The Laryngoscope

Pediatric Airway Tumors: A Report From the International Network of Pediatric Airway Teams (INPAT)

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Objective: Primary tracheobronchial tumors (PTTs) are rare heterogeneous lesions arising from any part of the tracheobronchial tree. Nonspecific symptoms may lead to delayed diagnosis that requires more aggressive surgical treatment. An analysis of cases collected by the International Network of Pediatric Airway Team was undertaken to ensure proper insight into the behavior and management of PTTs.

Methods: Patients <18 years of age with a histological confirmation of PTT diagnosed from 2000 to 2015 were included in this multicenter international retrospective study. Medical records, treatment modalities, and outcomes were analyzed. The patient presentation, tumor management, and clinical course were compared between malignant and benign histotypes. Clinical and surgical variables that might influence event-free survival were considered.

Results: Among the 78 children identified, PTTs were more likely to be malignant than benign; bronchial carcinoid tumor (n = 31; 40%) was the most common histological subtype, followed by inflammatory myofibroblastic tumor (n = 19; 25%) and mucoepidermoid carcinoma (n = 15; 19%). Regarding symptoms at presentation, wheezing (P = 0.001) and dyspnea (P = 0.03) were more often associated with benign growth, whereas hemoptysis was more frequently associated with malignancy (P = 0.042). Factors that significantly worsened event-free survival were age at diagnosis earlier than 112 months (P = 0.0035) and duration of symptoms lasting more than 2 months (P = 0.0029).

Conclusion: The results of this international study provide important information regarding the clinical presentation, diagnostic workup, and treatment of PTTs in children, casting new light on the biological behavior of PTTs to ensure appropriate treatments.

Key Words: Pediatric airway tumors, airway team, pediatric tracheobronchial tumors.

Level of Evidence: NA

***Laryngoscope*, 130:E243–E251, 2020**

INTRODUCTION

Pediatric primary tracheobronchial tumors (PTTs) represent a heterogeneous group of exceedingly rare tumors with an overall incidence of 0.0049 per 100 thousand children,[1] comprising only 0.2% of all tumors in this age group.[2,3]

Diagnosis is often delayed because of nonspecific clinical presentations showing variable symptoms that are usually mistaken for respiratory tract infections or asthma.[1,4–14]

Radical surgical resection seems to be the treatment of choice, whereas the endoscopic approach is recommended

Additional supporting information may be found in the online version of this article.

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Editor's Note: This Manuscript was accepted for publication on April 22, 2019.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.28062

only in highly selected cases depending on histological type and tumor location.[13,15,16]

Chemotherapy and radiotherapy are usually indicated only for the management of tumor relapse.[1,4–6,8,10,17]

To date, most of the literature comprises case reports or case series that mainly focus on each histological subtype.[3,6–10,12–14,18–35]

Because specific pediatric oncologic guidelines on preoperative workup, treatment, and follow-up are still lacking, the International Network of Pediatric Airway Teams (INPAT) has coordinated a large international cohort of PTT in children, including the entire Italian cohort collected by the *Tumori Rari in Età Pediatrica* (TREP) (Rare Tumors in Children), with a total of 14 institutions to provide a complete overview with regard to clinical presentation, diagnostic assessment, histological findings, and outcomes. Particular attention has been given to identifying the main prognostic factors, possibly influencing outcome and carefully evaluating treatment modalities. This is the largest series of pediatric PTTs ever reported in the literature.

MATERIALS AND METHODS

Patients

Patients younger than 18 years of age with histologically confirmed PTT diagnosed from January 2000 to December 2015 were included in this multicenter international retrospective study.

Medical records, treatment modalities, and outcomes were reviewed or retrieved when available; data were collected through special forms sent to every participating center.

Clinical presentation, tumor management, and event-free survival were compared between malignant and benign histotypes.

Hemangiomas, vascular malformations, and papillomatosis were excluded from this study, which focused on PTTs.

Clinical and surgical variables that might influence event-free survival were also considered.

Descriptive statistics were reported as absolute frequencies or percentages for qualitative data and as medians and minimum and maximum values for quantitative data.

Frequency data were analyzed using Pearson chi-square test, or Fisher exact test in cases of expected frequencies lower than 5.

Comparisons of quantitative data between two groups (benign vs. malignant lesions) were performed using the nonparametric Mann-Whitney U test, and comparisons of quantitative data among more than two groups (tumor histology) were performed by means of the nonparametric analysis of variance (Kruskal-Wallis test). To avoid multiple comparisons error, Bonferroni correction was applied when the comparison was related to more than two groups.

Incidence rates of death or disease progression were calculated and reported with their 95% confidence intervals (95% CI). Survival curves were drawn to assess disease-free survival, and time to the event was expressed as person-months.

