Prognostic analysis of recurrence in children and adolescents with differentiated thyroid cancer

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Abstract

Background: The standard treatment for pediatric differentiated thyroid carcinoma (DTC) still requires consideration because of a lack of clinical evidence. The purpose of this study was to summarize the clinical experiences and explore the risk factors for post-operative recurrence through a retrospective analysis to develop better clinical strategies for pediatric DTC.

Methods: This study retrospectively analyzed children and adolescents with DTC who were treated between January 1999 and December 2014 at the Cancer Hospital, Chinese Academy of Medical Sciences. Clinicopathological results and outcomes were collected. A log-rank test of Kaplan-Meier curves and the Cox regression model were used to determine the factors associated with recurrence.

Results: Data of 150 patients were collected in this study. During the follow-up, there was only one disease-related death. The recurrence rates at 3, 5, and 10 years were 13.6%, 18.7%, and 28.6%, respectively. There was a significant difference in the rate of recurrence according to age ($P < 0.001$), extrathyroidal extension ($P < 0.001$), lymph node metastasis ($P = 0.023$), and invasion of the trachea and esophageal wall ($P = 0.004$). Cox regression analysis demonstrated that age ($P = 0.006$) and extrathyroidal extension ($P = 0.013$) were significant dependent factors of post-operative recurrence.

Conclusions: The prognosis of DTC in children and adolescents is favorable. A close follow-up is recommended because of the high recurrence rate. A comparatively higher recurrence rate was observed in the younger age group, and new age-based divisions may be needed to conveniently evaluate the possibility of recurrence.

Keywords: Children and adolescents; Differentiated thyroid cancer; Recurrence

Introduction

Despite increasing at a rate of approximately one percent yearly,[1] differentiated thyroid carcinoma (DTC) is far rarer in children than that in adults. Recent data indicate that the thyroid cancer incidence is 19.13 per million for children and adolescents under 19 years of age.[2] DTC has some distinctive differences between children and adults, including aggressive clinical behaviors, a high relapse rate, and paradoxically favorable disease-specific survival.[3] The purpose of this study was to summarize the clinical experiences and explore the risk factors for post-operative recurrence through a retrospective analysis to develop better clinical strategies for pediatric DTC.

Methods

Ethical approval

This study was a retrospective analysis of children and adolescents with DTC. The study was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences (No. NCC2341). The requirement for obtaining informed consent from patients was waived due to the retrospective design of this study.

Patients

The medical records of a consecutive cohort of patients who were no more than 18.0 years old and who had a definitive diagnosis of DTC between January 1999 and

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December 2014 at the Cancer Hospital, Chinese Academy of Medical Sciences were reviewed. One hundred and eighty patients were included. The exclusion criteria were as follows: (1) the patient received the initial radical treatment at another hospital ($n = 16$); (2) the clinical data were incomplete and could not be used for further analysis ($n = 10$); (3) the patient had a history of exposure to head-neck radiation ($n = 1$); (4) the patient had a family history of thyroid cancer ($n = 2$); and (5) the post-operative pathology was classified as poorly DTC ($n = 1$). Ultimately, one hundred and fifty patients were included in our study.

Data collection

The demographic and clinical data registered at diagnosis included sex, age, chief complaints, duration of symptoms, and mobility of vocal cords were derived from electronic medical records. Surgical procedure-related data, including the extent of thyroid resection, area of neck dissection, and condition of tumor invasion, were collected from surgical records. Through a pathologic review, we obtained detailed tumor information. Conveniently, tumor number and location were sub-divided into monocentricity, unilateral multicentricity, and bilateral multicentricity groups, in which multicentricity refers to two or more carcinoma foci in the thyroid. Tumor size was defined as the largest dimension of the carcinoma.

Diagnosis and treatment

In the Department of Head-Neck Surgery, Cancer Hospital, Chinese Academy of Medical Sciences, ultrasonography is routinely used before an operation, and an additional cervicothoracic computed tomography (CT) scan is used for patients with suspicious lymphatic metastasis in lateral areas. All the patients involved in the study underwent surgery. Total thyroidectomy was preferred when the tumor was multicentric or the surrounding tissue was obviously infiltrated; post-operative ^{131}I treatment was also recommended for these patients. The other patients received hemithyroidectomy (with or without isthmus resection), defined as partial thyroidectomy in this study. Neck dissection of the central area was commonly performed except in rare cases in which the tumor was monocentric and negative for extrathyroidal extension. Neck dissection of the lateral area was not performed unless the lateral lymphatic metastasis was pathologically confirmed before or during the operation. Tracheotomy or tracheostomy was performed for patients exhibiting bilateral recurrent laryngeal nerve dysfunction.

