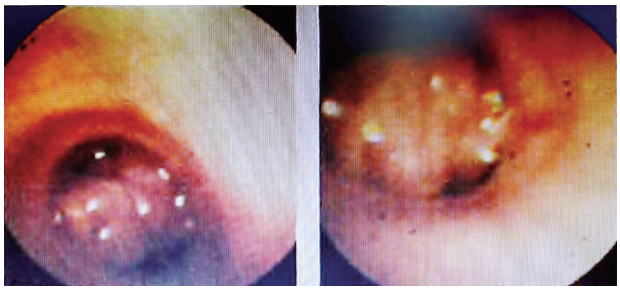

Fig. 2 Bronchoscopy of the left main bronchial space-occupying lesion of patient No. 6 (before surgery)

and 3 imaging features (atelectasis, bronchiectasis, and emphysema).

The Gaussian naïve Bayes, SVM and decision tree models were used to predict mucoepidermoid carcinoma (table 4). All cases were randomly assigned to a training set (11 cases) and a test set (5 cases). The training set was used to select characteristics and to construct recognition models. The test set was used to evaluate the prediction performance of the models. The area under the receiver operating characteristics (ROC) curve (AUC), accuracy, and the F1-score were used to evaluate the models. The SVM model exhibited the best performance, followed by the decision tree and the Gaussian naïve Bayes model. The SVM model used the sklearn python library and the kernel was linear. The relaxation coefficient was 6.13 and the other parameters were the default settings. The accuracy, AUC, and F1-score of the test set were all 1 (fig. 3), indicating that the model had good predictive efficiency in the test set.

3 DISCUSSION

PTTs are very rare malignancies in children. In

Table 4 Summary of the evaluation indices of the three models

Measure	Gauss naïve Bayes	Support vector machine (linear)	Decision trees
Accuracy	0.60	1.00	0.80
F1-score	0.60	1.00	0.78
AUC	0.58	1.00	0.75

AUC, area under the receiver operating characteristics curve. F1-score is a weighted average of the precision and recall.

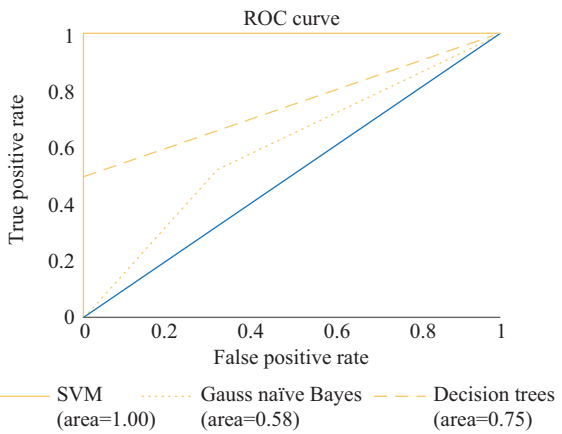

Fig. 3 The ROC curve for the three machine learning models
The area under the receiver operating characteristics (ROC) curve (AUC) of the SVM was 1.

this study, we found that the most common tumor was ME (31.3%) and that there was a higher rate of these tumors in boys than in girls. In contrast to data from an international study[5], we found that ME carcinoma is the most common type of PTT reported in China, which accounts for up to 74% of cases[6]. The data indicated that ME has a high incidence rate and is a particularly important form of cancer in children. The SVM model exhibited a high accuracy in identifying ME. In the absence of invasive pathological biopsy, this model may be used to analyze clinical data from patients with tracheobronchial tumors and can help to identify the types of tumor in patients. This approach may be particularly useful to inform clinical decision-making and provides an important reference for follow-up treatments. However, due to the small number of cases in our group, the model showed some instability and requires further validation in larger patient cohorts.

No specific respiratory symptoms are present during the early stages of the PPTs[1]. The incidence of specific symptoms, including hemoptysis and chest pain, are similar in children and adults[6], whereas non-specific symptoms such as fever, cough, and wheezing are more common in children. The X-rays of the 16 children identified lung infections in 7 cases, whereas the remaining 9 were negative. The misdiagnoses of PPTs had occurred due to pneumonia, asthma, or foreign bodies. Also, 1 child was misdiagnosed with tuberculosis for 5 years. Finally, these children were diagnosed with PTTs based on chest CT and bronchoscopy. From table 1, it can be seen that the study period was very long, up to 25 years, and that the number of confirmed cases increased significantly in the last 5 years. The rate of misdiagnosis of PTTs decreased gradually over time along with the time from the appearance of symptoms to a correct diagnosis. These trends in the data may be due to the increased use of chest CT and bronchoscopy. Chest CT can assess the size and location of lesions, the extent of infiltration into the surrounding tissues, the enlargement of mediastinal lymph nodes, and the involvement of the lung parenchyma[1, 7]. The high calcification rate (50%) seen in ME[8] can also be confirmed by CT. Bronchoscopy can visualize the location, shape, and size of the lesion, enabling biopsies to determine the nature of the lesion. However, bronchial lavage has a low positivity rate[9].

