



ORIGINAL ARTICLE

Pediatric differentiated thyroid carcinoma: The clinicopathological features and the coexistence of Hashimoto's thyroiditis



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KEYWORDS

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Summary *Background/objective:* The purpose of this study is to assess outcomes and the detailed clinicopathological features of differentiated thyroid carcinoma (DTC), including the relation of Hashimoto's thyroiditis and postoperative pathological features in child under 18 years old.

Methods: We reviewed patients with DTC under 18 years old (pediatric DTC patients) seen during recent 16 years. The clinicopathological features and outcomes of pediatric DTC were analyzed by comparison with patients of 19–20 years old or 21–44 years old.

Results: Sixty four children with DTC [median age 16 years (range, 5–18)] were studied. The ratio of female to male was 5:1, but no difference was found by comparison with adult of 21–44 years old. No difference was found in multifocality, but DTC in child showed larger tumor size ($P < 0.001$), higher rate of extrathyroidal extension ($P = 0.017$), more local or pulmonary metastasis ($P < 0.001$, $P < 0.001$ respectively) than adult thyroid carcinoma. High rate of Hashimoto's thyroiditis (19/43) without influence on pathological features was found in patients under 18 years old. No differences, except for distant metastasis, were found by comparison of clinicopathological features between patients under 18 years old and 19–20 years old. Pediatric patients possessed highest rates of persistent/recurrent disease, though only one child died.

Conclusion: Pediatric DTC has more aggressive behavior characterized by a high rate of extrathyroidal extension, local and pulmonary metastasis. Pediatric DTC has low mortality, but active treatments are needed for the high risk of persistent or recurrent diseases. Hashimoto's thyroiditis may be associated with the pathogenesis or mechanism of pediatric DTC.

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1. Introduction

Differentiated thyroid carcinoma (DTC) including papillary (PTC) and follicular (FTC) variants is the most common endocrine malignancy in adults. The prognosis of DTC is excellent, especially for patients under 45 years old.¹ Thyroid carcinoma is rare in pediatric patients, but it has been reported that the incidence of pediatric thyroid cancer is increasing. The annual age-adjusted incidence for pediatric thyroid cancer in 2004 was 0.54 cases per 100,000 and a significant increase in the annual incidence by 1.1% per year was founded.² Differentiated thyroid carcinoma is the predominant pathological type of pediatric thyroid cancer.

Compared with adult patients, children have larger thyroid cancers and present with higher incidence of lymph node or distant metastases than adults.³ Higher rates of cervical lymph node recurrences also have been reported, accounting for low recurrent-free survival of child DTC, and the 10-, 20-, and 30-disease-free survival were 83.6%, 70.7%, and 64.0%, respectively. But pediatric DTC thyroid cancer has a nice prognosis, and the 10-, 20-, and 30-cause-specific survival rates were 99.3%, 99.3%, and 96.5%, respectively.⁴ Another characteristic difference from adult PTC is that more frequent expression of the sodium/iodine symporter in pediatric thyroid glands leads to higher radioactive concentrations and radiation doses.⁵ A systematically review of the published literature on children and adolescents with well differentiated thyroid carcinoma and pulmonary metastases treated with radioiodine therapy demonstrated that the proportion of complete, partial, and no disease response to radioiodine therapy was 47.32%, 38.39%, and 14.29%, respectively.⁶

Many of previous researches focused on treatment and survival characteristics of pediatric DTC and patients included in some research came from a long time span even from 1940, which may covered up some significant clinicopathologic characters of pediatric DTC. And detailed clinicopathologic features of pediatric DTC such as the rate and pathological features of pediatric DTC associated with Hashimoto's thyroiditis were relatively unexplored. The purpose of this retrospective study is to assess the detailed clinicopathological features and outcomes of pediatric DTC patients (≤ 18 years old) admitted to hospital in northeast China, and its the first time to analyze the relation of Hashimoto's thyroiditis and postoperative pathological features of DTC in children (≤ 18 years old).

2. Materials and methods

This study retrospectively reviewed pediatric patients aged 18 years or younger admitted to the First Hospital of Jilin University for the treatment of differentiated thyroid carcinoma from January 2000 to November 2016. Pediatric patients were defined as children aged 18 years old or younger in this study. Patients without detailed clinical data were excluded and a total of 64 pediatric patients with the initial diagnosis were selected including patients who had been treated by other hospitals. We compared paediatric patients with 40 DTC patients aged 19–20 years old seen during the same period to uncover the differences between these two groups. A total of 158 consecutive

young DTC patients aged 21–44 years old who were admitted to our hospital for thyroid resections in 2009 were selected for comparison from the Patient Follow-up System. And younger children (≤ 12 years old) of paediatric patients were also analyzed.

