대한두경부종양학회지, 제36권 제2호, 2020. pp.9-15
Korean Journal of Head & Neck Oncology, Vol.36, No.2
https://doi.org/10.21593/kjhno/2020.36.2.9
ISSN 1229-5183(Print) / ISSN 2586-2553(Online)

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Age and Tumor Size is a Prognostic Factor in Pediatric/Adolescent Differentiated Thyroid Carcinoma

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= Abstract =

Background/Objectives: To analyze the clinical characteristics of differentiated thyroid cancer (DTC) in children and adolescents.

Materials & Methods: Medical records of 31 DTC cases that were diagnosed and treated at Korea Cancer Center Hospital between 2002 and 2018 were retrospectively reviewed.

Results: Most cases were papillary carcinoma (n=26), with female predominance (n=25). Median age was 16.4 years (range, 11.9-18.6 years). Extrathyroidal extension was present in 24 cases. Twenty cases had tumor involvement at cervical lymph nodes and three had lung metastasis. Twenty-two patients received radioactive iodide treatment with a median cumulative dose of 300 mCi (range, 100-920 mCi). During a median follow-up of 68.2 months (range, 2.3-191.4 months), serum thyroglobulin level was elevated in 15 patients. Among them, two cases had remnant thyroid tissue, 4 had recurrence at cervical lymph nodes, and the remaining 9 did not have any detectable lesion. All were alive, and 5-year event-free survival (EFS) was 45.2±10.1%. Age £15 years, tumor size, lymph node status (N1b), and distant metastasis had negative effects on EFS. On multivariate analysis, age and tumor size had prognostic significance.

Conclusion: For DTC of children and adolescents (£18 years old), age ≤15 years and tumor size were prognostic factor. Therefore, patients in this age group need meticulous follow-up. Further studies are necessary to answer the potential influence of age on the incidence and behavior of DTC.

Key Words : Thyroid carcinoma · Children · Adolescent · Prognosis

Introduction

Differentiated thyroid cancer (DTC) is rare in children and adolescents, with an age-adjusted incidence rate of 0.7-1.7 per 100,000.[1,2] DTC in children and adolescent is different from that in adults in clinical features and outcomes.[3] It is often more advanced (with increased incidence of bilateral and multifocal disease) and recurs more often than in adults.[4,5] On the other hand, an inverse relationship was found between patient age at presentation and the likelihood of positive response to treatment.[6] However, large-scale clinical studies are scarce in children and adolescents, and treatment regimen often refers to those for adults. Moreover,

Received : July 1, 2020
Revised : November 2, 2020
Accepted : November 4, 2020
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risk of cancer in thyroid nodules is higher in children and adolescents, compared to adults.[7-10] Pediatric papillary thyroid cancer shows a higher prevalence of gene rearrangement and a lower frequency of point mutations in the proto-oncogenes implicated in papillary thyroid cancer.[11] *BRAF* mutations are the most common abnormality in adults with papillary thyroid cancer, but they are rare in children with papillary thyroid cancer.[10,12,13]

In this retrospective study, we analyzed the clinical characteristics of pediatric/adolescent DTC cases that were diagnosed and treated at our hospital. Especially, we aimed to find clinical variables that are related with structural or biochemical recurrences of DTC.

Methods

Between 2002 and 2018, a total of 59 children and adolescents (£18 years old) with DTC were registered at Korea Cancer Center Hospital database. For this retrospective study, we selected 31 patients who met the following criteria: (1) diagnosis of differentiated thyroid carcinoma which includes papillary carcinoma and follicular carcinoma; (2) no history of previous treatment; (3) received treatment and was followed at our hospital. The Institutional Review Board of Korea Cancer Center Hospital approved this study (IRB No. 2019-01-006) and their medical records were reviewed.

The general treatment guidelines for thyroid carcinoma were as follows: Initially, patients underwent neck CT and full laboratory tests, including serum TSH, free T4, T3, thyroglobulin, anti-thyroglobulin antibody, anti-microsome antibody, parathyroid hormone and calcitonin. All patients underwent total/subtotal thyroidectomy or thyroid lobectomy depending on the disease stage at the time of diagnosis; afterwards, patients who had undergone total/subtotal thyroidectomy received radioactive iodine (RAI) therapy (100-200 mCi). The dose of RAI was empirically determined by the treating nuclear medicine physician, based on the tumor extent and patient age. RAI therapy was repeated when their serum thyroglobulin was elevated, or until no clinical evidence of remnant thyroid tissue and functioning metastasis based on post-treatment RAI scan. Cervical ultrasonography, chest CT, and diagnostic ^{123}I whole body scan were performed within 1 year after RAI therapy. Cervical ultrasonography was performed annually for 5 years, then once every 2 years. Regular follow-up evaluations were performed every 6 months with clinical assessment and with laboratory tests including complete blood counts (CBC), chemistry, serum TSH, thyroglobulin and anti-thyroglobulin antibody levels.

