Original article

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Clinical characteristics, risk stratifications, and long-term follow-up of childhood differentiated thyroid cancer: a single-center experience

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Purpose: Guidelines of the Pediatric American Thyroid Association (ATA) serve as a vital reference for managing the rare thyroid cancers in childhood. This study evaluates differentiated thyroid cancer (DTC) patients using the ATA guidelines, dynamic risk stratification (DRS), and other established risk classification systems.
Methods: Pediatric patients with DTC under observation after total thyroidectomy were included in the study. We assessed preoperative and postoperative features based on the ATA guidelines, other risk scoring systems (TNM; De Groot staging; metastasis, age, completeness of resection, invasion, and tumor size; and combined risk), and the DRS.
Results: A total of 41 patients was enrolled in the study, with a median follow-up duration of 5.14±3.94 years. Of the patients who underwent total thyroidectomy, 33 were diagnosed with papillary carcinoma and 8 with follicular thyroid carcinoma. During follow-up, cervical metastases were detected in 27 patients, and one had distant metastasis. All patients underwent total thyroidectomy, and 68% received lymph node dissection. Additionally, 16 patients received radioactive iodine therapy. Of the postoperative patients, 85.3% were classified as low risk. Based on DRS, patients were classified as having no evidence of disease (n=29, 70.7%), biochemical evidence of persistent disease (n=5, 12.2%), structural evidence of persistent disease (n=6, 14.6%), and recurrent disease (n=1, 2.5%). Notably, 98% of the patients showed no evidence of disease during their latest follow-up.
Conclusion: Persistent disease in patients classified as low risk according to the ATA guidelines resolved following radioactive iodine therapy, emphasizing the importance of risk stratification in postoperative care.

Keywords: Dynamic risk stratification, Pediatric differentiated thyroid cancer, Risk classification systems

Highlights

- Despite low-risk classification by American Thyroid Association 2015, persistent and recurrent disease was observed, highlighting the need to refine current pediatric differentiated thyroid cancer (DTC) risk stratification models.
- Our study underscores the potential benefit of radioactive iodine therapy in managing persistent disease in low-risk pediatric cases, without observed severe long-term side effects.
- Findings emphasize the necessity of individualized surveillance and the potential utility of dynamic response-to-therapy systems and molecular profiling in pediatric DTC.

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Introduction

Thyroid nodules and cancers are rare in children compared to adults; however, their incidence is increasing, and they rank among the leading cancers in children [1]. Differentiated thyroid cancer (DTC) is the most common type, encompassing papillary thyroid cancer, with an 82% prevalence, and follicular thyroid cancer, with a 10% prevalence [2]. While the malignancy rate of thyroid nodules in adults is approximately 5%, it is 25% in children. Pediatric patients are more likely to present with advanced-stage disease, including lymph node involvement, distant metastases, and multifocal disease. Early diagnosis and appropriate management of thyroid cancers are significant [1,3-5].

Managing thyroid cancer requires a risk-adapted approach that considers evolving risk estimates and anticipates early intervention based on treatment response and disease progression. Several risk stratifications have been proposed [2,6-10]. The 2015 American Thyroid Association (ATA) Management Guidelines highlight the management of thyroid nodules and cancers in pediatric patients. However, in clinical practice, lymph nodes or distant-organ metastases can occur in the low-risk group, even with appropriate monitoring. This creates the need to consider other risk classifications when managing patient follow-up. Adult dynamic risk stratification (DRS) has been effective in defining persistent/recurrent disease during follow-up [11], and attempts have been made to apply it to the pediatric age group [12].

This study aims to validate the ATA staging system and compare it with other approaches to risk stratification (TNM staging; De Groot staging; metastasis, age, completeness of resection, invasion, and tumor size [MACIS], and combined risk scoring), including DRS, in evaluating treatment responses in pediatric thyroid nodules and cancers. The risk stratification specified in the pediatric ATA guidelines was compared with those of other risk scoring systems to evaluate the effectiveness and predictive value of the approaches in assessing disease prognosis and guiding treatment decisions in pediatric thyroid nodules and cancers.