Post-operative follow-up

A total of 146 patients were followed up successfully, and four patients were lost before the final follow-up. Follow-up involved ultrasonography, thyroid function, and periodic serum thyroglobulin and cervicothoracic CT scan, and a whole body ^{131}I scan was performed when necessary. During the follow-up, a reoperation was performed if local-regional recurrence was suspected by imaging examinations or proven by biopsy. To assess the recurrence rate accurately, a recurrent event was defined as recurring disease in the cervical area or progressive disease in the distant metastasis at least 6 months after initial treatment. Additionally, whether post-operative ^{131}I treatment was administered and the times and doses were recorded.

Statistical analysis

Continuous data with normal distribution are expressed as the mean ± standard deviation. A log-rank test of Kaplan-Meier curves and the Cox regression model were used to determine the factors associated with recurrence. The recurrence-free survival rate at 3, 5, and 10 years of follow-up was evaluated with Kaplan-Meier survival curves. Differences were considered statistically significant with $P < 0.05$. Statistical analysis was performed using IBM SPSS, version 22 (IBM Corp., Armonk, NY, USA).

Results

Demographics and clinical characteristics

A total of 150 patients were included in the current study. The demographic and clinical characteristics are shown in detail in Table 1. The mean age at diagnosis was 14.7 ± 3.1 years; 51 patients were male, and 99 were female, with a female/male ratio of 1.94:1. When dividing patients into age sub-groups of 6.0 to 12.9 years, 13.0 to 15.9 years, and 16.0 to 18.0 years, the proportions of females were 52.9%, 62.5%, and 71.4%, respectively, and the proportion of females presented steadier growth with increasing age. The most common main complaint was a cervical area mass (82.0%). All the patients underwent initial thyroid surgery, including a total thyroidectomy in 82 patients (54.7%) and a partial thyroidectomy in 68 patients (45.3%). Pre-operative laryngoscopy detected abnormal motion of the vocal cord in seven (4.7%) patients (all were unilateral paralysis); four of these patients and seven other patients underwent simultaneous tracheotomy or tracheostomy during surgery. Distant metastasis was observed in 18 (12.0%) patients at diagnosis, all of whom presented with distant metastases to the lungs. One or more post-operative ^{131}I treatments (median 2.74) were administered in 84 (56.0%) patients. The single dose ranged from 30 to 120 mCi (1 mCi =3.7×10^7 Bq), and the cumulative dose of post-operative radioiodine ranged from 100 mCi to 800 mCi (median 200 mCi).

Pathological features

The pathological features are shown in Table 2. The majority of patients had papillary thyroid carcinoma (PTC, 98.0%, 147/150). The median tumor size was 24.2 mm (range 3.0–60.0 mm), with thyroid micro-carcinoma accounting for only 14.0% (21/150). The proportions of monocentricity, unilateral multicentricity, and bilateral multicentricity were 41.3%, 18.7%, and 40.0%, respectively. Extrathyroidal extension occurred in 57.3% of patients (86/150), and extracapsular extension in lymph node metastasis occurred in 22.0% of patients (33/150). The infiltrated surrounding tissue was divided into four sub-groups: surrounding muscle tissue (10.0%, 15/150), the recurrent laryngeal nerve (16.0%, 24/150), vessels in the neck area (5.3%, 8/150), and the wall of the

Table 1: Demographic and clinical characteristics of children and adolescents with differentiated thyroid carcinoma ($n = 150$).

Items	Results
Age (years), mean ± SD	14.7 ± 3.1
Gender	
Male	51 (34.0)
Female	99 (66.0)
Main complaint	
Cervical area mass	123 (82.0)
Hoarseness	7 (4.7)
Dyspnea	2 (1.3)
Medical examination	18 (12.0)
Vocal cord motion	
Unilateral vocal cord paralysis	7 (4.7)
Normal	143 (95.3)
Pre-operative thyroglobulin	
Above normal	42 (28.0)
Normal	108 (72.0)
Distant metastasis at diagnosis	
Yes	18 (12.0)
No	132 (88.0)
Extent of thyroid excision	
Partial thyroidectomy	68 (45.3)
Total thyroidectomy	82 (54.7)
Tracheotomy or tracheostomy	
Yes	11 (7.3)
No	139 (92.7)
Post-operative ^{131}I therapy	
Yes	84 (56.0)
No	66 (44.0)

Data are expressed as mean ± SD or *n* (%). SD: Standard deviation.