To identify factors that could predict treatment outcome of pediatric/adolescent DTC, Kaplan-Meier survival analysis was used to examine relations between clinicopathologic variables and EFS. The variables assessed included age, sex, pathologic diagnosis, tumor size, multifocality, extrathyroidal extension (ETE), lymph node involvement, and distant metastasis at the time of diagnosis. Events were defined as either elevated serum thyroglobulin level or clinically detectable diseases during the follow-up period. The log-rank test was used to calculate survival differences according to clinicopathologic variables. Factors found to influence the EFS on univariate analysis were analyzed by multivariate analysis using Cox's proportional hazard regression model, results of which are reported with relative risks and 95% confidence intervals. Patients were divided into 2 groups, using the cut-off value of 15 years. Chi-square tests were used to compare the above-mentioned variables between the two age groups. All calculations were performed using SPSS version 13.0 software (SPSS Inc, Chicago, IL), and *P*-values of < 0.05 was considered significant.

Results

Patient Characteristics and Treatment

The clinicopathologic characteristics of the patients are summarized in Table 1. All patients were older than 10 years with a median age of 16.4 years (range, 11.9-18.6 years). The pathologic diagnosis was papillary carcinoma in 26 patients (including 2 follicular variant and 3 microcarcinoma), and follicular carcinoma in 5 cases. There were 25 female and 6 male patients. Three cases had previous cancer history and one patient had synchronous primary tumors, including papillary thyroid carcinoma. Case No. 2 had a rhabdomyosarcoma at the maxillary sinus and was treated with surgery and chemotherapy. However, thyroid cancer developed 38 months after rhabdomyosarcoma treatment was completed. Case No. 27 received treatment for

Table 1. Summary of the 31 patients

Case	sex	Age (years)	Disease history	Diagnosis	TNM stage					Surgery	RAI (mCi)	Events (mo)	FU (mo)
					T			N	M				
					Size (cm)*	Number	ETE						
1	F	18.4		PCfv	2.5	2	+	+	-	TT	176		164.5
2	F	16.2	RMS	PC	2.8x2.3	1	-	-	-	Lobectomy	356	↑Tg (18.6)	191.4
3	F	15.4		PC	3.5x3.5	1	+	+	-	TT	360	↑Tg (16.6)	184.4
4	F	16.9		PC	1	Multiple	-	ND	-	subtotal T	330	↑Tg (20.7)	141.7
5	F	15.1		PC	2.3x1.5	2	+	+	-	TT	300	Recur at cervical LNs (30.3)	165.4
6	F	17.3		PC	1x0.8	1	+	+	-	TT	330	↑Tg (15.9)	164.2
7	F	16.7		FC	2.5x2.5	1	+	ND	-	Lobectomy			60.3
8	F	17.5		PC	1.6x1.6	10		-	-	TT	100		51.9
9	M	17.7		FC	2.6x2	1	+	ND	-	Lobectomy/CT	150		148.1
10	F	13.2		PC	4x2.5	Multiple	+	+	-	TT	450	Recur at cervical LNs (13.5)	140.5
11	F	16.9		PC	4x2.2	Multiple	+	+	lung	TT	920	↑Tg (15.4)	137.1
12	M	15.6		PC	5x4	Multiple	+	+	lung	TT		↑Tg (17.3)	134.1
13	F	15.3		PC	4x2.5	3	+	+	-	TT	180	Recur at cervical LNs (40.5)	133.3
14	F	14.2		PC	3.3x2.2	1	+	+	-	TT	510	remnants (2.8)	128.2
15	F	15.6		PC	1.4x1.0	1	+	-	-	TT	100		61.6
16	F	16.5		PC	1.1x0.7	1	-	-	-	TT	100		74.3
17	F	17.1		PC	3x2.2	2	+	+	-	TT	180		76.3
18	F	17.1		PC	0.4x0.3	1		+	-	Lobectomy			2.3
19	F	14.4		FC	4.5x4	1	+	ND	-	Lobectomy/CT	300	↑Tg (12.1)	80.4
20	F	16.4		FC	4x3.8	2	+	-	-	Lobectomy		recur at right thyroid (39.1)	68.2
21	F	17.5		PC	0.8x0.7	1	-	+	-	Lobectomy			67.3
22	F	14.8	NBL, OS	PCfv	3.5x2.7	1	+	+	-	Lobectomy			34.6
23	M	11.9		PC	1.2x1.0	1	+	+	-	TT	250	↑Tg (9.9)	44.5
24	F	18.0		PC	0.4x0.4	2	+	-	-	Lobectomy			39.4
25	F	18.6		PC	3x2.5	1	+	+	-	TT	200	↑Tg (21.9)	32.8
26	M	16.2	Ewing	PC	3.1x2.2	1	-	+	-	Lobectomy			33.9
27	F	13.6	RMS	FC	1.5x1.2	1	+	-	-	Lobectomy			34.8
28	F	15.9		PC	2x1.9	4	+	+	-	TT	100		31.8
29	M	18.2		PC	5x3.3	1	+	+	lung	TT	600	↑Tg (11.6)	27.2
30	M	12.9		PC	2.7x2.2	Multiple	+	+	-	TT	300	remnants (3.1)	22.5
31	F	17.9		PC	2.3x2	1	+	+	-	TT	150		18.2