Materials and methods

The study included 41 cases diagnosed with DTC and followed for at least one year between 2000 and 2022 at our clinic.

1. Follow-up

All patients received thyroid-stimulating hormone (TSH) suppression therapy. Within the first year of follow-up, all patients underwent at least one neck ultrasound evaluation after the initial treatment. During the first year of follow-up, serum thyroglobulin (Tg) and thyroglobulin antibody (TgAb) levels were measured at least twice under levothyroxine suppression. Patients were followed every month for the first 6 months, every 3 months starting from the second 6 months, and then every 6 months after the second year, depending on individual risk and the clinical course of the disease. The treatment protocol at our center was based on the pediatric ATA guidelines for patients after 2015. For cases before 2015, the treatment decisions were made in multidisciplinary meetings based on the adult ATA guidelines [8,9], and the treatment consisted of total thyroidectomy/completion total thyroidectomy, cervical lymph node dissection, administration or non-administration of ablative or therapeutic doses of radioactive iodine (RAI), and levothyroxine suppression therapy. For cases before 2015, RAI therapy was applied in patients with low risk for 3 main purposes: to eliminate thyroid remnants for easier follow-up in low-risk patients, to reduce the risk of recurrence by targeting potential cancer cells in intermediate-risk patients, and to treat known metastatic or recurrent disease. Decisions were based on individual risk factors [13,14]. Initial treatment was defined as the first surgical procedure (including "completion thyroidectomy"), the first (if applicable) RAI ablation, or initiation of thyroid hormone therapy. Recurrence was defined as the occurrence of a new disease, confirmed by RAI uptake or biopsy, in any patient who remained disease-free for at least 4 months after the initial treatment [15]. The follow-up duration was the time from thyroidectomy to the last medical visit. All patients included in the study received suppressive TSH treatment. Clinical and laboratory features of the cases were obtained retrospectively. The preoperative risk assessment included an evaluation of family history of thyroid cancer, a history of neck radiotherapy, and ultrasonographic features of the nodule (size, structure, presence of microcalcifications, margin, and intranodal vascularity). Large nodule size, presence of microcalcifications, increased intranodal vascularity, irregular nodule margin, and solid nodules were considered risk factors for thyroid cancer. Fine-needle aspiration biopsy (FNAB) results were classified according to ATA guidelines [1].

2. FNAB Bethesda classification

According to The 2023 Bethesda System for Reporting Thyroid Cytopathology [16], patients undergoing biopsy from thyroid nodules were categorized into 6 groups: nondiagnostic, benign, atypia of undetermined significance, follicular neoplasm, suspicious for malignancy, and malignant.

3. ATA staging

Postoperatively, patients were staged according to the ATA guidelines, and all patients were grouped into 3 risk categories:

(1) Low risk: disease confined to the thyroid, minimal metastasis to central lymph nodes (pretracheal/paratracheal/prelaryngeal [Delphian lymph node, level 6]).

(2) Intermediate risk: extensive level-6 involvement, minimal lateral lymph node involvement, retropharyngeal or superior

mediastinal lymph node involvement, T3 disease (tumor confined to the thyroid > 4 cm in size or minimal extrathyroidal extension independent of size).

(3) High risk: Regional extensive disease (extensive lateral/retropharyngeal/superior mediastinal lymph node involvement), locally invasive T4 tumor, invasion of a capsule with subcutaneous fat tissue, larynx, trachea, esophagus, recurrent laryngeal nerve-invading tumor (4A), tumor invading prevertebral fascia or carotid artery and/or mediastinal vessels (4B) [1].

4. MACIS scoring

The MACIS score, which is used to predict persistent or recurrent disease, was calculated for all patients using the formula 3.1 + 0.3 (tumor size [cm]) + 1 (if completely resected) + 1 (if locally invasive) + 3 (if distant metastasis is present). A MACIS score greater than 4 was considered predictive of recurrence [7].

5. DeGroot staging

DeGroot et al. [6] classified patients into 4 stages based on the extent of disease spread. Patients with intrathyroidal disease were classified as stage I, those with any cervical lymph node involvement as stage II, those with extrathyroidal tumor invasion or inadequate lymph node resection as stage III, and those with distant metastasis as stage IV.