Surgery is the most common treatment for PTT in children[10] and sleeve lobectomy is often the preferred approach that is used to preserve lung function[1, 5, 6]. The benefits of adjuvant radiotherapy and chemotherapy are unclear and thus these treatments are not commonly used. Chemotherapy is associated with lower long-term survival rates and a poor quality-of-life after treatment[11]. However, chemotherapy and radiotherapy are still recommended for children with recurrent tumors[7], and radiotherapy is a viable option for patients with positive surgical margins[12]. Studies of targeted therapy for PTT have shown that recurrent respiratory papillomatosis responds well to bevacizumab[13]. Also, adjuvant treatment with ALK inhibitors such as cyclozolidinib can improve the prognosis of children with IMT and partial ALK gene rearrangement[14-16].

In addition to surgical resection, bronchoscopic intervention is an effective treatment for PTT[9]. However, endoscopic resection has several limitations including a high risk of transmural injury, an inability to coagulate larger diameter vessels, and a risk of airway tree dislocation[17]. CT angiography before fibrilloscopic intervention showed that 2 patients in the current cohort had large vessels deep within the tumor. After consultation with a cardiologist to reduce the risk of bleeding, both patients underwent minimally invasive vessel closure. In addition to the higher intraoperative risk, the recurrence rate was higher after local resection compared to surgical treatment. In total, 43% of the patients who underwent local resection experienced tumor recurrence during the follow-up period[6]. As some of these patients later required tracheal cricotomy, single local tumor resection through bronchoscopy is not recommended. At present, bronchoscopy is mainly used to assess the degree of airway narrowing, to obtain biopsies, and to perform temporary palliative treatments such as deburring, lavage, or Argon plasma coagulation (APC) plus cryotherapy[7] in patients with unresectable lesions. The use of bronchoscopy in treatment can reduce airway obstructions and improve the quality-of-life for patients.

Several factors are known to affect the prognosis of children with PTT, including histologic classification, pathologic grade, tumor size, lymph node status, distant metastasis, and the extent and ability of surgery[18–20]. Of these factors, the pathologic type of disease is the most important factor[20]. ME can be classified as a low-, intermediate-, or high-grade tumor[21, 22]. The Adult Tracheobronchial ME Study reported that the 5-year survival rate of patients with low-grade ME was 57%, whereas the survival rate of patients with high-grade ME was significantly lower[22, 23], with a 1-year survival rate of only 20%[19]. The study also showed significantly higher rates of survival in patients who had undergone surgery compared to those who did not undergo surgery. In contrast, the 5-year survival rate of children with ME is estimated to be 95%. In this study, no deaths were reported in children with low- to intermediate-grade ME. However, patients with high-grade ME or distant metastases had the lowest survival rate. The presence of a (11; 19) (q21; p13) translocation is also associated with a good prognosis in children[19]. Except for one child in our cohort who was diagnosed with sarcoma and died during hospitalization, the prognosis of the 11 children who were followed up with

was good. Three patients experienced tumor recurrence, with 2 of them undergoing subsequent tracheotomy. We found that 3 of the patients who relapsed were all benign, especially those with papillomatosis who underwent multiple tumor resections. These findings were consistent with data reported in national and international studies[6, 24]. Patients with papillomatosis are prone to relapse but have a good prognosis. In this study, these patients remained well after a maximum follow-up of 182 months. The other 8 patients did not experience tumor recurrence after a maximum follow-up of 76 months. Guidelines suggest that bronchoscopy should be performed every 6 months for the first year and then annually thereafter[25].

In summary, pediatric PTT is a relatively rare disease with an insidious onset and an uncharacteristic clinical presentation[1, 7]. Increased tumor volume may cause narrowing of the trachea and bronchi. These symptoms, when combined with respiratory tract infection, can result in fever, cough, breathlessness, and wheezing. These conditions can be easily confused with bronchial foreign bodies, asthma, pneumonia, and other bronchial diseases leading to an incorrect or missed diagnosis[8, 26, 27]. The lack of definitive diagnosis can result in the need for chest CT and bronchoscopy, which can delay treatment. Consequently, the risk of extensive adhesions and the involvement of surrounding tissues, or even spread to distant airways can increase and worsen the prognosis[14, 16]. PTT should be considered in patients with chronic cough, wheezing, or progressive dyspnea who respond poorly to conventional treatment. A thorough examination of the respiratory tract by chest CT and bronchoscopy may reduce the likelihood of misdiagnosis and improve treatment and prognosis.

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Conflict of Interest Statement

The authors have no conflicts of interest related to this study.

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