Survival curves were constructed according to the Kaplan-Meier method and compared by the log-rank test. One of the survival curves compared disease-free survival in children with age at disease onset ≤112 months versus >112 months. This cutoff point was chosen by means of a statistical approach, the analysis of the receiver operating characteristic (ROC) curve, using as outcome variable the event-free status. The area under the ROC curve was 0.74 (95% CI: 0.63 – 0.83). Using the cutoff point of ≤112 months, the sensitivity and the specificity, both expressed as percentages, were 87.5% and 64.3%, respectively.

Finally, a Poisson regression model was fitted to evaluate the role of clinicopathological variables in influencing hazard ratios.

Statistically significant variables in the univariate analysis and clinically important variables were subsequently included in the multivariable analysis.

Quantitative variables were dichotomized using the cutoff value obtained by means of ROC curve analysis.

The following variables were considered: age at diagnosis (≤112 months vs. >112 months), symptom duration (≤2 months vs. >2 months), preoperative chemotherapy (yes vs. no), and postoperative chemotherapy (yes vs. no).

The likelihood ratio test was used for comparison, and a P value less than 0.05 was considered statistically significant. Statistica version 9.0 (StatSoft Corp., Tulsa, OK) and Stata version 7.0 (StataCorp, College Station, TX) were used for bivariate and multivariate analyses, and MedCalc version 5.0 (by Frank Schoonjans) was used for analysis of the ROC Curve.

RESULTS

A total of 78 children younger than 18 years of age with PTT were collected (patient presentation and tumor features are summarized in Table I). The data were collected from nine pediatric oncology registries.

The patients had a median age of 10.2 years (range 1 month–17.6 years), and a slight predominance of males (1.2: 1 male to female ratio) was observed in our series.

Respiratory symptoms were nonspecific: the most common symptoms included cough (n = 50; 67.6%), pneumonia (n = 33; 44.6%), and dyspnea (n = 30; 40.5%), followed by wheezing (n = 27; 36.5%) and fever (n = 26; 35.1%).

TABLE I.
Sociodemographic and Clinical Characteristics of the Study Patients (N = 78).

	N (%)
Gender: males/total (%)	43/78 (55.1 %)
Origin: Europe	56/78 (71.8 %)
South America	22/78 (28.2 %)
Age at diagnosis: – median (range)	10.2 years (1 month–17.6 years)
Syndromic: yes	12/78 (15.4 %)
Symptoms: cough	50/74 (67.6 %)
Pneumonia	33/74 (44.6 %)
Dyspnea	30/74 (40.5 %)
Wheezing	27/74 (36.5 %)
Fever	26/74 (35.1 %)
Hemoptysis	11/78 (14.9 %)
Chest pain	8/74 (10.8 %)
Weight loss	8/74 (10.8 %)
Duration of symptoms: – median (range)	6 months (1 month–10 years)
Site: larynx	6/78 (7.7 %)
Trachea	9/78 (11.5 %)
Larynx + trachea	3/78 (3.8 %)
Larynx + trachea + bronchus	1/78 (10.8 %)
Main bronchus	20/78 (25.6 %)
Lobar bronchus	39/78 (50.0 %)
Atelectasis: yes	33/78 (42.3 %)
Malignant tumor	48/78 (61.5 %)

TABLE II.
Analysis by Tumor Behavior.

	Malignant Lesions (n = 48)	Benign Lesions (n = 30)	*P* Value
Gender			
Male	26 (60.5%)	17 (39.5%)	0.83
Female	22 (62.9%)	13 (37.1%)	
Origin			
Europe	36 (64.3%)	20 (35.7%)	0.43
South America	12 (54.6%)	10 (45.5%)	
Age at diagnosis (months) (median; range)	n = 48 144 (8–211)	n = 30 110.5 (1–192)	0.054†
Syndromes			
Yes	6 (50.0%)	6 (50.0%)	0.52*
No	42 (63.6%)	24 (36.4%)	
Symptoms			
Yes	45 (61.6%)	28 (38.4%)	1.00*
No	3 (60.0%)	2/5 (40.0%)	
Chest pain			
Yes	4 (50.0%)	4 (50.0%)	0.70*
No	41 (62.1%)	25 (37.9%)	
Cough			
Yes	29 (58.0%)	21 (42.0%)	0.47
No	16 (66.7%)	8 (33.3%)	
Pneumonia			
Yes	23 (69.7%)	10 (30.3%)	0.16
No	22 (53.7%)	19 (46.3%)	
Dyspnea			
Yes	12 (40.0%)	18 (60.0%)	0.003
No	33 (75.0%)	11 (25.0%)	
Wheezing			
Yes	10 (37.0%)	17 (63.0%)	0.001
No	35 (74.5%)	12 (25.5%)	
Hemoptysis			
Yes	10 (90.9%)	1 (9.1%)	0.042*
No	35 (55.6%)	28 (44.4%)	
Weight loss			
Yes	3 (37.5%)	5 (62.5%)	0.25*
No	42 (63.6%)	24 (36.4%)	
Atelectasis			
Yes	24 (72.7%)	9 (27.3%)	0.08
No	24 (53.3%)	21 (46.7%)	
Duration of symptoms (months) (median; range)	n = 42 9.5 (1–120)	n = 28 3 (1-36)	0.53
Side			
Right	20 (74.1%)	7 (25.9%)	0.96
Left	25 (73.5%)	9 (26.5%)	
Site			
Upper airways	3 (15.8%)	16 (84.2%)	<0.0001
Other	45 (76.3%)	14 (23.7%)	