6. Combined risk classification

Patient at high risk were defined as those aged <10 years with an MACIS score >8, an advanced TNM stage, postoperative Tg >70 ng/mL, and a positive anti-Tg status. Patients at low risk were defined as those aged ≥10 years with an MACIS score <6, a low TNM stage, postoperative TG <70 ng/mL, and a negative anti-Tg status [17]. All patients were classified into one of these risk categories.

7. American Joint Committee on Cancer Staging

If distant metastasis (M1) was detected, the disease was considered stage II; all other pediatric patients were evaluated as stage I disease [10].

8. Dynamic risk stratification

DRS was performed for initial treatment evaluation within 6 to 24 months postoperatively and for final treatment evaluation in patients receiving RAI therapy 6 to 24 months after treatment. Classification followed the approach used by Tuttle et al. [11] in adults and was defined as follows:

(1) No evidence of disease: suppressed Tg <1 ng/mL, absence of TgAb, and no structural evidence of disease.

(2) Biochemical evidence of persistent disease: suppressed Tg ≥1 ng/mL or stimulated Tg ≥2 ng/mL.

(3) Structural evidence of persistent disease: any evidence of disease shown through cross-sectional imaging (ultrasonography, computed tomography, or magnetic resonance imaging), functional imaging (RAI scanning), or biopsy (cytology or histology).

(4) Recurrent disease (recurrence): new biochemical evidence (suppressed Tg ≥1 ng/mL and/or stimulated Tg ≥2 ng/mL), structural evidence, or functional evidence of disease.

Disease-related death was defined as a situation resulting in death without any disease-unrelated cause during follow-up [11].

9. Modified pediatric DRS

Zanella et al. [12] modified the adult DRS for use in pediatric patients. Cases were reclassified according to this stratification. Patients were divided into 4 categories according to their response: excellent, indeterminate, biochemically inadequate, or structurally inadequate.

This risk stratification was as follows.

1) In patients receiving RAI

An excellent response was defined as normal imaging and Tg < 0.2 ng/mL or stimulated Tg < 1.0 ng/mL. A biochemically incomplete response was defined as normal imaging and Tg > 1.0 ng/mL or stimulated Tg > 10 ng/mL or increasing TgAb levels. A structurally incomplete response was defined as any evidence of structural or functional disease with any Tg or TgAb level. An indeterminate response was defined as nonspecific findings in imaging studies or Tg-T4 between 0.2 and 1.0 ng/mL or suppressed Tg or TgAb between 1.0 and 10.0 ng/mL with stable or declining levels.

2) In patients not receiving RAI

An excellent response was defined as normal imaging and Tg < 0.2 ng/mL or stimulated Tg < 2.0 ng/mL. A biochemically incomplete response was defined as normal imaging and Tg-T4 > 5.0 ng/mL or stimulated Tg > 10.0 ng/mL or increasing Tg or TgAb levels. A structurally incomplete response was defined as any evidence of structural or functional disease with any Tg or TgAb level. An indeterminate response was defined as nonspecific findings in imaging studies or Tg between 0.2 and 5.0 ng/mL or stimulated Tg between 2.0 and 10.0 ng/mL with stable or declining levels. Recurrent disease (recurrence) was defined as newly detected biochemical or structural evidence of disease in a previously disease-free patient.

10. Statistical analysis

In this descriptive clinical study, the clinical and laboratory data of patients were reported as mean±standard deviation, minimum and maximum for continuous variables, and absolute numbers and percentages for risk stratifications. The data were analyzed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA).

11. Ethical statement

Written consent was obtained from parents if all included children. The study was performed according to the Helsinki Declaration. This study protocol was reviewed and approved by the ethics committee of Ankara University (I10-656-21).

Results

This retrospective study included 41 pediatric and adolescent patients with DTC (female:male=35:6). The mean age at diagnosis was 14.75±3.14 years (range, 6.0–19.5 years), and the mean follow-up duration was 5.14±3.94 years (range, 1–15 years). At presentation, 6 patients had a family history of DTC, and no patient had received prior radiotherapy.

