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Clinicopathologic Characteristics of Differentiated Thyroid Carcinoma in Children and Adolescents

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Abstract

Objective: To investigate the clinicopathologic features of differentiated thyroid carcinoma in children and adolescents. **Methods:** The clinical data of 7 children and adolescents with differentiated thyroid carcinoma were retrospectively analyzed, and the clinicopathologic features of differentiated thyroid carcinoma were analyzed by gender, tumor size and BRAF mutation. **Results:** There were 7 cases of thyroid papillary carcinoma. The mean age of patients was (18.71 ± 2.75), and the mean tumor diameter was (2.4 ± 1.04) cm. Lymph node metastasis rate was 100% (7/7). In children and adolescents, the lesion volume was larger, membrane invasion and vascular cancer thrombus were more likely to occur, BRAF mutation was less common, and the difference was statistically significant. **Conclusion:** Children and adolescents with differentiated thyroid carcinoma are more aggressive and prone to membrane invasion and lymph node metastasis; BRAF mutation is less common than in adults.

Keywords

Children and Adolescents, Thyroid Papillary Carcinoma, Clinicopathological Features, BRAF Mutation

1. Introduction

Background: Thyroid cancer in children and adolescents is clinically uncommon, accounting for 0.5% to 3.0% of all childhood tumors. In recent years, the incidence has been increasing rapidly, and now it ranks third in the substantial tumors of children and adolescents. Most of the patients had local invasion, regional lymph node metastasis and distant metastasis. Some of the patients still

have poor prognoses despite comprehensive treatment mainly with surgery.

Thyroid carcinoma in children and adolescents is a rare malignant tumor, accounting for about 0.5% - 3% of minor malignant tumors [1]. The incidence increased with age, with differentiated thyroid carcinoma (DTC), differentiated thyroid carcinoma, giving priority. Some studies have found that DTC patients <21 years old and >21 years old are different in tumor manifestations and biological behaviors even if the pathological type is the same [2]. Most works of literature include children and adolescents under 21 years old. The incidence of prepuberty was almost the same in both sexes, while the incidence of post-puberty was 1:4 in both sexes [3]. A study found that children's and adolescents' DTC are different from the clinical characteristics of adults' DTC to delete [4]. The volume of the lesion is larger, and it is often found in cervical lymph nodes or has a high rate of distant metastasis. The tumor cells express a high amount of sodium iodide symporter (NIS) in their bodies, which increases the likelihood of relapse after treatment. But overall survival rate is higher characteristics. In this paper, the clinical and pathological data of 7 children and adolescents with DTC were retrospectively summarized, and the clinicopathologic characteristics of DTC were analyzed based on gender and age factors.

2. Data and Methods

2.1. Clinical Data

From November 2018 to January 2023, 7 children and adolescents with PTC (Papillary thyroid carcinoma) were hospitalized in the Seventh Affiliated Hospital of Sun Yat-sen University, including 1 male and 6 female. The age range was 14 to 21 years old, and the mean age was (18.71 ± 2.75) years old. Inclusion criteria: the age of 21 years old or less, all patients undergoing thyroid full cut or times full cutting operation, the pathological diagnosis of PTC or thyroid follicular carcinoma (follicular thyroid carcinoma, FTC). Exclusion criteria: incomplete clinical data.

2.2. Methods

Clinical and postoperative pathological data of all patients were collected, including 7 cases in the adolescent and children group, including 1 male and 6 female. In addition, 100 adult cases of papillary thyroid carcinoma during the same period were collected as the control group, and the clinicopathologic characteristics of the two groups were compared, including the size of the lesion, whether there were multiple lesions, whether there was an invasion of the thyroid capsule, whether there was an invasion of the vascular cancer thrombus and nerve tract, lymph node metastasis and distant metastasis, and the expression of BRAF mutation.

2.3. Statistical Methods

SPSS21.0 software was used for statistical analysis of the data. Measurement data

were expressed as x ± s, and t-test was used for comparison between groups. Qualitative data were expressed by percentage, and Fisher's exact probability method was used for comparison between groups. $P < 0.05$ was considered statistically significant.

3. Result

3.1. Clinical Features

Among children and adolescents, the ratio of male to female was 1:6. About 86% (6/7) were found to have diseases due to symptoms and signs such as neck mass, neck thickening and hoarseness, and 14% (1/7) were found to have thyroid nodule saving by physical examination. Thyroglobulin (T_g) is below the normal level before treatment in most patients I, and T_g may be increased obviously in patients with lung metastasis. Lung metastasis was more common in female patients and was seen in the younger age group. There was no statistical significance in the above clinical features between the children and adolescents group and the adult group (all $P > 0.05$, Table 1).