P value refers to the chi-square test unless otherwise specified.
**P*: Fisher exact test.
†*P*: Mann-Whitney U test.

TABLE III.
Clinical Characteristics and Outcome in Patients With Malignant Neoplasia (N = 47).

	Relapse or Death	Alive and Disease-Free	*P* (Fisher Exact Test)
Site: main or lobar bronchus	4/44 (9.1 %)	40/44 (90.9 %)	0.29
Larynx, trachea	1/3 (33.3 %)	2/3 (66.7 %)	
Hystology			
Mucoepidermoid carcinoma	3/15 (20.0 %)	12/15 (80.0 %)	0.55
Carcinoid	2/30 (6.7 %)	28/30 (93.3 %)	
Large cell carcinoma	0/1 (0.0 %)	1/1 (100.0 %)	
Hodgkin lymphoma	0/1 (0.0 %)	1/1 (100.0 %)	
Complication*			
Yes	1/11 (9.1 %)	10/11 (90.9 %)	1.00
No	4/32 (12.5 %)	28/32 (87.5 %)	
Treatment†			
Chemotherapy only	0/1 (0.0 %)	1/1 (100.0 %)	1.00
Endoscopic resection	0/4 (0.0 %)	4/4 (100.0 %)	
Surgical resection	5/41 (12.2 %)	36/41 (87.8 %)	

*Information about complications was missing in 4 cases out of 47.
†Information about treatment was missing in 1 case out of 47.

A delayed diagnosis was often observed (duration of symptoms: median 6 months, range 1 month–10 years), with earlier detection for tumors in the upper airways (median: 3 months; n = 17) compared with tumors in the lower respiratory tract (median: 9 months; n = 53), although the difference was not statistically significant ($P = 0.07$).

The diagnostic workup typically included chest X-ray (n = 31; 39.7%) and computed tomography (CT) scan (n = 70; 89.7%). In 33 cases (42.3%), signs of pulmonary atelectasis were present.

Diagnosis was obtained after initial biopsy in 66 patients (85%), endoscopically in 52 cases (79%), through percutaneous fine needle aspiration in 10 cases (15%), and with an open approach in four cases (6%).

Regarding the anatomic site, PTTs were commonly found in the main stem bronchi (n = 20; 25.6%) or in the inferior or superior lobar bronchi (n = 39; 50%). Lesions involving larynx and trachea were rare: six (7.7%) were found in the larynx, nine (11.5%) in the trachea, and three in both the larynx and trachea (3.8%) (Table I).

Histology results revealed a great predominance of malignant lesions (61.5% vs. 38.5%). As shown in Table II, carcinoids (n = 31; 64.6%) and mucoepidermoid carcinomas (n = 15; 31.3%) were the most common histotypes in this group, accounting for 95.8% of all malignant forms. Inflammatory myofibroblastic tumors (n = 19; 63.3%) were the most common benign lesions identified. Other histological entities are reported in Table II.

The majority of patients underwent primary resection (n = 74 of 77; 96.1%). Sixty-two patients (80.5%) underwent an open approach with different extents of resection (lobectomy, sleeve resection, pneumonectomy), whereas an endoscopic approach was used in 12 patients (15.6%) (data not shown).

Seven (9%) patients developed local recurrence: five out of 62 (8.1%) after open surgery and two out of 12 (16.7%) after endoscopic surgery.

TABLE IV.
Demographics and Clinical Features by Major Tumor Histology.

