소아청소년 갑상선암 환자들의 예후인자

변병현[1] · 이국행[2] · 김동호[3] · 임중섭[3] · 임일한[1] · 임상무[1] · 이병철[2] · 이준아[3+]

원자력병원 핵의학과[1], 이비인후과[2], 소아청소년과[3]

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

Byung Hyun Byun, MD[1], Guk Haeng Lee, MD[2], Dong Ho Kim, MD[3], Jung Sub Lim, MD[3], Ilhan Lim, MD[1], Sang Moo Lim, MD[1], Byeong Cheol Lee, MD[2], Jun Ah Lee, MD[3+]

Department of Nuclear Medicine[1], Otolaryngology[2], Pediatrics[3]
Korea Cancer Center Hospital, Seoul, Korea

= 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,

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 ultra-

sonography 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
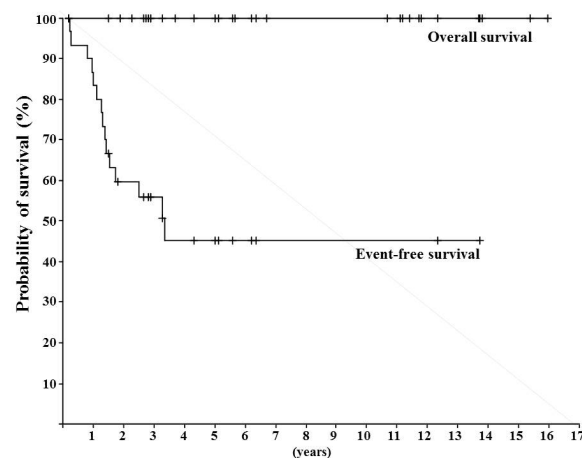

Fig. 1. Overall and event-free survival of the 31 patients with pediatric/adolescent DTC.

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

References

1. Siegel DA, King J, Tai E, Buchanan N, Ajani UA, Li J. *Cancer incidence rates and trends among children and adolescents in the United States, 2001-2009. Pediatrics. 2014;134:e945-955.*

2. Cho YY, Jang HW, Joung JY, Park SM, Jeong DJ, Kim SW, et al. *Trends in thyroid cancer incidence in Korean children (1999-2012) based on palpation and nonpalpation detection methods. Eur Thyroid. 2015;4:252-259.*

3. Welch Dinauer CA, Tuttle RM, Robie DK, McClellan DR, Svec RL, Adair C, et al. *Clinical features associated with metastasis and recurrence of differentiated thyroid cancer in children, adolescents and young adults. Clin Endocrinol (Oxf). 1998;49:619-628.*

4. Jarzab B, Handkiewicz Junak D, Wloch J, Kalemba B, Roskosz J, Kukulska A, et al. *Multivariate analysis of prognostic factors for differentiated thyroid carcinoma in children. Eur J Nucl Med. 2000;27:833-841.*

5. Handkiewicz-Junak D, Wloch J, Roskosz J, Krajewska J, Kropinska A, Pomorski L, et al. *Total thyroidectomy and adjuvant radioiodine treatment independently decrease locoregional recurrence risk in childhood and adolescent differentiated thyroid cancer. J Nucl Med. 2007;48:879-888.*

6. Russo M, Malandrino P, Moleti M, Vermiglio F, D'Angelo A, La Rosa G, et al. *Differentiated thyroid cancer in children: Heterogeneity of predictive risk factors. Pediatr Blood Cancer. 2018;65:e27226.*

7. Niedziela M. *Pathogenesis, diagnosis and management of thyroid nodules in children. Endocr Relat Cancer. 2006;13:427-453.*

8. Gharib H, Papini E, Valcavi R, Baskin HJ, Crescenzi A, Dottorini ME, et al. *American Association of Clinical Endocrinologists and Associazione Medici Endocrinologimedical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract. 2006;12:63-102.*

9. Gupta A, Ly S, Castroneves LA, Frates MC, Benson CB, Feldman HA, et al. *A standardized assessment of thyroid nodules in children confirms higher cancer prevalence than in adults. J Clin Endocrinol Metab. 2013;98:3238-3245.*

10. Parisi MT, Eslamy H, Mankoff D. *Management of differentiated thyroid cancer in children: Focus on the American Thyroid Association pediatric guidelines. Semin Nucl Med. 2016;46: 147-164.*

11. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, et al. *Management guidelines for children with thyroid nodules and differentiated thyroid cancer. Thyroid. 2015; 25:716-759.*

12. Penko K, Livezey J, Fenton C, Patel A, Nicholson D, Flora M, et al. *BRAF mutations are uncommon in papillary thyroid cancer of young patients. Thyroid. 2005;15:320-325.*

13. Yamashita S, Saenko V. *Mechanisms of disease: Molecular genetics of childhood thyroid cancers. Nat Clin Pract Endocrinol Metab. 2007;3:422-429.*