Medical records of clinicopathological features were evaluated including details of patients' presentations, imaging data, pathology reports, treatments. Most of the patients' medical records were handwritten without the original electronic version of the detailed pathological report about 10 years ago, the pathologic analysis of thyroid carcinoma was recorded by attending doctor with writing bias. In order to reduce the writing bias of medical records, only 43 paediatric DTC patients and 34 DTC patients of 19–20 years of age with detailed pathological records were selected for the analysis of pathological features. The follow-up period was defined as the length of time from the initial therapy or intervention to the last known contact as documented by medical record review or an interview conducted by one of the authors. Recurrence was defined as disease diagnosed by radioiodine scan or pathological diagnosis during follow-up. Persistent disease was defined as patient with focus unresectable or without complete remission after the second time of radioactive iodine therapy or 6 months after the initial management. Survival data less than 6 months were censored and not regarded as persistent disease in patients with residual disease. The thyroid stimulating hormone (TSH), thyroglobulin antibodies (A-TG), thyroid peroxidase antibody (TPOAb), pathological features and follow-up were reviewed between patients with and without Hashimoto's thyroiditis.

Numerical data are expressed as median and ranges and categorical data as numbers and percentages. All calculations were performed using SPSS software. Chi-square test was used to compare categorical parameters and *t* test for continuous variables. Mean-Whitney U Test was used for abnormal distribution data. Survival rates from the date of initial surgery until death or tumor recurrence were estimated by the Kaplan–Meier method. All tests were two-sided and *P* values < 0.05 were regarded as statistically significant.

3. Results

3.1. The clinical features

A total of 64 cases of pediatric DTC [median age 16 years (range, 5–18)] and 40 DTC patients of 19–20 years old were studied. And 158 young adult DTC (21–45 years) were selected for comparison. The pediatric group included 8 patients (female 7, male 1) younger than 10 years (≤ 10), 12 patients (female 10, male 2) younger than 12 years (≤ 12 years), and the youngest patient was 5 years old. The number of patients younger than 20 years old (≤ 20) increased rapidly with age and the DTC patients of 19–20 years old accounted for 38.5% (40/64) (Fig. 1). The pediatric DTC patients were rarely seen before 2009, but increase in the number of newly diagnosed pediatric DTC patients was significant in 2010 (Fig. 2).

Seven patients were found with lung metastases including 5 patients diagnosed before the initial treatments

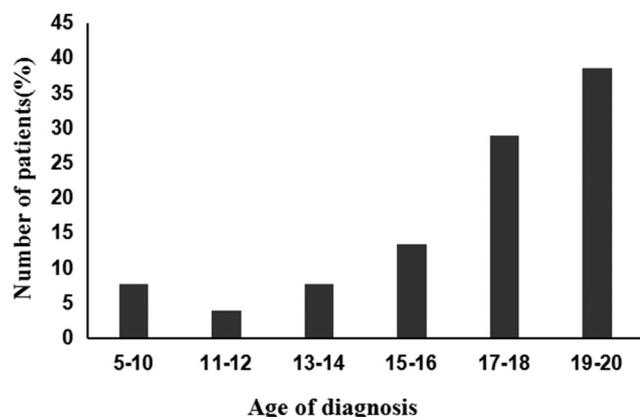


Figure 1 The age of diagnosis of DTC patients ≤ 20 years old.

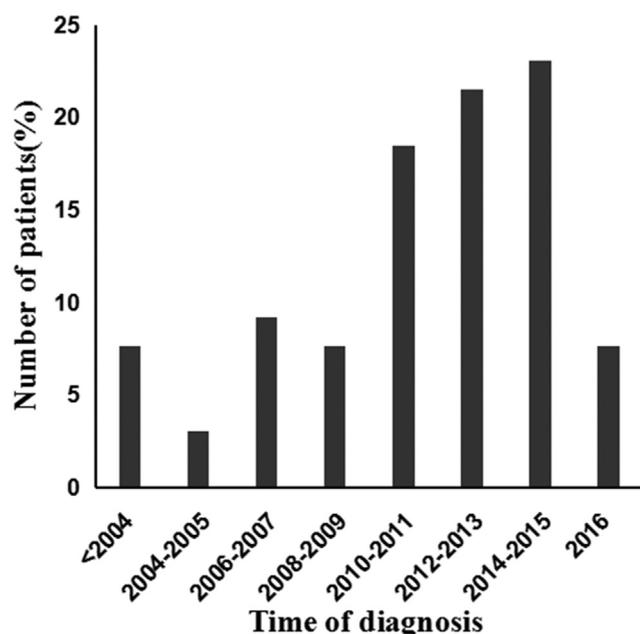


Figure 2 The diagnosis time of pediatric DTC patients (≤ 18 years old).