Table 2: Pathological features of 150 children and adolescents with differentiated thyroid carcinoma, *n* (%).

Items	Results
Pathological type	
Papillary	147 (98.0)
Follicular	3 (2.0)
Tumor size	
≤10 mm	21 (14.0)
>10 mm	129 (86.0)
Lesion number and location	
Monocentric	62 (41.3)
Unilateral multicentric	28 (18.7)
Bilateral multicentric	60 (40.0)
Extrathyroidal extension	
Yes	86 (57.3)
No	64 (42.7)
Extracapsular extension in lymph node metastasis	
Yes	33 (22.0)
No	117 (78.0)
Tumor invasion of surrounding tissues	
Surrounding muscle tissue	15 (10.0)
Recurrent laryngeal nerve	24 (16.0)
Vessels in the neck area	8 (5.3)
Wall of the trachea and esophagus	18 (12.0)
Lymph node metastasis	
None	19 (12.7)
1a	21 (14.0)
1b	110 (73.3)
Vascular tumor thrombus	
Yes	12 (8.0)
No	138 (92.0)

trachea and esophagus (12.0%, 18/150). Lymphatic metastasis was positive in 131 (87.3%) patients (21 for 1a and 110 for 1b according to the American Joint Committee on Cancer tumor-node-metastasis staging, 8th edition).

Risk factors for recurrence

The mean follow-up duration was 102.9 months. During the follow-up, one patient died of sudden asphyxia after a reoperation for central neck area recurrence. We assumed that unrecognized nerve injury was the main cause of death. Recurrence was found in 32 (21.3%) of the 150 patients. A statistical analysis performed with Kaplan-Meier curves showed that the probabilities of recurrence at 3, 5, and 10 years were 13.6%, 18.7%, and 28.6%, respectively. A log-rank test showed a significant difference in the incidence of recurrence according to age ($P < 0.001$), extrathyroidal extension ($P < 0.001$), lymph node metastasis ($P = 0.023$), and invasion of the trachea and esophageal wall ($P = 0.004$) [Table 3 and Figure 1]. The Cox regression analysis demonstrated that age (hazard ratio [95% confidence interval]: 0.870 [0.788–0.962], $P = 0.006$) and extrathyroidal extension (hazard ratio [95% confidence interval]: 3.720 [1.277–10.814], $P = 0.013$) were significantly dependent factors for post-operative recurrence. The overall analysis did not indicate that post-operative ^{131}I therapy or the extent of thyroid excision were significant factors. However, the administration of ^{131}I therapy was a protective factor in the sub-group with extrathyroidal extension ($P = 0.016$). When the age sub-groups were further studied, the log-rank test showed that total thyroidectomy was associated with low recurrence in the group aged ≥12.0 years ($P = 0.038$).

Discussion

Without radiation exposure and hereditary, pediatric DTC is relatively infrequent,[4-6] accounting for only 1.5% of all PTCs.[7] It tends to be characterized by mild clinical behaviors and a favorable prognosis.[3] In our series, there was only one disease-related death; however, the presence of bilateral lesions or reoperative conditions should be considered warning signs.

With the advancement of technology, the success rate of detection to recurrent thyroid cancer is gradually increasing.[8] In our study, the Kaplan-Meier curve showed that the probability of recurrence at 10 years was 28.6%, which is consistent with previous reports of approximately 20% to 47%.[7,9-12] The high risk of recurrence in pediatrics distinguishes pediatric DTC from its adult counterpart. One recent study examined DTC patients with a high risk of recurrence with a median age of 43 years and reported a

Table 3: Univariate analysis of factors of 150 children and adolescents with differentiated thyroid carcinoma.