14. Lee YA, Jung HW, Kim HY, Choi H, Kim HY, Hah JH, et al. *Pediatric patients with multifocal papillary thyroid cancer have higher recurrence rates than adult patients: a retrospective analysis of a large pediatric thyroid cancer cohort over 33 years. J Clin Endocrinol Metab. 2015;100:1619-1629.*

15. Mihailovic J, Nikoletic K, Srbovan D. *Recurrent disease in juvenile differentiated thyroid carcinoma: prognostic factors, treatments, and outcomes. J Nucl Med. 2014;55:710-717.*

16. Newman KD, Black T, Heller G, Azizkhan RG, Holcomb 3rd GW, Sklar C, et al. *Differentiated thyroid cancer: determinants of disease progression in patients <21 years of age at diagnosis: a report from the Surgical Discipline Committee of the Children's Cancer Group. Ann Surg. 1998;227:533-541.*

17. Remiker AS, Chuang J, Corathers S, Rutter MM, Rutter MJ, Myer 4th CM, et al. *Differentiated thyroid cancer in the pediatric/adolescent population: evolution of treatment. J Pediatr Hematol Oncol. 2019;41:532-536.*

18. Roberts KG. *Genetics and prognosis of ALL in children vs adults. Hematology Am Soc Hematol Educ Program. 2018;2018:137-145.*

19. Huang X, Shu C, Chen L, Yao B. *Impact of sex, body mass index and initial pathologic diagnosis age on the incidence and prognosis of different types of cancer. Oncol Rep. 2018;40:1359-1369.*

20. Mitsutake N, Knauf JA, Mitsutake S, Mesa C Jr, Zhang L, Fagin JA. *Conditional BRAFV600E expression induces DNA synthesis, apoptosis, dedifferentiation, and chromosomal instability in thyroid PCCL3 cells. Cancer Res. 2005;65:2465-2473.*

21. Saavedra HI, Knauf JA, Shirokawa JM, Wang J, Ouyang B, Elisei R, et al. *The RAS oncogene induces genomic instability in thyroid PCCL3 cells via the MAPK pathway. Oncogene. 2000; 19:3948-3954.*

22. Monaco SE, Pantanowitz L, Khalbuss WE, Benkovich VA, Ozolek J, Nikiforova MN, et al. *Cytomorphological and molecular genetic findings in pediatric thyroid fine-needle aspiration. Cancer Cytopathol. 2012;120:342-350.*

23. Fenton CL, Lukes Y, Nicholson D, Dinauer CA, Francis GL, Tuttle RM. *The ret/PTC mutations are common in sporadic papillary thyroid carcinoma of children and young adults. J Clin Endocrinol Metab. 2000;85:1170-1175.*

24. Van Nostrand D, Neutze J, Atkins F. *Side effects of ''rational dose'' iodine-131 therapy for metastatic well-differentiated thyroid carcinoma. J Nucl Med. 1986;27:1519-1527.*

25. Smith MB, Xue H, Takahashi H, Cangir A, Andrassy RJ. *Iodine 131 thyroid ablation in female children and adolescents: long-term risk of infertility and birth defects. Ann Surg Oncol. 1994;1:128-131.*

26. Baugnet-Mahieu L, Lemaire M, Leonard ED, Leonard A, Gerber GB. *Chromosome aberrations after treatment with radioactive iodine for thyroid cancer. Radiat Res. 1994;140:429-431.*

27. Sawka AM, Lakra DC, Lea J, Alshehri B, Tsang RW, Brierley JD, et al. *A systematic review examining the effects of therapeutic radioactive iodine on ovarian function and future pregnancy in female thyroid cancer survivors. Clin Endocrinol. 2008;69:479-490.*

28. Sawka AM, Lea J, Alshehri B, Straus S, Tsang RW, Brierley JD, et al. *A systematic review of the gonadal effects of therapeutic radioactive iodine in male thyroid cancer survivors. Clin Endocrinol. 2008;68:610-617.*

29. Rivkees SA, Mazzaferri EL, Verburg FA, Reiners C, Luster M, Breuer CK, et al. *The treatment of differentiated thyroid cancer in children: emphasis on surgical approach and radioactive iodine therapy. Endocr Rev. 2011;32:798-826.*

30. Rubino C, de Vathaire F, Dottorini ME, Hall P, Schvartz C, Couette JE, et al. *Second primary malignancies in thyroid cancer patients. Br J Cancer. 2003;89:1638-1644.*

31. Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. *Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. World J Surg. 2010;34:1192-1202.*

32. Iyer NG, Morris LG, Tuttle RM, Shaha AR, Ganly I. *Rising incidence of second cancers in patients with low risk (T1N0) thyroid cancer who receive radioactive iodine therapy. Cancer. 2011;117:4439-4446.*