	Carcinoid (n = 31)	Inflammatory Myofibroblastic Tumor (n = 19)	Mucoepidermoid Carcinoma (n = 15)	Other (n = 13)	*P* Value
Gender	(n = 31)	(n = 19)	(n = 15)	(n = 13)	
Male	19 (61%)	14 (74%)	5 (33%)	5 (38%)	0.06
Female	12 (39%)	5 (26%)	10 (67%)	8 (62%)	
Provenance:	(n = 31)	(n = 19)	(n = 15)	(n = 13)	
Europe	25 (81%)	16 (84%)	10 (67%)	5 (39%)	0.026*
South America	6 (19%)	3 (16%)	5 (33%)	8 (61%)	
Syndromes					
Yes	5 (16.1%)	4 (21.0%)	1 (6.7%)	2 (15.4%)	0.75*
No	26 (83.9%)	15 (79.0%)	14 (93.3%)	11 (84.6%)	
Symptoms					
Yes	28 (90.3%)	17 (89.5%)	15 (100%)	13 (100%)	0.53*
No	3 (9.7%)	2 (10.5%)	0 (0%)	0 (0%)	
Cough					
Yes	16/28 (57.1%)	14/18 (77.8%)	12/15 (80.0%)	8 (61.5%)	0.34*
No	12/28 (42.9%)	4/18 (22.2%)	3 (20.0%)	5 (38.5%)	
Pneumonia					
Yes	16/28 (57.1%)	6/18 (33.3%)	12 (80.0%)	8 (61.5%)	0.30*
No	12/28 (42.9%)	12/18 (66.7%)	3 (20.0%)	5 (38.5%)	
Dyspnea					
Yes	6/28 (21.4%)	10/18 (55.6%)	5 (33.3%)	9 (69.2%)	0.014
No	22/28 (78.6%)	8/18 (44.4%)	10 (66.7%)	4 (30.8%)	
Wheezing					
Yes	7/28 (25.0%)	7/18 (38.9%)	3 (20.0%)	10 (76.9%)	0.007*
No	21/28 (75.0%)	11/18 (61.1%)	11 (80.0%)	3 (23.1%)	
Fever					
Yes	9/28 (32.1%)	6/18 (33.3%)	8 (53.3%)	3 (23.1%)	0.41*
No	19/28 (67.9%)	12/18 (66.7%)	7 (46.7%)	10 (76.9%)	
Hemoptysis					
Yes	8/28 (28.6%)	1/18 (5.6%)	2 (13.3%)	0 (0.0%)	0.06*
No	20/28 (71.4%)	17/18 (94.4%)	13 (86.7%)	13 (100%)	
Chest pain					
Yes	2/28 (7.1%)	3/18 (16.7%)	2 (13.3%)	1 (7.7%)	0.53*
No	26/28 (92.9%)	15/18 (83.3%)	13 (86.7%)	12 (92.3%)	
Weight loss					
Yes	1/28 (3.6%)	4/18 (22.2%)	2 (13.3%)	1 (7.7%)	0.22*
No	27/28 (96.4%)	14/18 (77.8%)	13 (86.7%)	12 (92.3%)	
Atelectasis					
Yes	15 (48.4%)	7 (36.8%)	7 (46.7%)	4 (30.8%)	0.68
No	16 (51.6%)	12 (63.2%)	8 (53.3%)	9 (69.2%)	
Preoperative chemotherapy					
Yes	1 (3.2%)	3[†] (15.8%)	0 (0.0%)	1 (7.7%)	0.19*
No	30 (96.8%)	16 (84.2%)	15 (100%)	12 (92.3%)	
Postoperative chemotherapy					
Yes	3 (9.7%)	4[†] (21.0%)	1 (6.7%)	2 (15.4%)	0.59*
No	28 (90.3%)	15 (79.0%)	14 (93.3%)	11 (84.6%)	
Relapse					
Yes	2 (6.4%)	0 (0.0%)	3 (20.0%)	2 (15%)	0.12*
No	29 (93.6%)	19 (100%)	12 (80.0%)	11 (84.6%)	

(Continues)

TABLE IV.
Continued

	Carcinoid (n = 31)	Inflammatory Myofibroblastic Tumor (n = 19)	Mucoepidermoid Carcinoma (n = 15)	Other (n = 13)	*P* Value
Outcome					
Alive free of disease	29 (93.6%)	16 (84.2%)	13 (86.7%)	9/12 (75.0%)	0.33*
Alive with disease	1 (3.2%)	3 (15.8%)	2 (13.3%)	2/12 (16.7%)	
Dead	1 (3.2%)	0 (0.0%)	0 (0.0%)	1/12 (8.3%)	

Numbers in round parentheses represent column percentages.
*P: Fisher exact test.
†Chemotherapy refers to nonsteroideal anti-inflammatory drugs.

TABLE V.
Number and Percentage of Deaths or Disease Progression in PA in European patients (N = 78) (N = 8/78; 10.3; Pb: Fisher Exact Test).