and 2 patients during follow-up. Compared with adult patients, pediatric patients had higher rates of distant metastasis ($P < 0.001$) and same female to male ratio ($P = 0.601$). Distant metastasis was more common in pediatric patients younger than 12 years ($P = 0.025$). Compared with pediatric patients, patients aged 19–20 also had high level of female to male ratio ($P = 0.071$), but lower rates of distant metastasis ($P < 0.042$) (Table 1).

A total of 62 patients of the pediatric age group received surgery as the primary treatment, and 2 patients bore with neck neoplasms unresectable. More than 29 pediatric patients received ^{131}I therapy. Two pediatric patients were found with diabetes, even though the past history of many pediatric patients was incomplete.

3.2. The pathological features

High rate of diffuse sclerosing variant of papillary thyroid carcinoma was found in pediatric DTC patients. Fig. 3

showed the neck contrast-enhanced CT and ultrasonography of a 9 years old female child with a family history of thyroid carcinoma. Compared with young adult DTC (Table 1), there was a significantly higher rate of extrathyroidal extension (21/37, $P = 0.017$), lymph node metastasis (32/37, $P < 0.001$), lateral cervical lymph node metastasis (21/37, $P < 0.001$), coexisting Hashimoto's thyroiditis (19/43, $P = 0.001$) in pediatric DTC patients. The median tumor size of pediatric DTC was 1.3 cm (range, 0.3–9). No difference was found in the rate of multifocality ($P = 0.401$). Compared with patients of 13–18 years old, younger children (≤ 12 years) had higher rate of bilateral cervical lymph node metastasis ($P = 0.042$).

Comparing pediatric DTC patients with DTC patients of 19–20 years old (Table 1), there was no difference in tumor size [median tumor size 1.3 cm, (range, 0.3–9) vs median tumor size 1.3 cm, (range, 0.2–4), $P = 0.842$], multifocality (23/42 vs 15/30, $P = 0.690$), extrathyroidal extension (21/37 vs 9/23, $P = 0.184$), lymph node metastasis (32/37 vs 26/34, $P = 0.276$), coexisting Hashimoto's thyroiditis or nodular goiter ($P = 0.599$, $P = 0.160$ respectively). But no patient aged 19–20 years old was found with distant metastasis ($P = 0.042$).

3.3. Follow-up

At the last follow-up, one pediatric patient died of airway obstruction and pulmonary metastases (Fig. 4) from papillary thyroid carcinoma 18 years after the initial surgery at 5 years old. Another pediatric patient died of pulmonary metastases from osteosarcoma. During the follow-up, 14% (9/64) pediatric patients were found with pulmonary metastases or unresectable cervical tumor and a 14-year-old pediatric patient with thyroid carcinoma unresectable suffered from noticeable dyspneic respiration after exercises caused by airway obstruction.

At the follow-up evaluation after the initial management, the pediatric group had a lower probability of persistent/recurrent disease-free survival compared with adult group ($P < 0.001$) or 19–20 years old DTC patients ($P = 0.019$) as shown in Figs. 5 and 6. And younger children (≤ 12 years) tended to be more likely to have a persistent/recurrent disease than patients of 13–18 years old ($P = 0.008$). Though the follow-up period may be too short for the pediatric patients diagnosed recently to catch more recurrent events, 8.1% (5/62) pediatric patients were found with cervical recurrence in 5 years after the initial management.

3.4. Characters of pediatric DTC patients with Hashimoto's thyroiditis

Thyroid function and pathological features of 43 pediatric DTC patients with detailed pathological report were studied and 19 patients were found with Hashimoto's thyroiditis (Table 2). There was no difference in tumor multifocality ($P = 0.711$), tumor size ($P = 0.094$), extrathyroidal extension ($P = 0.603$), lymph node metastasis ($P = 0.348$) or the level of thyroid stimulating hormone ($P = 0.464$) in pediatric DTC patients with or without (control) Hashimoto's thyroiditis. But high level of A-TG and TPOAb were

Table 1 The clinicopathological features of differentiated thyroid carcinoma (DTC).

