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Original Article

Evaluation of Prognosis of Juvenile Differentiated Thyroid Carcinoma

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Differentiated thyroid carcinoma (DTC) in juvenile patients is often an extensive and aggressive disease with a high frequency of recurrence. However, the prognosis is excellent, with a low mortality rate even when advanced disease is present, although prognostic factors and treatment strategy remain uncertain. Between April 2004 and March 2017, 33 juvenile patients (< 30 years old) were diagnosed with DTC and treated at our institution. We retrospectively investigated prognosis and factors including sex, reason for discovery, treatment, pathological factors and treatment progress to clarify the risk factors. All patients underwent curative surgical treatment. Pathologically, lymph node metastasis was identified in 25 patients (75%). Thirteen patients (39%) had bilateral cervical metastasis. In addition, 9 (27%) had more than 10 metastatic lymph nodes. The 2 patients with more than 20 metastatic lymph nodes were treated with radioactive iodine (RAI). Five patients (15%) had local recurrences and received surgery. There have been no further recurrences or deaths. However, no factors were determined to significantly predict the recurrence of juvenile DTC. Local recurrent disease was treated with surgery and/or RAI until remission, and survival was excellent in juvenile DTC.

Key words: differentiated thyroid carcinoma, juvenile, children

Juvenile differentiated thyroid carcinoma (DTC), papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) are rare malignancies, collectively accounting for 0.5-3% of childhood carcinomas [1]. However, recent data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program have shown that the incidence of thyroid cancer in childhood is increasing [2, 3]. DTC in children is, in many ways, a disease distinct from DTC in adults [4-8]. Although children most often present with extensive and aggressive disease and have a higher frequency of recurrence, their prognosis is excellent, with a low mortality rate even when advanced disease is present.

Recently, the American Thyroid Association (ATA), recognizing these differences, released 2 separate guidelines for thyroid nodules and DTC specific to children and adults [9, 10]. The current recommendation for the initial management of these young patients is total thyroidectomy followed by radioactive iodine (RAI), if the patient is a good candidate, and levothyroxine suppressive therapy [4, 5, 9]. Several prognostic factors have been well established and are currently cited in the ATA Adult DTC Guidelines: extremes of age, relatively large tumors, multicentricity, extrathy-

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roidal extension (Ex), lymph node metastasis, vascular invasion, and elevated postoperative thyroglobulin [10]. In contrast, conflicting results related to these prognostic factors have been reported in juvenile cases [11-13]. Local cancer relapse is more frequent in juveniles than in adults. Recurrence in cervical lymph nodes requires surgical intervention, with the potential risk of postoperative complications. Despite the high recurrence rate, juvenile DTC generally has an excellent outcome and overall prognosis [14-17]. This study aimed to retrospectively analyze the probability of recurrence, prognostic factors, treatments, and outcomes of juvenile DTC.

Patients and Methods

We defined patients under age 30 years as having juvenile onset. Between April 2004 and March 2017, 33 juvenile patients were diagnosed with DTC and treated at the Okayama University Hospital. We retrospectively investigated clinical and pathological factors, operative methods, factors related to recurrence, postoperative treatment plans, and treatment progress. This study was approved by the Ethics Committee of Okayama University Hospital (No.1907-010) and adhered to the Declaration of Helsinki.

Treatment. We tailor our DTC surgical strategies to individual patients, as described below. We consider total thyroidectomy to carry a risk of serious complications, especially in juveniles, such as recurrent nerve paralysis, postoperative bleeding, hypothyroidism, hypocalcemia, and so on. We usually select hemithyroidectomy unless gland metastasis and/or cervical lymph node metastasis is present, in which case RAI treatment is indicated. In addition, all patients who received total thyroidectomy and/or RAI were also treated with L-thyroxine at suppressive doses. We do not alter our DTC treatment policy according to age.

Ipsilateral modified neck dissection was performed for patients with >1 cm tumor size, extrathyroidal extension and lymph node metastases. We preoperatively diagnosed lymph node metastasis using ultrasound (US) or positron emission tomography/computed tomography (PET/CT). If it was difficult to diagnose the metastases, we performed fine-needle aspiration biopsy.

Statistical analysis. This was a non-planned, retrospective, exploratory project. All available cases were studied without a predefined sample size calculation to detect a specific effect size or reach a certain level of power. We used Cox proportional hazard model analysis to identify factors potentially related to recurrences. Data were analyzed with EZR (version 1.37). *P* values of < 0.05 were considered to indicate a statistically significant difference [18].