Items	χ^2	*P* values
Age (6.0–12.9 years *vs.* 13.0–15.9 years *vs.* 16.0–18.0 years)	17.703	<0.001
Gender (female *vs.* male)	0.106	0.745
Pre-operative thyroglobulin (above normal *vs.* normal)	0.117	0.732
Post-operative ^{131}I therapy (yes *vs.* no)	1.112	0.292
Extent of thyroid excision (total *vs.* partial)	1.057	0.304
Extent of thyroid excision (12.0 years old and above) total *vs.* partial	4.307	0.038
Lesion number and location (monocentric *vs.* unilateral multicentric *vs.* bilateral multicentric)	3.763	0.152
Tumor size (≤10 *vs.* >10 mm)	0.393	0.531
Extrathyroidal extension (yes *vs.* no)	13.739	<0.001
Extracapsular extension in lymph node metastasis (yes *vs.* no)	0.639	0.424
Lymph node metastasis (yes *vs.* no)	5.174	0.023
Invasion of surrounding muscle tissue (yes *vs.* no)	0.000	0.983
Invasion of recurrent laryngeal nerve (yes vs. no)	0.349	0.555
Invasion of vessels in the neck area (yes *vs.* no)	1.136	0.287
Invasion of the trachea and esophagus (yes *vs.* no)	8.428	0.004
Vascular tumor thrombus (yes *vs.* no)	3.674	0.055