Parameter	≤18			19–20	21–44	P^1	P^2	P^3
	≤12	13–18	Total					
Median age (Range)	9.5 (5–12)	17 (13–18)	16 (5–18)	–	37 (21–44)	–	–	–
Gender (Female:Male)	10:2	43:9	53:11	27:13	126:32	0.071	0.601	1.000
Tumor type								
CPTC	3	52	57	38	157	–	–	–
Diffuse sclerosis	2	4	6	0	0			
FVPTC	0	1	1	1	0			
FTC	0	0	0	1	1			
Median tumor size (Range)*	1.5 (0.3–9)	1.3 (0.3–4.8)	1.3 (0.3–9)	1.3 (0.2–4)	0.65 (0.1–4)	0.842	<0.001	–
Multifocality	4/6	19/36	23/42	15/30	75/158	0.690	0.401	0.849
Extrathyroidal extension	5/6	16/31	21/37	9/23	56/158	0.184	0.017	0.206
Lymph node metastasis	6/6	26/31	32/37	26/34	87/158	0.276	<0.001	0.567
Lateral cervical lymph node metastasis	5/6	16/31	21/37	10/34	17/158	0.020	<0.001	0.206
Bilateral cervical lymph node metastasis	3/6	3/31	6/37	4/34	–	0.737	–	0.042
Nodular goiter	2/6	16/37	18/43	9/34	–	0.160	–	–
Hashimoto's thyroiditis	3/6	16/37	19/43	13/34	30/158	0.599	0.001	1.000
Distant metastasis	4/12	3/52	7/64	0/40	0/158	0.042	<0.001	0.025

CPTC, classical papillary carcinoma; FVPTC, follicular variant of papillary thyroid carcinoma; FTC, follicular thyroid carcinoma. *The unit of tumor size is cm. P^1 , the P value of patients ≤18 vs 19, 20 years old. P^2 , the P value of patients ≤18 vs (21–44) years old. P^3 , the P value of patients ≤12 vs (13–18) years old.

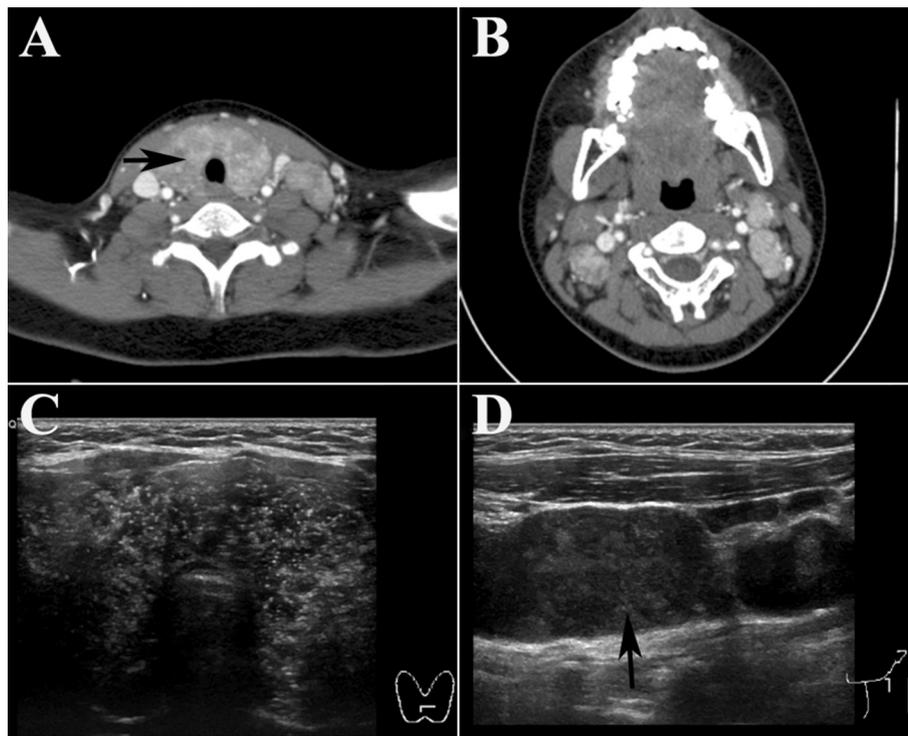


Figure 3 The neck contrast-enhanced CT (A, B) and ultrasound (C, D) of diffuse sclerosing variant of papillary thyroid carcinoma. The patient was a 9 years old female child with a family history of thyroid carcinoma. A, diffuse enhancement of the thyroid (arrow). B, bilateral cervical lymph node metastasis. C, diffuse small calcification of thyroid (snowstorm sign). D, ultrasound of lateral cervical lymph node metastasis (arrow).