3.2. Pathological Features

All the patients were pathologically diagnosed as PTC after surgery, including 7 cases of thyroid papillary carcinoma, all of which were subtypes of typical papillary carcinoma. Unilateral tumors were found in 5 patients and bilateral tumors in 2 patients. The mean tumor diameter was 2.4 cm. All 7 cases involved thyroid

Table 1. Comparison of clinical features of children, adolescents and adults with thyroid cancer.

Clinical features	Children and teenager	Adult	x^2	P
Gender			C	0.855
Male	1	25		
Female	6	75		
Symptom and Sign			C	0.768
Yes	6	73		
No	1	27		
Pulmonary Metastasectomy			F	0.065
Yes	1	0		
No	6	100		
I^{131} Thyroglobulin before Treatment			F	0.386
Above-Normal	1	6		
Normality/Subnormality	6	94		

F: Fischer exact test C: continuity correction.

capsule. There was 1 case with vascular thrombus, and the lymph node metastasis rate was 100% (7/7). Lymph nodes were dissected in 2 cases in the unilateral and central group, and in 5 cases in the bilateral and central group.

3.3. Comparison of Clinicopathological Features between Children and Adolescents

Compared with adults, children and adolescents with breast cancer have larger lesion diameter, are more likely to invade thyroid capsule, and are more likely to develop intravascular cancer thrombosis, which may reveal the reason why breast cancer is more likely to develop distant metastasis. There were fewer BRAF mutations than in the adult type, and the differences were statistically significant ($P = 0.043$, $P = 0.049$, $P < 0.001$, $P = 0.046$). The incidence of cervical lymph node metastasis was significantly higher in children and adolescents ($P = 0.001$), and lymph node metastasis occurred in all the cases we counted. There was no significant difference in the number of tumor and nerve tract invasions between children, adolescents and adults ($P > 0.05$, Table 2).

4. Discussion

Thyroid cancer is rare in children and adolescents. The International Cancer Society reports a prevalence rate of 5.0 to 5.4 per million children and adolescents under 20 years of age. The incidence has increased in recent years. The incidence rate of males and females was almost the same before puberty, and the ratio of males to females after puberty was 1:4. The etiology is still unclear, and currently it is considered that the history of head and neck radiation is an important pathogenic factor [5], and it may also be related to genetic factors. 90% - 95% of thyroid cancer in children and adolescents is DTC, which is different from that in adults in clinical manifestations, pathological features and biological behaviors. Although it has the advantages of low incidence and good prognosis, it also has the disadvantages of large lesion size, high probability of cervical lymph node or distant metastasis, and high recurrence rate after treatment. Therefore,

Table 2. Comparison of clinicopathologic features between children, adolescents and adults with thyroid cancer.

	BRAF	Mutant	Multif	Ocality	Tumor	Size	Lymph-Node	Metastasis	Presence of	Tumor Capsule	Bundle	Invasion	Intramuscular	Cancer Thrombus
	+	−	>1	≤1	>1	≤1	+	−	+	−	+	−	+	−
Children and teenager (n = 7)	2	5	2	5	6	1	7	0	7	0	0	7	1	6
Adult (=100)	87	13	39	61	39	61	63	37	62	38	8	92	7	93
x^2	C		C		C		F		F		F		F	
P	**0.001**		0.883		**0.043**		**0.046**		**0.049**		1.000		**< 0.001**	

Bold values were statistically significant ($P < 0.05$); F: Fischer exact test; C: Continuity correction.