Results

Patient characteristics and preoperative diagnosis. Patient characteristics are presented in Table 1. The median age was 25 (11-30) years. Six patients (18%) were male and 27 female (82%); the male/female ratio was 1 : 4.5. The median follow-up period was 61 months (4-122). The reasons for detection of malignancy were as follows: examination at a school or company workplace in 10 cases (30%); self-detection of a neck lump

Table 1 Clinicopathological characteristics and preoperative diagnosis of juvenile DTC patients (n = 33)

Characteristics	N = 33
Sex	
Male	6 (18%)
Female	27 (82%)
Age (median year)	25 (11–30)
Observation period (median month)	61 (4–122)
Discovery motive	
Neck lump	7 (21%)
Pointed out by friends	2 (6%)
Examination by school or company	10 (30%)
Follow-up of other thyroid disorder	2 (6%)
Hospital consultation with a cold	5 (15%)
found by CT inspection with other diseases	7 (21%)
Tumor location	
Unilaterality	29 (88%)
Right lobe	18 (54%)
Left lobe	11 (33%)
Bilaterality	4 (12%)
Tumor size (median mm)	23 mm
T1	15 (45%)
T2	14 (42%)
T3	4 (12%)
Lymph node metastasis	
N0	22 (66%)
N1a	3 (9%)
N1b	8 (24%)

in 7 (21%); detection during CT for other diseases in 7 (21%); notification by friends in 2 (6%); and follow-up for other thyroid disorders in 2 (6%).

The tumor locations were unilateral in 29 cases (88%) and bilateral in 4 (12%). The median clinical tumor size was 23 mm (9-60: cT1 was confirmed in 15 cases (45%), cT2 in 14 (42%) and cT3 in 4 (12%)). Eleven patients (33%) were judged to have lymph node metastasis by US or PET/CT. Three (9%) had N1a and 8 (24%) had N1b disease. No patients had distant metastasis. Regarding TNM staging, all patients were classified as stage I.

Treatment. Surgical treatments are listed in Table 2. Seven patients (21%) underwent total thyroidectomy, 4 (12%) because they had thyroid cancer beyond glandular metastasis. All 7 patients had lymph node metastasis. The dissection range was ipsilateral cervical dissection in 27 cases (81%) and bilateral cervical dissection (BCLN) in 5 (15%). We added RAI to the treatment regimen for 2 patients because both had over 20 metastatic lymph nodes and Ex.

Pathological diagnosis. The pathological diagnoses are listed in Table 2. Thirty-one patients (91%) had PTC, 1 (3%) had FTC, and 1 (3%) had widely invasive FTC. The median tumor size was 26 mm (7-70). Sixteen cases (48%) had Ex. Regarding pT staging, 11 patients (33%) had pT1, 6 (16%) pT2, 14 (42%) pT3, 1 (3%) pT4a, and 1 (3%) pT4b.

Cervical lymph node metastasis was identified in 25 patients (75%). Thirteen patients (39%) had bilateral cervical metastasis. In addition, 9 (27%) had more than 10 metastatic lymph nodes.

Prognosis. During a median follow-up of 61 months, 28 patients (84%) remained disease free and 5 (15%) had local recurrences. The characteristics of patients who had recurrent disease, including treatments and progress, are presented in Table 3. Three patients (9%) underwent surgical removal of metastatic lymph nodes; one was treated with BCLN, and one with total thyroidectomy + BCLN. These patients tended to have numerous metastatic lymph nodes. Postoperatively, we did not administer RAI, due to concerns about adverse effects on fertility. There have been no further recurrences or deaths in these patients. The risk factors related to recurrence were analyzed by Cox proportional hazard model analysis (Table 4). The hazard ratios were 0.9 for age, 1.98 for sex, 1.02 for tumor size, 0.61 for Ex, and 0.95 for the number of lymph nodes. However, none of these factors reached statistical significance.

Discussion

In recognition of the age-related differences in DTC, The American Thyroid Association released two separate guidelines for thyroid nodules and DTC specific to children and adults [9,10]. The current recommendation for the initial management of young patients is total thyroidectomy followed by RAI, based on suitable indications, and levothyroxine suppressive therapy [4,5,9].

In previous reports, juvenile DTC was usually extensive and aggressive with a higher frequency of recurrence than other thyroid tumors. The prognosis is excellent, however, with a low mortality rate, even when advanced disease is present. Our research yielded

Table 2 Postoperative pathological diagnosis including the existence of extrathyroid extension and lymph node metastasis.

Operation of thyroid	
Hemithyroidectomy	26 (78%)
Total thyroidectomy	7 (21%)
Cervical lymph node dissection	
D1	5 (15%)
D2	22 (66%)
D3	5 (15%)
Pathological diagnosis	
Papillary carcinoma	31 (91%)
Follicular carcinoma	1 (3%)
Follicular carcinoma, widely invasive	1 (3%)
Tumor diameter (median mm)	26 mm
T1	11 (33%)
T2	6 (18%)
T3	14 (42%)
T4a	1 (3%)
T4b	1 (3%)
Extra-thyroid extension	
Ex 0	17 (51%)
Ex 1	16 (48%)
Lymph node metastasis	
N0	8 (24%)
N1a	12 (36%)
N1b	13 (39%)
Number of node metastasis	
1～4	8 (24%)
5～9	8 (24%)
≧10	9 (27%)

Table 3 Characteristics, pathological factors, treatments and outcomes of 5 patients with local recurrences