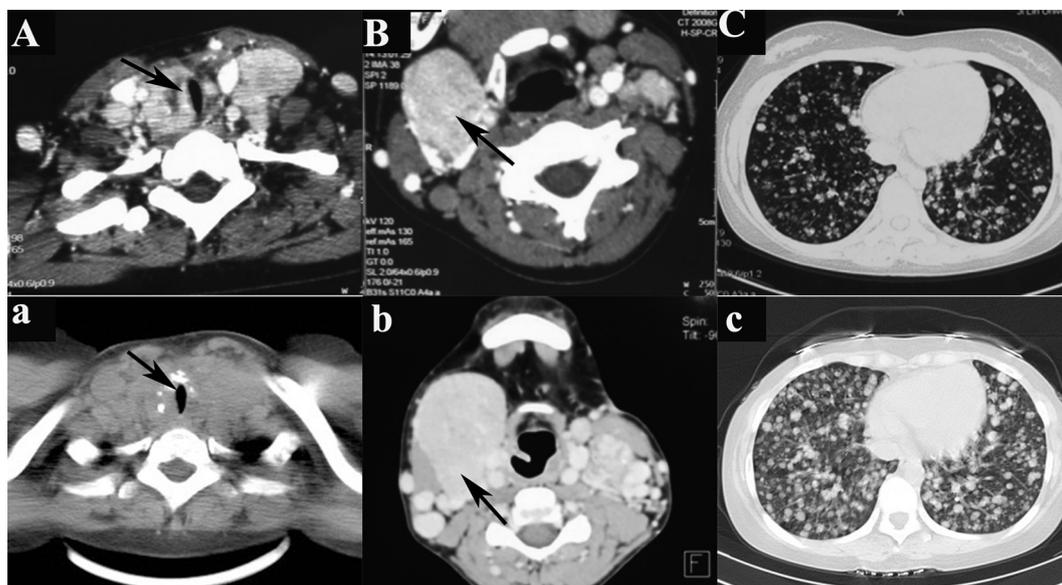


Figure 4 Computed tomography (CT) of neck and lung. A, B, C showed CT performed in 2009 and a, b, c in 2016. A and a, the trachea (arrow) was depressed or narrowed by the recurrent papillary thyroid carcinoma. B and b, the lateral cervical lymph node (arrow). C and c, significant progress was found in lung metastasis within 7 years (from 2009 to 2016).

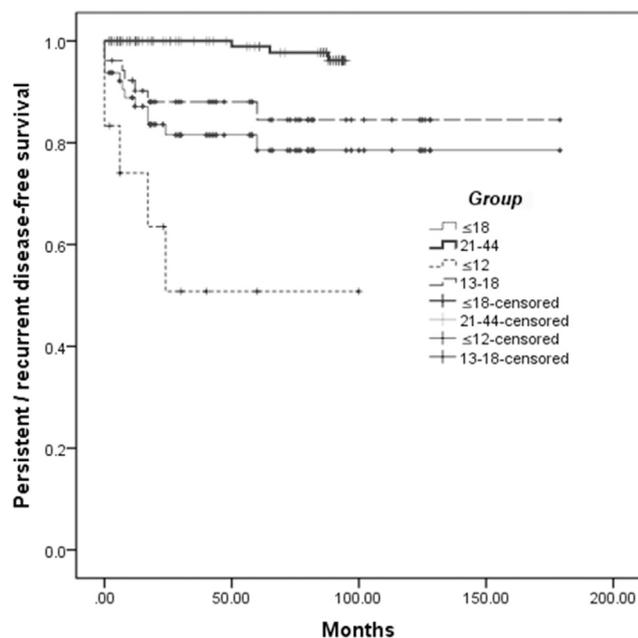


Figure 5 Persistent/recurrent disease-free survival of pediatric DTC patients and young adult DTC patients (≤ 18 vs 21–44 years, $P < 0.001$; ≤ 12 vs 13–18 years, $P = 0.008$).