*In patients had more than 2 tumors, size of the largest tumor is presented.
Abbreviations: CT, completion thyroidectomy; ETE, extrathyroidal extension; Ewing, Ewing sarcoma; F, female; FC, follicular carcinoma; FU, follow-up; M, male; NBL, neuroblastoma; ND, not determined; OS, osteosarcoma; PC, papillary carcinoma; PCfv, follicular variant papillary carcinoma; RAI, radioactive iodide therapy; RMS, rhabdomyosarcoma; subtotal T, subtotal thyroidectomy; TT, total thyroidectomy

rhabdomyosarcoma of vulva at the age of 3. As she grew, multiple café-au-lait spots and neurofibromas appeared. She was diagnosed as follicular carcinoma of thyroid, 8.8 years after treatment was completed. Case No. 22 was diagnosed as neuroblastoma when she was 4 months old, and received intensive treatment comprising surgery, high-dose chemotherapy and MIBG therapy. When she was 14.5 years old, the patient was diagnosed with osteosarcoma of left humerus. More, thyroid cancer was incidentally detected on chest CT, which was performed for metastatic surveillance. Case No. 26 was a 16-years-old boy diagnosed simultaneously with papillary thyroid carcinoma and Ewing sarcoma of the chest wall. Gene studies were not performed routinely, and was performed in five cases. Among them, two cases had *BRAF* V600E mutation (case No. 16 & 18).

At the time of diagnosis, three patients had lung metastasis. Tumor sizes were £2 cm in 11 cases (35.5%), >2 cm and £4 cm in 17 (54.8%), and > 4 cm in three patients (9.7%). Five patients had microcarcinoma (£1 cm). Eighteen patients had one tumor, five had two tumors and eight presented ≥3 tumors. ETE was present in 24 cases (77.4%) and 20 cases had a tumor involvement at the cervical lymph nodes.

Twenty-one patients received total or subtotal thyroidectomy. Those with microcarcinoma, follicular carcinoma and pre-

vious or synchronous primary tumors received a lobectomy. After surgery, 22 patients received radioactive iodide (RAI) treatment, including 2 cases with microcarcinoma. Case No. 4 received RAI on year 2004, when controversy existed regarding the RAI for low-risk patients. Case No. 6 had ETE and multiple lymph node involvement. The median cumulative dose of RAI was 300 mCi (range, 100-920 mCi). Serum thyroglobulin level was a useful marker; being elevated in most cases (n=25/27, 92.6%), and returning to normal after surgery.

Clinicopathologic characteristics affecting the event-free survival

Patients were followed for a median time of 68.2 months (range, 2.3-191.4 months). During follow-up, serum thyroglobulin level was elevated in 15 patients; two with remnant thyroid tissue, four structural disease (at cervical lymph nodes or contralateral lobe), and nine with biochemical disease (without clinical detectable tumor). At the time of writing, all patients were alive, and the event-free survival (EFS) at 5 years was 45.2±10.1% (Fig. 1). Age £15 years, large tumor size, lymph node status (N1b), and presence of distant metastasis at the time of diagnosis showed negative effects on EFS (Table 2). On multivariate analysis, age and tumor