	Sex	Year of diagnosis	Tumor location	Surgical treatment	Tumor size (mm)	Ex	Number of metastatic lymph node(s)	Period until local recurrence (months)	Treatment for recurrence	Disease free period after treatment of local recurrence (months)
1	M	11	R	Hemi-thyroidectomy ＋BCLN	13	＋	14	3	Surgical removal of metastatic lymph node	67＋
2	F	23	L	Hemi-thyroidectomy ＋CLND	21	＋	7	24	Surgical removal of metastatic lymph node	43＋
3	F	25	R	Hemi-thyroidectomy ＋BCLN	18	－	7	72	Surgical removal of metastatic lymph node	72＋
4	M	29	R	Total thyroidectomy ＋BCLN	exited gland metastasis (right 40, left 15)	＋	20	120	BCLN	122＋
5	F	30	R	Hemi-thyroidectomy ＋BCLN	34	＋	14	24	Total thyroid-ectomy ＋BCLN	109＋

※M: male, F: female, R: right, L: left

Table 4 The hazard ratios of risk factors by Cox proportional hazard model analysis

Risk factor	Hazard rate	95% CI	p value
Sex (male/female)	1.98	(0.18–21.5)	0.58
Age (year)	0.9	(0.74–1.09)	0.28
Tumor size (mm)	1.02	(0.9–1.15)	0.78
Tumor location (unilaterality/bilaterality)	0.64	(0.07–5.84)	0.7
The number of metastatic lymph nodes	0.95	(0.8–1.13)	0.57
Over 10 metastatic lymph nodes (10＜/≦10)	0.74	(0.13–4.16)	0.73
Extrathyroidal extension	0.61	(0.12–3.05)	0.55
Operation (partial/total thyroidectomy)	0.22	(0.02–2)	0.18

the same results. Ex, more than 10 metastatic lymph nodes, and cervical lymph node metastasis were found in 48%, 27% and 75% of our cases, respectively. None had remote recurrence.

On the other hand, the results for recurrence factors have differed among studies. Mihailovic *et al.* evaluated potential prognostic factors in patients who were relatively young at diagnosis, and found that less aggressive initial treatment and tumor multifocality were associated with recurrence. They also found no associations between recurrence and either sex or metastasis, whether distant or involving lymph nodes [11].

Demidchik *et al.* studied 740 children and found that age and multifocality strongly affected recurrent nodal disease [19]. Enomoto *et al.* studied 142 pediatric patients with DTC, with a median follow-up of 22 years, and reported that age (< 16 years), a familial history of thyroid cancer, tumor size, large lymph node metastases, and Ex were risk factors for recurrent disease [20]. Conversely, Vaisman *et al.* reported that the only two factors associated with recurrent disease were lymph node metastasis and distant metastasis. In his cohort, age, sex, tumor size, and multicentricity did not predict the success of initial therapy [12].

As may be seen from these reports, prognostic and recurrent factors remain to be clarified. There may be differences in the causes of DTC. Demidchik's report is from Belarus, which was strongly influenced by Chernobyl, so we consider it might be characteristic of DTC affected by radiation. Moreover, the definitions of young age differ among studies and are difficult to determine in the context of DTC. Enomoto's report considers children < 20 years old, and the median follow-up term is over 20 years. We consider the results of this report to be of great value due to the long follow-up period. In our study, the median age was 25 years and 26 patients (79%) were over 20 years old. If we could have followed them for a longer time or increased the number of cases, we might have obtained better results.

Other reports have shown that the extent of initial surgical treatment is a factor predicting recurrence. Some studies have revealed total thyroidectomy to be associated with better recurrence-free survival [21, 22]. Nevertheless, others found no relationship between the extent of surgery and the recurrence rate [14, 23]. Recurrence risk might be related to RAI treatment. Chow *et al.* reported that RAI reduced the risk of both locoregional and distant recurrences. They detected neither secondary malignancy nor impairment of fertility in patients undergoing RAI, and there were no impacts on pregnancy outcomes [24].

No risk factors in our analysis were clearly associated with either recurrence or overall survival, at least in the short term. Furthermore, no distant metastases were detected in our patients. Previous reports on distant metastasis noted different rates, some as low as 2.3%, with most being in the 6-25% range [2, 8, 15, 17, 19, 22, 25].

Overall, thyroid cancer in juveniles has an excellent prognosis, with 97-99% survival at 10 years, and 90-95% survival at 20 years [14, 19, 22, 25]. Hogan *et al.* reported 90% survival at 30 years, and Hay *et al.* described a 98% survival rate at 30-50 years after surgery [2, 17].

There were some limitations to this research. First, our study was a retrospective observational study, so the number of patients was small and the follow-up period short. Second, juvenile persons often move for school or work, so follow-up at the same hospital is difficult. Third, we were not actively conducting thyroid ultra-sound screening for juveniles, and the motive for discovery was often accidental.

Further study with a larger number of juvenile patients and longer observation period is needed.

In conclusion, juvenile thyroid cancer tends to be more highly associated with lymph node metastasis and extrathyroidal invasion than adult thyroid cancer. Local recurrent disease has been treated with surgery and/or RAI until remission and the survival rate is excellent. Further consideration is warranted to determine the optimal treatment strategy, including surgical procedures and radiation and their risk factors.

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