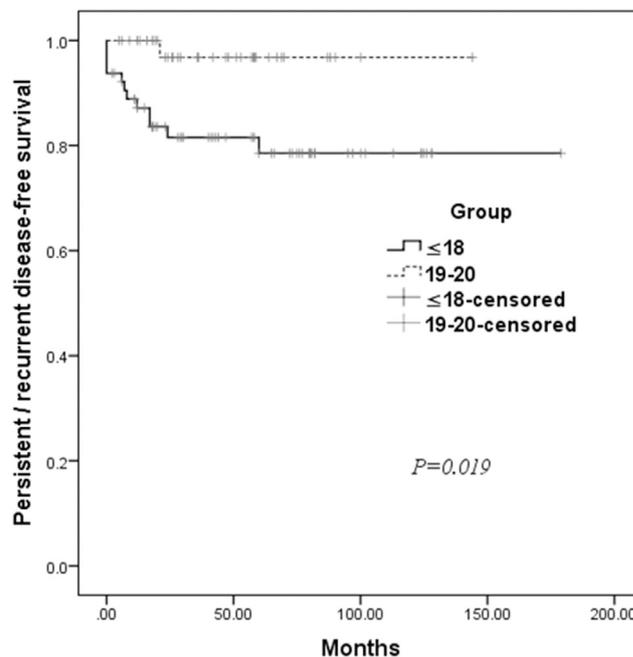


Figure 6 Persistent/recurrent disease-free survival of pediatric DTC patients and 19–20 years old DTC patients ($P = 0.019$).

found in pediatric DTC patients with Hashimoto's thyroiditis ($P = 0.001$, $P = 0.025$, respectively).

In the short term after the initial management, there was no difference in persistent/recurrent disease-free survival between pediatric DTC patients coexisting with Hashimoto's thyroiditis and pediatric DTC patients without Hashimoto's thyroiditis (Fig. 7).

4. Discussion

Thyroid cancer is the most common endocrine malignancy in children and differentiated thyroid carcinoma (DTC) is the most common pathological types.³ DTC in children is rare, but it has been reported that its incidence has been increasing in parallel to the overall increase in the incidence of DTC in adults.⁷ No randomized double-blind

Table 2 Comparison of thyroid function tests and pathological features of pediatric DTC patients with and without Hashimoto's thyroiditis.

Parameter	Control*	Hashimoto's thyroiditis*	P value
TSH	2.77 (2.18, 4.75)	3.82 (2.78, 4.43)	0.464
A-TG	18.81 (10.00, 28.42)	288.30 (85.10, 1810.75)	0.001
TPOAb	17.87 (11.53, 23.54)	116.00 (17.32, 461.50)	0.025
Multifocality	52.2% (12/23)	57.9% (11/19)	0.711
Median tumor size (Range)**	1.3 (0.2, 5)	2.0 (0.6, 9)	0.094
Extrathyroidal extension	52.6% (10/19)	61.1% (11/18)	0.603
Lymph node metastasis	80% (16/20)	94.1% (16/17)	0.348
Distant metastasis	8.3% (2/24)	5.3% (1/19)	—

Control*, pediatric patients without Hashimoto's thyroiditis; Hashimoto's thyroiditis*, pediatric DTC patients with Hashimoto's thyroiditis; TSH, thyroid stimulating hormone; A-TG, antithyroglobulin antibodies; TPOAb, thyroid peroxidase antibody. TSH, A-TG, TPOAb were indicated with median (upper quartiles, lower quartiles). ** The unit of tumor size is cm.

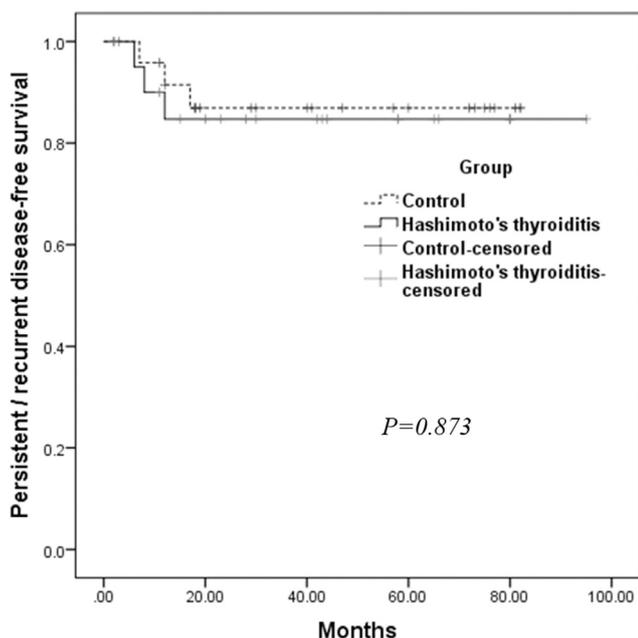


Figure 7 Persistent/recurrent disease-free survival of pediatric DTC patients without Hashimoto's thyroiditis (control) and pediatric DTC patients with Hashimoto's thyroiditis ($P = 0.873$).