When the ultrasonographic characteristics of the patients were examined, the most common location of nodules was the right lobe (n=15, 36.59%). Multicentric location was observed in 10 patients (24.39%), hypervascularity in 19 (46.34%), microcalcifications in 11 (26.83%), and heterogeneous parenchyma in 23 (56.1%). Regarding echogenicity, 25 patients (60.98%) had hypoechoic nodules, 8 (19.51%) had isoechoic nodules, 3 (7.32%) had hyperechoic nodules, and 5 (12.2%) had mixed echogenicity. Single nodules larger than 1 cm were found in 24 patients (58.54%). The nodules were solid in 26 cases (63.4%), cystic in 4 (9.76%), and mixed in 11 (26.83%). Lymph node involvement was observed in 14 patients. During follow-up, lung metastasis was detected in 1 patient.

According to the ATA risk stratification based on the ultrasonographic pattern of thyroid nodules, the distribution was as follows: 9 (21.95%) with a high-suspicion pattern, 16 (39.02%) with an intermediate-suspicion pattern, 14 (34.15%) with a low-suspicion pattern, and 2 (4.88%) with a very low-suspicion pattern. No benign cases were reported. After the biopsy, the distribution according to the Bethesda classification was as follows: 5 Bethesda II (12.2%), 8 Bethesda III (19.51%), 7 Bethesda IV (17.07%), 6 Bethesda V (14.63%), and 15 Bethesda VI (36.59%).

In this study, all patients underwent total thyroidectomy, and 18 underwent lymph node dissection (67% central and 23% strawberry-picking style). Among the patients in the intermediate-risk group, 16 (40%) received RAI treatment (average dose=103.8±41.4 mCi), and no complications related to RAI treatment were observed in the long-term follow-up.

Pathological examination revealed that 33 cases (80%) had papillary thyroid cancer and 8 had follicular thyroid cancer. Among the cases of papillary thyroid cancer, the histological distribution was as follows: 26 classic variants, 5 follicular variants, 1 solid variant, and 1 diffuse sclerosing variant. The tumor size was 13.82±10.31 mm (range, 1.1–50 mm).

According to the TNM classification, the tumors were distributed as follows: T1aN0M0 (n=12, 29.3%), T1aN1aM0 (n=1, 2.4%), T1aN1bM0 (n=1, 2.4%), T1bN0M0 (n=8, 19.5%), T1bN1aM0 (n=7, 17.1%), T1bN1bM0 (n=3, 7.3%), T2N0M0 (n=6, 14.6%), T2N1aM0 (n=2, 4.9%), T3N1bM0 (n=1, 2.4%).

Based on the postoperative ATA risk stratification, 35 patients (85.4%) were classified as low risk, 5 (12%) as intermediate risk, and 1 (2%) as high risk. The evaluations of postoperative ATA risk stratification based on the Bethesda classification, preoperative thyroid ultrasound ATA risk classification, and postoperative ATA risk classification are detailed in Tables 1 and 2. Table 2 specifically shows the classification of preoperative

Table 1. Evaluation of fine-needle aspiration findings based on thyroid ultrasonography (USG) characteristics according to the preoperative ATA risk classification

Preoperative thyroid USG ATA risk classification	İİAB Bethesda Classification
Highly suspicious pattern (n=9)	Bethesda II (n=1), Bethesda III (n=1), Bethesda IV (n=2), Bethesda V (n=1), Bethesda VI (n=4)
Moderately suspicious pattern (n=16)	Bethesda II (n=2), Bethesda III (n=1), Bethesda IV (n=2), Bethesda V (n=4), Bethesda VI (n=7)
Low suspicious pattern (n=14)	Bethesda II (n=2), Bethesda III (n=5), Bethesda IV (n=2), Bethesda V (n=1), Bethesda VI (n=4)
Very low suspicious pattern (n=2)	Bethesda II (n=0), Bethesda III (n=1), Bethesda IV (n=1), Bethesda V (n=0), Bethesda VI (n=0)

ATA, American Thyroid Association.