	No. of Deaths/ Relapses (%)	IR × 1,000 Persons-Month (95% Confidence Interval)	*P* Value Log-Rank
Gender			
Male (n = 43)	5 (11.60%)	2.584 (1.076–6.208)	0.66
Female (n = 35)	3 (8.60%)	1.949 (0.629–6.044)	
Origin			
Europe (n = 56)	5 (8.90%)	1.960 (0.816–4.709)	0.56
South America (n = 22)	3 (13.60%)	3.250 (1.048–10.078)	
Age at diagnosis			
≤112 months (n = 46)	1 (2.17%)	0.463 (0.065–3.290)	0.0062
>112 months (n = 32)	7 (21.88%)	5.319 (2.536–11.158)	
Syndromes			
Yes (n = 12)	2 (16.67%)	3.869 (0.968–15.469)	0.55
No (n = 66)	6 (0.09%)	2.029 (0.912–4.517)	
Symptoms			
Yes (n = 73)	8 (10.96%)	2.398 (1.120–4.795)	0.44
No (n = 5)	0 (0.00%)	0 (0.00–0.00)	
Duration of symptoms			
≤2 months (n = 19)	5 (26.32%)	7.874 (3.277–18.918)	0.0043
>2 months (n = 51)	2 (3.92%)	0.757 (0.189–3.029)	
Site			
Upper (n = 19)	4 (21.05%)	5.755 (2.160–15.335)	0.07
Other (n = 59)	4 (6.78%)	1.439 (0.540–3.835)	
Atelectasis			
Yes (n = 33)	2 (6.06%)	1.135 (0.284–4.539)	0.28
No (n = 45)	6 (13.33%)	3.505 (1.575–7.801)	
Preoperative chemotherapy			
Yes (n = 5)	2 (40.00%	13.699 (3.426–54.773)	0.0317
No (n = 73)	6 (8.22%)	1.803 (0.800–4.013)	
Treatment			
Endoscopic (n = 12)	2 (16.67%)	4.866 (1.217–19.457)	0.15
Surgical (n = 62)	5 (80.6%)	1.668 (0.694–3.008)	
Other (n = 3)	1 (33.33%)	23.810 (3.354–169.026)	
Complications			
Yes (n = 14)	2 (14.29%)	1.582 (0.594–4.216)	0.32
No (n = 56)	4 (7.14%)	2.525 (0.632–10.100)	
Histology			
Inflammatory myofibroblastic tumor (n = 19)	0 (0.00%)	0 (0.00–0.00)	0.11
Carcinoid (n = 31)	2 (6.45%)	1.254 (0.314–5.014)	

(Continues)

TABLE V.
Continued

	No. of Deaths/ Relapses (%)	IR × 1,000 Persons-Month (95% Confidence Interval)	*P* Value Log-Rank
Mucoepidermoid carcinoma (n = 15)	3 (20.00%)	4.754 (1.533–14.741)	
Other (n = 13)	3 (23.08%)	4.500 (1.451–13.946)	
Behavior			
Benign (n = 30)	3 (10.00%)	2.451 (0.791–7.600)	0.95
Malignant (n =)	5 (10.42%)	2.222 (0.925–5.339)	
Postoperative chemotherapy			
Yes (n = 10)	3 (30.00%)	10.309 (3.325–31.965)	0.0225
No (n = 68)	5 (7.35%)	1.571 (0.654–3.774)	

IR = incidence rates.

TABLE VI.
Best-Fitted Poisson Regression Models.

	(HR)*	95% CI#	*P* Value*
Patients (No. of events = 8/77; 10.4%).			
Age at diagnosis ≤112 months versus >112 months	11.48	1.41–93.30	0.0035

Event of interest: EFS; time variable measured from surgery to date of death or relapse (months) for PTT.
CI = confidence interval; EFS = event-free survival; HR = hazard ratio.

Postoperative complications, primarily air leakage (postoperative pneumothorax) and pleural effusion, occurred in 14 out of 70 patients (20%).

Relapse ($P = 0.32$), perioperative complications ($P = 1.0$), and event-free survival ($P = 0.28$) were not influenced by the surgical approach used (endoscopic vs. open).

Tracheotomy was necessary in five out of 78 (6.4%) patients and was the only treatment performed in a single case.

A minority of patients received neoadjuvant (n = 5; 6%) or adjuvant chemotherapy (n = 11; 14%), whereas chemotherapy was the only treatment used in two patients (3%): one with an inflammatory myofibroblastic tumor (in this case, chemotherapy refers to nonsteroidal anti-inflammatory drugs) and one with Hodgkin lymphoma.

In terms of outcomes, with a mean follow-up of 51 months (range 1–123), 67 (86%) patients were alive without evidence of disease at the time of writing this article; eight (10%) had relapsed; and two had died of disease (1 of relapse) (Supporting Table V, available online).

As Table II shows, malignant masses were diagnosed earlier than benign and masses (median 48 vs. 30 months), but no statistical significance was found ($P = 0.054$).