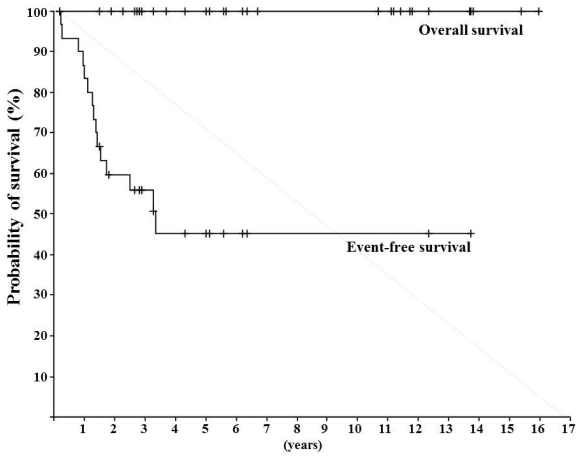

Fig. 1. Overall and event-free survival of the 31 patients with pediatric/adolescent DTC.

Table 2. Univariate and multivariate analysis for EFS according to clinicopathologic variables

Variables		5-yr EFS (%)	*P*-value	Multivariate analysis		
				RR	95% CI	*P*-value
Age	>15 years	62.0±12.5	0.035	1		
	£15 years	19.2±15.2		5.48	1.28-23.44	0.02
Sex	Male	33.3±19.3	0.14	NA	NA	NA
	Female	48.4±11.5				
Pathologic diagnosis	PC	32.7±11.5	0.19	NA	NA	NA
	PmCa	100				
	PCfv	100				
	FC	53.3±24.8				
Tumor Size	£2 cm	70.0±14.5	0.01	1		
	>2 cm, £4 cm	38.0±13.8		7.65	1.15-51.05	0.04
	>4 cm	0		27.45	2.71-277.995	0.005
Multifocality	Yes	18.8±15.8	0.14	NA	NA	NA
	No	55.7±11.4				
ETE	Yes	39.0±11.6	0.28	NA	NA	NA
	No	66.7±19.3				
Lymph node involvement	No	68.6±18.6	0.11	NA	NA	NA
	Yes	34.5±13.3				
	N0	68.6±18.6	0.014	1		
	Nx	47.6±14.0		0.35	0.04-2.99	0.34
	N1a	100		0.00		0.99
	N1b	25.0±15.3		5.51	0.96-31.64	0.07
Metastasis at diagnosis	No	50.2±10.8	0.01	1		
	Yes	0		1.26	0.15-10.63	0.83

Abbreviations: EFS, event-free survival; ETE, extrathyroidal extension; NA, not analyzed; PC, papillary carcinoma; PCfv, follicular variant papillary carcinoma; PmCa, papillary microcarcinoma; FC, follicular carcinoma

size remained statistically significance (Table 2).

Moreover, we observed that DTC of a patient ≤15 years have a more aggressive feature. Sex, tumor size, multifocality, and cervical lymph node involvement were not statistically different between the two groups (Table 3). Peculiarly, microcarcinoma was found only in patients > 15 years (n=5). All the cases ≤15 years had ETE, while 61.1% (n=11/18) of the tumors of patients > 15 years had ETE (P=0.01). Though the number of courses (median 2 *vs.* 1.5) and cumulative dose (median 342.7 mCi vs. 299.3 mCi) of RAI therapy were slightly higher in patients who were ≤15 years, this was not statistically different (P=0.67). Compared to the patients > 15 years, cases ≤15 years suffered more events, and had a lower 5-year EFS (P=0.035, Table 3).

Discussion

This retrospective study analyzed the clinicopathologic characteristics of DTC in children and adolescents, and found that age and tumor size were an important prognostic factor. DTC in patients £15 years had a more aggressive feature than adolescents, with more ETE and recurrence. Most of our cases were treated similarly as adult patients, using total/subtotal thyroidectomy, RAI therapy and monitoring serum thyroglobulin levels. However, some cases that were diagnosed in early 2000's received RAI after lobectomy, when controversy existed regarding the use of RAI for low-risk patients. Our patients had an excellent overall survival (100% at the time of writing), including those with lung metastasis and local recurrence.