controlled clinical trial exists for the treatment of pediatric DTC patients. The management of DTC in children usually referred to guidelines of the management for adults with thyroid nodules and cancers until the first management guidelines for children with thyroid nodules was published in 2015.⁸ Survival of the pediatric DTC has been widely studied, however detailed clinicopathologic features of pediatric DTC were seldom studied. And many of the previous studies enrolled child patients younger than 20 or 21 years old, which may covered up some features of younger children. Here we analyzed clinicopathologic features of pediatric DTC patients ≤ 18 years old comparing with young adult DTC patients and DTC patients of 19–20 years old in the First Hospital of Jilin University in China.

Consistent with previous published studies, our research found that the female children had higher prevalence of

DTC than male in children ≤ 18 years old. And female patients were more common in 8 patients younger than 10 years (female 7, male 1), different from previous outcomes.⁹ Machens et al¹⁰ also showed a high ratio of female to male ratio (20/3) in young children (≤ 11 years old) with papillary thyroid carcinoma. Adolescent patients of thyroid cancer has a female to male preponderance of 5:1 that is not seen in young children, but the ratio need further statistical proof in differentiated thyroid carcinoma.^{8,11} No national data in China has calculated the incidence of pediatric thyroid carcinoma. Although it was influenced by many factors such as the accuracy of detection using the ultrasound, we found that the number of newly diagnosed pediatric DTC patients increased significantly in recent years.

Treatment of pediatric DTC in our department including radioiodine therapy referred adult guidelines, and prophylactic central lymph node dissection was conducted to all the patients. With the conduct of prophylactic central lymph node dissection, the analysis of pathological features especially lymph node metastasis may be more accurate for the bias in surgical procedures was little. Papillary thyroid carcinoma (PTC) accounts for more than 90% of all childhood thyroid cancer and follicular thyroid cancer (FTC) is uncommon.^{12,13} In our study, PTC was also the most common pathological subtype of pediatric DTC, and no FTC was found. Except for classical papillary carcinoma, diffuse sclerosing variant of papillary thyroid carcinoma was the second most common subtype (9.4%) in children from northern China close to South Korea, both of which have high incidence of thyroid cancer. A study of 68 pediatric thyroid cancer found that diffuse sclerosing variant is a major subtype (41.2%) of papillary thyroid carcinoma in the young < 20 years at diagnosis in South Korea.¹⁴ Previous research show that children with DTC were more likely to have aggressive pathological characters such as high rate of local or lung metastasis, extrathyroidal extension. Our data found that 86.5% (32/37) children ≤ 18 years old were with lymph node metastasis, 56.8% (21/37) were with lateral cervical lymph node metastasis at the initial operation and younger child (≤ 12 years old) tended to have bilateral cervical lymph node metastasis.

Distant metastases were present in 5.8–24.5% of patients at diagnosis and occurred almost exclusively in the

lungs.^{15–17} In our research 10.9% (7/64) pediatric DTC patients had lung metastasis during the course and all the pathological types were papillary thyroid carcinoma. Therapeutic response of lung metastasis was not evaluated after the treatment of ¹³¹I. In a previous study, radioactive iodine (RAI) treatment could reduce the rate of local-regional relapse in patients with no distant metastasis and result in complete remission in half of those with distant metastasis.¹⁶ Children with RAI-avid pulmonary metastases visualized with a DxWBS are good candidates for RAI therapy and pulmonary function testing should be considered in all children with diffuse pulmonary metastases.⁸

Previous researches have showed that children and adolescents with thyroid carcinoma have a favorable outcome, though children often present with more advanced locoregional disease and distant metastases than their adult counterparts.² Disease specific mortality of the pediatric patients in our study was lower, and only 1 child died of airway obstruction and pulmonary metastases 18 years after the initial surgery for the limited experience in the early days of our country and the untimely treatment for the cervical recurrent nodules. The prognosis of two pediatric patient with thyroid carcinoma unresectable including one patients suffered from noticeable dyspneic respiration after exercises caused by airway obstruction was expected to be poor. Consistent with previous research, there was a lower probability of persistent/recurrent disease-free survival compared with adult group in 5 years, especially for younger child (≤ 12 years old).