In addition, regarding symptom occurrence, dyspnea ($P = 0.002$) and wheezing ($P = 0.001$) appeared more frequently in patients with benign tumors. Conversely, hemoptysis was found to be a warning symptom of malignancy ($P = 0.042$).

The upper airways were more frequently involved in benign lesions, whereas distal airways were more frequently invaded by malignant ones ($P < 0.0001$).

Regarding tumor management and postoperative outcomes (Supporting Table VI), no significant differences were found between benign and malignant PTTs.

In contrast, the surgical approach (P value = 0.034) and need for tracheotomy ($P = 0.007$) differed significantly between the benign and malignant groups, with tracheotomy more often performed in cases of benign lesions.

Table III reports the outcome for patients with malignant tumors. No statistically significant associations were observed between site, histological type, type of treatment, presence of complications, and outcome.

Table IV reports the same analysis disaggregated by the main histological entities.

Univariate analysis revealed that younger age at diagnosis (<112 months) ($P = 0.0062$), symptoms lasting less than 2 months (P value = 0.0043), and preoperative ($P = 0.03$) and postoperative ($P = 0.02$) chemotherapy were all associated with worse outcomes (Table V).

Finally, a Poisson regression model was fitted on a total of 77 patients to evaluate the role of clinicopathological variables in influencing event-free survival (Table VI).

The following variables were fitted to the model: age at diagnosis and pre- and postoperative chemotherapy. Symptom duration could not be considered in the multivariable analysis due to the high number of missing values.

Age at diagnosis emerged as statistically significant in the Poisson regression model (odds ratio: 11.48; 95% CI: 1.41–93.3; $P = 0.0035$). This evidence was also present in the bivariate analysis. As shown in Figure 1, patients with age at diagnosis ≤112 months had a higher risk of negative outcome compared to patients with an age at diagnosis >112 months in both the group of patients with benign tumors (panel A) and the group with malignant tumors (panel B) ($P = 0.035$; log-rank test). In contrast, in the group of patients with age at diagnosis ≤112 months, there was no difference in event-free survival between

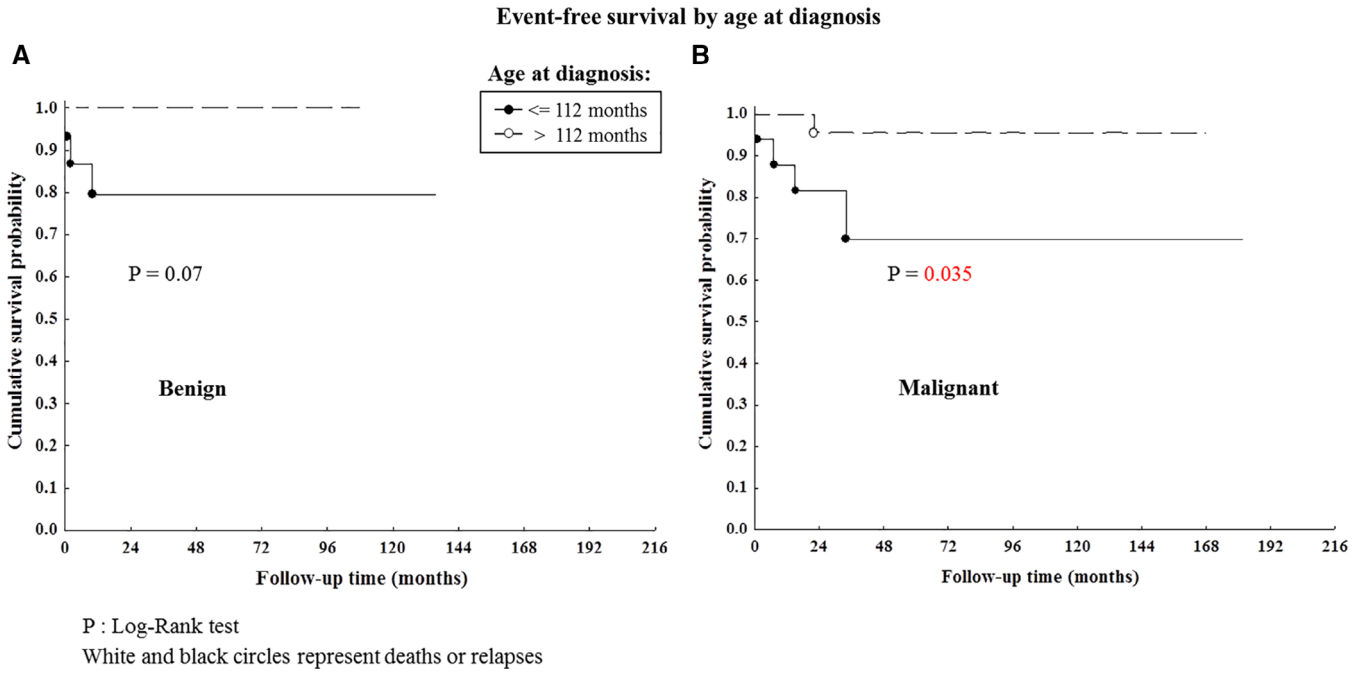

Fig. 1. Survival analysis. Event of interest: event-free survival; time variable measured from surgery to date of death or relapse (months) for primary tracheobronchial tumors.