Our study has several limitations. First, this was a retrospective study involving a small number of patients, and treatments did not exactly follow the ATA guidelines, especially for those with follicular carcinoma or synchronous primary tumors. For follicular carcinoma, controversy exists about the long-term outcomes and risk-stratification of children who would benefit from more extensive thyroid surgery and RAI. It is suggested that minimally invasive FTC (< 4 cm) and with no or minimal vascular invasion should be treated on a case-by-case basis, but lobectomy alone rather than total thyroidectomy with RAI may be sufficient.[11] Second, proportion of patients with advanced disease (77.4% had ETE) was higher, compared to other case series. We assume that selection bias might exist, related with referral system or delayed diagnosis of rare tumor in children. We could not precisely determine the American Thyroid Association (ATA) pediatric risk levels of the 31 patients, due to retrospective nature of our study.[11] However, we surmise that substantial number of cases might belong to intermediate- and high-risk group.

We observed that age ≤15 years and tumor size were associated with advanced disease at presentation (ETE), and an independent prognostic factor for recurrences of DTC. Previous studies have reported that multifocality is more frequent in pediatric than in adult patients, and was considered a risk factor for recurrence.[3,14] However, our data failed to show prognostic significance of multifocality on outcome of DTC in children and adolescents. Age has also

Table 3. Tumor characteristics and outcome according to age

			£15 years (n=13)	>15 years (n=18)	*P*-value
Sex (M:F)			3:10	3:15	0.66
Tumor size	£2 cm		4 (30.8%)	7 (38.9%)	0.64
	>2 cm, £4 cm		7 (53.8%)	10 (55.6%)	
	>4 cm		2 (15.4%)	1 (5.6%)	
Multifocality			5 (38.5%)	3 (16.7%)	0.17
Involvement of neck lymph nodes*			10 (83.3%)	10 (66.7%)	0.47
Extrathyroidal extension			13 (100%)	11 (61.1%)	0.01
Metastasis			1 (7.7%)	2 (11.1%)	0.75
Events	Yes		9 (69.2%)	6 (33.3%)	0.048
	Recurrence	biochemical	4	5	
		structural	3	1	
	Remnant		2	0	
5-year event-free survival			19.2±15.2%	62.0±12.5%	0.035

*Dissection of neck nodes was performed in 27 cases, 12 in £15 years, 15 in >15 years, respectively.

been indicated as a prognostic factor by some studies.[15-17] It has been reported that age at diagnosis between 10 and 15 years were prognostic factors associated with persistent/recurrent disease.[17] In many cancers, age is an important prognostic factor and implies different molecular pathogenesis.[18,19] We adopted same treatment approach both for children and adolescents with DTC, however, patients ≤15 years had a more tumor recurrence and lower EFS. Albeit the aggressive feature, our children with DTC showed good response to treatments. This might be the consequence of high expression in thyroid cells of sodium-iodide symporter (NIS) protein, involved in response to RAI therapy.[20,21] We assume that differential molecular characteristics of pediatric DTC, such as *RET/PTC* rearrangement and less genomic instability, might be one of the reasons for better response in children and adolsecents.[13,22,23]

Despite a relatively short follow-up period, we did not observe any serious long-term sequelae in the 23 patients who received RAI treatment, including secondary malignancies. The most controversial part about the treatment guideline in pediatric/adolescent DTC is the use of adjunctive ^{131}I therapy, especially concern on the risk of long-term side effects.[24-29] Follow-up studies spanning several decades reported an increase in all-cause mortality for survivors of pediatric DTC.[30] The predominant cause was secondary malignancies related to radiation.[31,32] In 2015, the ATA had published the Management Guideline for Children and Thyroid Nodules and DTC.[11] To select children who might benefit from additional surgery and/or RAI therapy, children with DTC should be stratified into three risk levels based on their clinical presentation, tumor size, and evidence of regional invasion and metastasis.[11] Unfortunately, some of the surgery data (esp. lymph node status) are missing and we could not determine the risk levels of the 31 patients. However, we estimate that substantial number of cases might belong to intermediate- and high-risk group.

In summary, albeit excellent overall survival, age (≤15 year) and tumor size were adverse prognostic factors for pediatric/adolescent DTC, related with more ETE and recurrences. We cautiously assume that higher recurrence rate might result in more frequent RAI therapy in children, despite concerns on the long-term side effects related with radiation. Therefore, while applying the same ATA treatment guidelines on pediatric/adolescent DTC, meticulous follow-up might be necessary for young children who are younger than 15 years. Future studies should be designed to involve a higher number of children and adolescents to answer the potential influence of age on the incidence and behavior of thyroid cancer in this age group.

Acknowledgement

This study was supported by a grant of the Korea Institute of Radiological and Medical Sciences (KIRAMS), funded by Ministry of Science and ICT (MSIT), Republic of Korea. (No.50541-2019)

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