Management guidelines for children with thyroid nodules and differentiated thyroid cancer recommend that the preoperative evaluation of the newly diagnosed pediatric PTC patient is critical for medical therapy and a comprehensive neck US using a high-resolution probe (7.5 MHz or higher) or Doppler technique should be obtained by an experienced ultrasonographer.⁸ As the conduct of prophylactic central lymph node dissection in China for pediatric child thyroid cancers, the diagnosis should attach importance to preoperative assessment especially for the lung or lateral cervical lymph node metastasis. Cross-sectional imaging using contrast-enhanced computed tomography (CT) should be considered. Radioiodine therapy could decrease recurrence or progress of patients with known residual disease.^{18,19} Determinants associated with a higher success rate of the initial ablative ¹³¹I therapy in pediatric DTC patients are female gender, a lower local tumor stage and higher ¹³¹I activities.²⁰ However, the data of radioiodine therapy for pediatric DTC were from retrospective cohorts with investigator bias and no randomized double-blind controlled clinical trial exists. Radioiodine therapy was usually suggested in our pediatric patients as the high rate of lung and lateral cervical lymph node metastasis. The potential benefits of radioiodine therapy in children need further study.

The genetic background of pediatric DTC patients is different from that of adults. RET/PTC rearrangements are more common in PTC from children than adult.^{21,22} Child thyroid carcinoma has a lower rate of BRAFV600E and RAS mutations than adults.²³ Lower frequency of BRAF point mutations which can lead to the decreased expression of sodium-iodide symporter, which may account for the high

ratio of radioiodine sensitivity and the favorable outcome. Child thyroid cancer appears to have greater and more frequently detectable sodium-iodide symporter than adult.¹⁶ Additional study is needed to verify genetic landscape and its relationship with the unique features of child thyroid differentiated carcinoma.

The autoimmune thyroiditis or thyroid nodular goiter in children with DTC was seldom reported before, here we analyzed the detailed postoperative pathological reports of child DTC patients ≤ 18 years old. There were 44.2% (19/43) pediatric DTC coexisting with Hashimoto's thyroiditis and 41.3% (18/43) with nodular goiter. There was no difference in tumor multifocality, tumor size, extrathyroidal extension, lymph node metastasis, the level of thyroid stimulating hormone or persistent/recurrent disease-free survival in pediatric DTC patients with or without Hashimoto's thyroiditis. The prevalence of chronic autoimmune thyroiditis in children peaks in early to mid-puberty.²⁴ The link between DTC and Hashimoto's thyroiditis is still controversial. Several hypotheses support the relationship in adult patients. In chronic inflammation, chemokines, cytokines, and growth factors that cause damage to stromal cells thereby resulting in tumor development,²⁵ and the elevated levels of TSH in patients with Hashimoto's thyroiditis stimulate follicular epithelial proliferation, which may promote the development of papillary carcinoma.²⁶ However the high coincidence may be subject to selection bias. Prevalence rate of PTC in patients with HT is 1.20% in FNA specimens and 27.56% in thyroidectomy specimens.²⁷ Though population-based FNA studies did not find a statistically correlation, a report of 300 children and adolescents with a diagnosis of HT found that thyroid nodule rate on an HT background was found to be 13% and the thyroid malignancy rate diagnosed by FNA was as high as 0.67%.²⁸ Whether Hashimoto's thyroiditis is associated with the pathogenesis or mechanism of pediatric DTC needs for further study.

The first management guidelines for children with thyroid nodules and differentiated thyroid cancer recommended the pediatric age should be limited to a patient ≤ 18 years of age, as establishing a uniform upper limit of age will afford an opportunity to better define the potential impact of growth on tumor behavior.⁸ As many of former researches retrospective analyzed child DTC patients ≤ 20 years of age, we analyzed clinicopathological features and outcome of pediatric DTC patients ≤ 18 years old comparing with DTC patients of 19–20 years old to identify the differences. No differences except for distant metastasis were found between these two groups, and high rate of lung metastasis was the typical feature in young children. Researches of child thyroid carcinoma should considerate heterogeneity of different age groups.

5. Conclusion

Differentiated thyroid carcinoma in children has more aggressive behavior characterized by a high rate of extrathyroidal extension, local and pulmonary metastasis. Pediatric DTC has low mortality, but active treatments and regular follow-up are needed for the high risk of disease persistence or recurrence. Hashimoto's thyroiditis may be

associated with the pathogenesis or mechanism of pediatric DTC.

Conflicts of interest

None.

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