patients with benign versus malignant tumors (P = 0.86) (Fig. 2) (5 negative outcomes were observed in the group of patients with benign tumors and 3 in the group of malignant tumors). In the group of patients with age at diagnosis >112 months, only one negative event (relapse followed by death in a male with malignant carcinoid tumor) was observed; therefore, the survival analysis and statistical test could not be performed.

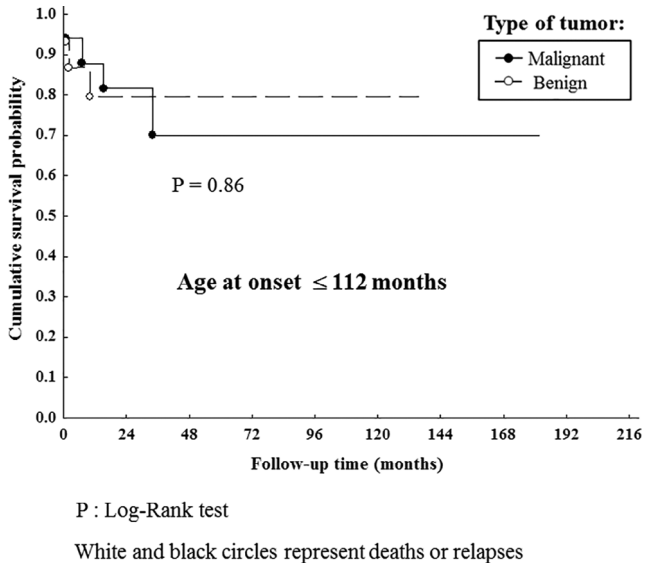

Fig. 2. Survival analysis. This survival curve only includes patients presenting under 112 months of age (N = 32). Event of interest: event-free survival; the two curves are drawn for patients with malignant versus benign tumors.

DISCUSSION

Low-incidence pediatric tumors usually attract little research attention, resulting in great difficulties in diagnosis and evidence-based treatment decisions; thus, multicenter international study groups are critical for formulating optimal guidelines.

For the first time, an international survey collected the largest series of PTTs. Clinical presentations and treatment were critically analyzed to provide a complete overview of medical and surgical management.

Consistent with previous reports,[1,3,6,7,26,27] the results of our series confirm that PTTs are more likely to be malignant than benign (62% vs. 38%), although event-free survival is comparable for both malignant and benign tumors (P = 0.95).

Among malignancies, a predominance of carcinoid and mucoepidermoid carcinoma was reported,[8,9,11,15,18,21,36,37] although rare malignant subtypes (e.g., large cell carcinoma and bronchial location of Hodgkin lymphoma) were also observed.

Inflammatory myofibroblastic tumor (n = 19)[7,14,18,27] and granular cell tumor (n = 3)[12,33] were the most frequent benign subtypes recorded in our population, but single cases of lipoblastoma,[38] teratoma, and rhabdomyoma were also observed.

The median age at diagnosis was 10 years, consistent with previous data[7–11,18,33,39]; however, multivariate analysis demonstrated that younger children (cutoff: 112 months) presented a worse outcome in terms of disease progression and death (P = 0.0035).

A long history (median 6 months, range 1–120 months) of respiratory symptoms resistant to conventional therapy was consistent with previous reports,[1,4–11,14] but our data showed that symptoms lasting less than 2 months were