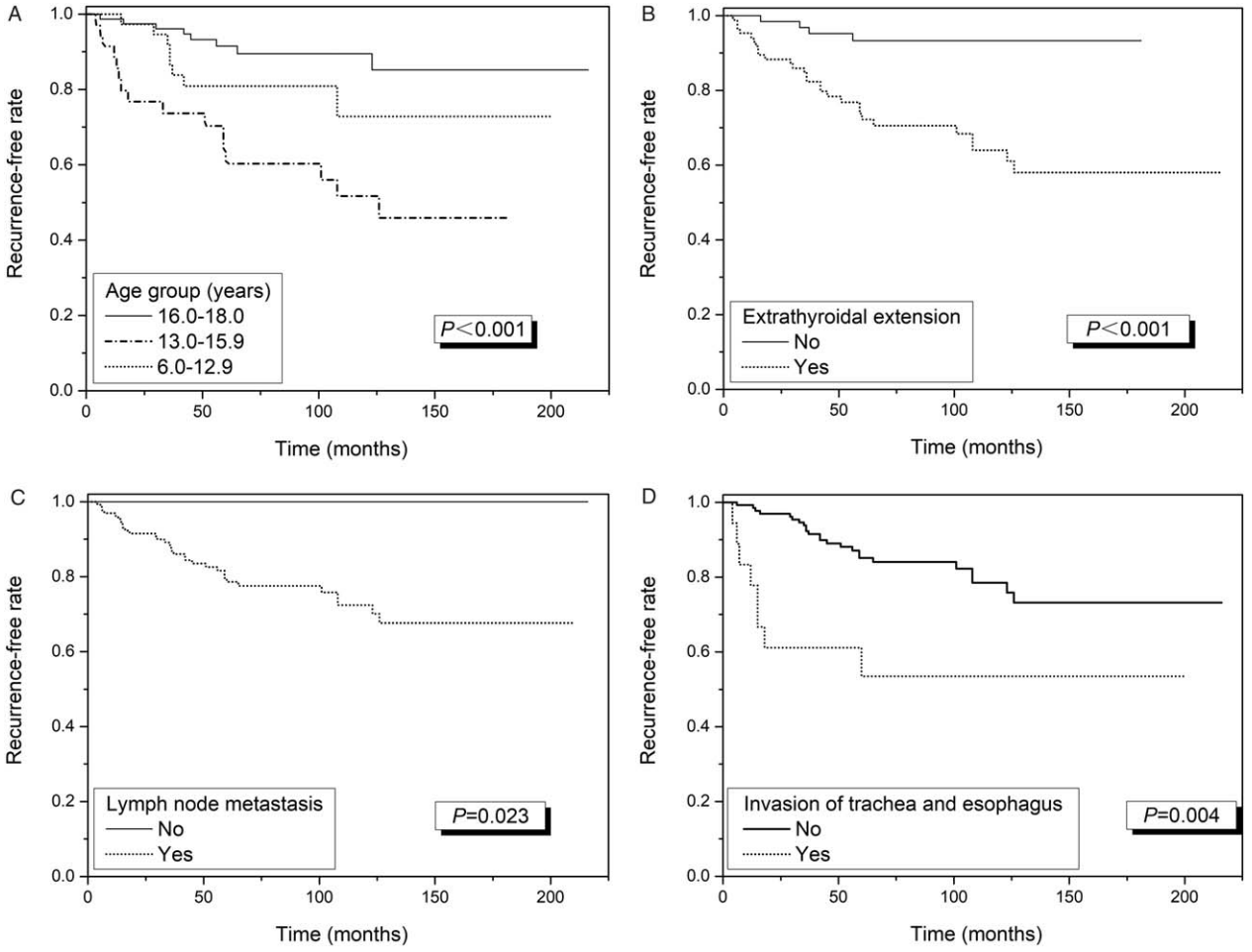

Figure 1: Rate of recurrence in 150 children and adolescents with differentiated thyroid carcinoma. Comparison of recurrence-free survival rates according to age sub-groups of 6.0 to 12.9, 13.0 to 15.9, and 16.0 to 18.0 years (A), extrathyroidal extension (B), lymph node metastasis (C), invasion of trachea and esophagus (D).

recurrence rate at 10 years of 16.8%,[13] nearly half the value in the present study.

In this study, we determined that younger age, extrathyroidal extension, lymph node metastasis, and invasion of the trachea and esophageal wall were associated with high recurrence. It is also noteworthy that the *P* value of

vascular tumor thrombus ($P = 0.055$) was very close to the boundary of statistical significance. We considered it inappropriate to exclude vascular tumor thrombus as a significant factor due to the small number of patients with vascular tumor thrombus in our study. In the multivariate analysis, age, and extrathyroidal extension were significant factors. Age, as a strong prognostic factor, is correlated with recurrence in the majority of previous reports[7,14-16]; some studies, such as those by Park *et al*,[17] failed to prove that younger age was a risk factor for recurrence, but in the same study, the younger age group exhibited more aggressive disease. Our data showed that as age increased, the sex ratio (female/male) widened, and the recurrence rate decreased. Differences in growth and development between sexes in the early stages of life may influence the occurrence and progression of thyroid cancer. An association between extrathyroidal extension and recurrence was also found in previous literature.[7,18,19] Our study confirms that extrathyroidal extension is a significant predictor of recurrence. In addition, patients with extrathyroidal extension had a higher likelihood of benefiting from post-operative ^{131}I therapy. Verburg *et al*[20] reported 76 children and adolescents with DTC, focusing on complete remission and successful ablation with ^{131}I therapy. In that study, female sex, low T stage, and high ^{131}I activity were determinants of a high rate of successful ablation. The results are partly reinforced by ours.

The extent of thyroid excision has always been a controversial issue.[9,19] Hay *et al*[11] studied 215 children and adolescents with PTC. At 40 years, the end of follow-up, the tumor recurrence rates after bilateral lobar resection and unilateral lobectomy were 25% and 65%, respectively ($P = 0.002$). Conversely, Wang *et al*[21] demonstrated that the extent of resection is not a risk factor for recurrence and recommended partial resection to avoid the possibility of post-operative complications after total thyroidectomy. Our data support the beneficial effect of total thyroidectomy in patients aged >12 years. However, we cannot ignore overly conservative operative procedures due to the propensity of our surgeons for very young patients, which could lead to statistical mistakes. Therefore, further studies of younger patient groups are required to determine the impact of total thyroidectomy.

Other literature has demonstrated that the presence of symptoms is associated with recurrence.[3,22] In our experience, almost all pediatric DTC patients visited the outpatient clinic with palpable cervical area masses found by their parents, and a small minority presented with hoarseness or dyspnea. Consequently, we believe there is little sense in debating the relationship between the presence of symptoms and recurrence. It should be noted that as we designed our study, we wanted to involve lymph node metastasis counts or density, but unlike in adult patients, we found a large proportion (more than 10%) of severe blended or sticking of lymph node metastasis specimens. In these patients, the number of lymph nodes could not be counted accurately.

In summary, the prognosis of pediatric DTC is favorable, and disease-specific death is rare. However, age and extrathyroidal extension strongly affect the recurrence rate. In view of the authors, aggressive treatment strategies and a close follow-up are recommended for younger patients and those with extrathyroidal extension. Additionally, new age-based divisions may be needed to conveniently evaluate the possibility of recurrence. Total thyroidectomy is still a controversial issue. In addition, the completeness of neck dissection in each area should be ensured.

Conflicts of interest

None.

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