attention should be paid to recurrence and metastasis in the clinical diagnosis and treatment of children and adolescents with DTC. Cervical lymph node metastasis is usually present at the time of diagnosis; the proportion is as high as 40% - 80%, but only 20% - 50% in adults. Distant metastasis is most likely to occur in the lung, accounting for about 20% - 30%, while metastasis in bone, brain and other tissues is rare [6]. The average age of patients in this study was 18.7 years old, and the male-to-female ratio was 1:6. 86% (6/7) of the patients were diagnosed with DTC due to symptoms such as neck mass, hoarseness, and coughing after drinking water. However, in most adults, DTC is detected through physical examination. It may be that children and adolescents with DTC tend to ignore their own discomfort due to their young age and poor self-expression ability, and parents often pay attention to them only when they show obvious clinical symptoms and signs. Thyroid cancer is easily ignored and delayed. The average diameter of tumors in this study was 2.4 cm, which was relatively large, and a close examination revealed a cervical mass. In this study, there were 7 cases of papillary thyroid carcinoma in adolescents and children, all of which were typical and invaded the thyroid capsule. Lung metastasis occurred in 1 patient. Compared with adult DTC, children and adolescents are more likely to be invaded by thyroid capsule, and the tumor is more aggressive, prone to recurrence, cervical lymph node metastasis and distant metastasis. The results of this study showed that the incidence of lymph node metastasis and thyroid capsule invasion was 100%, the incidence of lung metastasis was 14%, and the incidence of vascular cancer thrombus was 14%. Farahati *et al*. [7] reported that in 1039 patients with papillary thyroid carcinoma, cervical lymph node metastasis and distant metastasis were 90% and 7% in adolescents and 35% and 2% in adults, respectively. Extra-thyroid invasion was 24% in adolescents and 16% in adults. This study was consistent with the study of Farahati *et al*. in lymph node metastasis, with a higher incidence of distant metastasis.

The incidence of mutations in DTC is much lower in children and adolescents than in adults. Most studies report a mutation rate of less than 20%, and the incidence increases with age [8] [9]. $BRAF^{V600E}$-positive children are still more common through typical papillary carcinoma, which is characterized by tumor volume. Children are still more common with classic papillary carcinoma, its tumor volume is smaller, less invasive tumor, with multifocal tumor, external invasion, lymph node metastasis, distant metastasis, prognosis and taken sensitivity factor has no obvious correlation [10] [11]. It is concluded that $BRAF^{V600E}$ mutation has different clinical manifestations and prognoses in children and adolescents and adult DTC. Some rare BRAF mutations, such as $BRAF^{k601E}$ (c.1801A > G) mutations and BRaf.T599del, have also been confirmed in children and adolescents with DTC, and their relationship with thyroid cancer risk needs further study [12]. Compared with adults, fusion genes may play a more important role in the tumorigenesis and development of thyroid cancer in children and adolescents. The ret gene is located on the long arm of chromo-

some 10 (10q11.2) and encodes a tyrosine kinase receptor. The most common form of rearrangement is the fusion of the C-terminal kinase domain of RET with the N-terminal of the ligand gene, which is collectively referred to as RET/PTC fusion in PTC. The N-terminal domain of the ligand gene usually has a structure that promotes dimerization, allowing tyrosine residues located in the RET kinase domain to dimerize and phosphorylate in a ligand-independent manner, resulting in voluntary kinase activation that drives tumorigenicity. Accidental or therapeutic exposure to ionizing radiation in childhood is associated with the occurrence of RET/PTC fusion [13]. RET/PTC occurs in 5% to 15% of sporadic Adult-PTC, 22% to 65% of sporadic children and adolescents, and as high as 33% to 76% of children with a clear history of radiation exposure. NTRK genes associated with thyroid cancer include: The genes include NTRK1 and NTRK3 genes, which are located on chromosome lq23.1 and 15q25.3 respectively and encode transmembrane receptor tyrosine kinase protein Trk, TrkA and TrkC respectively. Most NTRK fusion consists of the 3' region of the NTRK gene and the 5' region of the ligand gene connected within or between chromosomes. Fusion of NTRK1 and NTRK3 is uncommon in Adult-PTC (2%), but occurs in sporadic childhood and adolescent PTC in 13.6% to 26.0%, and is more common in follicular PTC [14]. The most common form of PTC in children and adolescents is ETV6-NTRK3, which is t(12; 15) (p13; q25) ectopic, second only to RET fusion [9]. The biological characteristics of tumors in children with NTRK3 fusion were intermediate between those with BRAF mutation and those with RET fusion, *i.e.*, the mean age of patients with NTRK3 fusion was older and less clinicopathologically invasive than those with RET fusion. Compared with BRAF mutants, the average age of NTRK3 fusions was younger and the risk of aggressive behavior was greater [12]. Different ligand fusion genes may have different clinical manifestations, and the molecular mechanism behind them needs further study.

5. Conclusion

DTC in children and adolescents has unique clinicopathologic features, mainly manifested as large tumor diameter, extra-thyroid invasion, high incidence of lymph node metastasis and lung metastasis, especially in children. Due to the relatively small number of cases in this study, the pathological characteristics and pathogenesis of DT and DTCC in children and adolescents still require further study in a larger sample size.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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