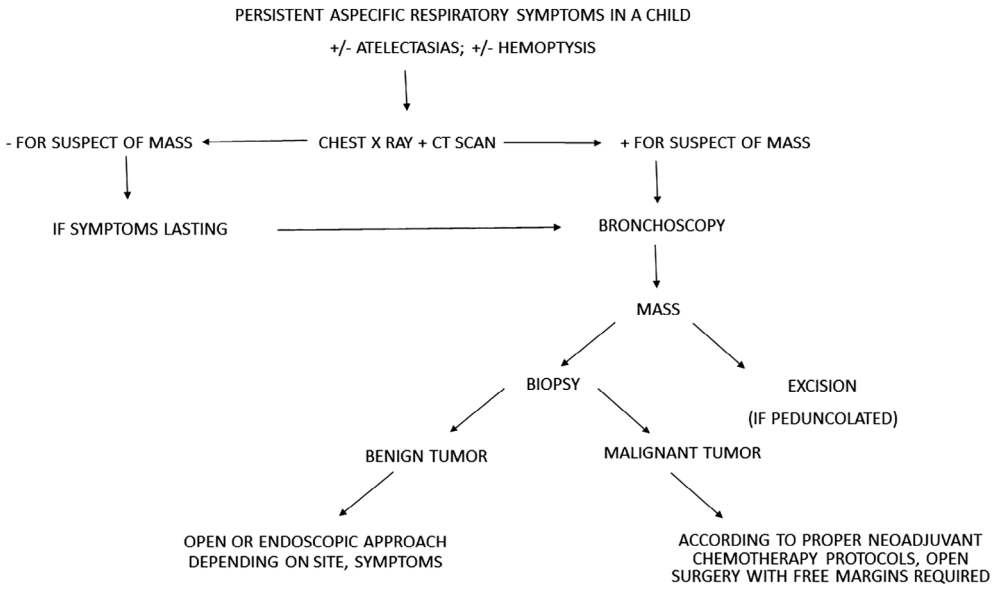

Fig. 3. Flow chart of general management of PTT. PTT = primary tracheobronchial tumors.

associated with a worse event-free survival (P = 0.0029). This may be explained by the hypothesis that a malignant tumor is more likely to have faster growth, with an early onset and worsening of respiratory symptoms.

It is important to note that, in contrast with earlier studies,[7] most patients (n = 70; 90%) routinely underwent CT scans, which allows the early detection and better definition of small pulmonary lumps, consistent with the current algorithm for recurrent respiratory symptoms in pediatric populations.[6–9,11,21,33,35,40,41]

Magnetic resonance imaging was also used in nine patients (12%) because it provides high-quality images without exposing the child to ionizing radiation.[6,42] Moreover, seven patients (9%) underwent positron emission tomography imaging for the evaluation of suspected PTT, as recommended by some authors.[43,44]

Underlining the diagnostic challenge represented by PTTs, several diagnostic imaging examinations per patient in our series were necessary to properly characterize the lump before any treatment was provided (mean 2 preoperative tests per child; range 1–4 tests per child).

Bronchoscopy played a fundamental role in the diagnostic workup because adequate biopsy specimens could be obtained to perform accurate diagnosis and appropriately schedule the treatment plan.[10,12,33,35,39] In our series, bronchoscopy was reserved for biopsy (n = 52 per 66, 79%), and endoscopic resections were attempted only in selected cases (n = 17 per 77; 16%).

Although some authors described the safety and feasibility of endoscopic ablation,[11,33,45,46] its use is still recommended—but only for small, pedicled intraluminal lesions that do not infiltrate the tracheobronchial wall.[12–16]

As stressed in the literature,[1,5,11,14,15,17,47,48] a relatively homogeneous approach to PTT was undertaken in our population, and complete surgical resection was regarded as the preferred initial treatment for almost all patients.

In particular, the treatment of choice in cases of infiltrative laryngotracheal tumors was single-stage laryngotracheal reconstruction,[12] whereas in cases of tracheobronchial involvement, parenchyma-sparing surgical approaches such as sleeve resections and bronchoplasties were considered mandatory to prevent respiratory and functional sequelae.[1,5,8,10,15,17,33,34,49–54]

Some authors proposed video-assisted pulmonary lobectomy in particular situations and also reported favorable outcomes for sequelae of this minimally-invasive procedure.[55,56]

Tracheostomy was required only in five cases with severe obstructive symptoms, as reported in the literature.[12,54] Chemotherapy and radiotherapy played a limited role for the palliation of severe symptoms in cases of primary unresectable lesions[14,47,48] or after surgical resection[1,5,6,8,10,17] for selected tumor histology.

CONCLUSION

Our data confirm the excellent prognosis for PTTs in relation to survival outcomes and tumor recurrence, underlining the fundamental role of complete tumor resection even in cases of delayed diagnosis.

Our series, however, was a retrospective multicenter experience in which the patients may have followed very different follow-up protocols; thus, recurrence and progressive disease might be undervalued and should be considered with care. Based on the preliminary results of this series, a flowchart for the general management of PTT is provided to define the endoscopic and open surgical approaches according to tumor malignancy (Fig. 3).

It is important to highlight that recurrent respiratory symptoms should raise the suspicion of PTTs to allow prompt diagnosis and parenchyma-sparing surgeries that can preserve the maximum amount of healthy tissue and avoid possible functional impairment.

A larger international prospective pediatric registry would be useful to validate formal guidelines because the present data, collected from the Italian TREP study, has provided

very important information regarding the clinical presentation, diagnostic workup, and treatment of PTTs in children.

Increasing the prospective recruitment of patients could cast new light on the biological behavior of PTTs, thus determining more appropriate and possibly histology-oriented treatments.

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