Table 2. Evaluation of preoperative Bethesda classification and postoperative ATA risk classification

Preoperative ATA thyroid nodule risk classification	Postoperative ATA risk classification		
İİAB Bethesda Classification	Low (n=35)	Moderate(n=5)	High (n=1)
Bethesda II (n=5)	4	1	0
Bethesda III (n=8)	8	0	0
Bethesda IV (n=7)	7	0	0
Bethesda V (n=6)	5	1	0
Bethesda VI (n=15)	11	3	1

ATA, American Thyroid Association.

thyroid nodules according to postoperative ATA risk status. A single patient with a Bethesda II tumor was categorized as at moderate risk postoperatively, while all patients classified as Bethesda III and IV were assigned to the low-risk category.

According to De Groot staging, 27 patients (65.85%) were classified as stage 1 (isolated thyroid tissue involvement), 12 (29.27%) as stage 2 (+ cervical lymph node involvement), 1 as stage 3 (local metastasis), and 1 as stage 4 (distant metastasis).

Based on the combined risk, 39 patients (95%) were classified as low risk, and 2 (5%) were classified as high risk. These 2 patients were in De Groot stage 3 and stage 4, respectively, and had TNM T1bN1bM0 staging. One patient progressed to M1 after T1bN1bM0 staging. Among the patients, 38 (92.7%) had negative anti-Tg, and 3 (7%) had positive anti-Tg. The 3 patients with positive anti-Tg were in the low-risk group.

The mean MACIS score was 3.81±0.88, with a median of 3.49 (range, 3.22–8.46). According to the adult DRS, after the initial treatment, the clinical status was classified as follows: no evidence of disease (n=29, 70.7%), persistent biochemical evidence of disease (n=5, 12.2%), persistent structural evidence of disease (n=6, 14.6%), and recurrent disease (n=1, 2.5%). The distribution of patients according to TNM stage is shown in Table 3.

Among the patients with T1aN0M0 staging, 1 had persistent biochemical evidence of disease. One patient with T1aN1bM0 staging had persistent structural evidence of disease, and 1 with T1bN0M0 staging had persistent biochemical evidence of disease. Among patients with T1bN1aM0 staging, 2 had persistent biochemical evidence of disease, and 1 had persistent structural evidence of disease. Among patients with T1bN1bM0 staging, 2 had persistent structural evidence of disease, and 1 had recurrent disease. Among patients with T2N0M0 staging, 1 had persistent biochemical evidence of disease, and 2 had persistent structural evidence of disease. The remaining patients showed no evidence of disease (Table 4).

According to the pediatric DRS classification, patients were grouped as follows: excellent response (n=32), indeterminate response (n=4), biochemical incomplete response (n=4), and structural incomplete response (n=1). The distribution of these groups according to the ATA risk scoring is shown in Table 5.

In the DRS, 2 patients had an inadequate response 6 to 24 months after RAI treatment, and 2 had persistent/recurrent disease at the last follow-up. No patients with persistent/recurrent disease had received prior RAI ablation.

Discussion

Table 3. Distribution of adult dynamic risk classes according to the American Joint Committee on Cancer (AJCC/TNM staging) after initial treatment

Adult dynamic risk classification (n)	TNM stage I (n=40)	TNM stage II (n=1)
No evidence of disease (n=29)	29	0
The biochemical evidence of persistent disease (n=5)	5	0
The structural evidence of persistent disease (n=6)	6	0
Recurrent disease (n=1)	0	1

Table 4. Adult dynamic risk classification after initial treatment according to subgroups of TNM staging

Subgroups of TNM staging	Adult dynamic risk classification (n=41)			
	No evidence of disease (n=29)	The biochemical evidence of persistent disease (n=5)	The structural evidence of persistent disease (n=6)	Recurrent disease (n=1)
T1aN0M0 (n=12)	11	1	0	0
T1aN1aM0 (n=1)	1	0	0	0
T1aN1bM0 (n=1)	0	0	1	0
T1bN0M0 (n=8)	7	1	0	0
T1bN1aM0 (n=7)	4	2	1	0
T1bN1bM0 (n=3)	0	0	2	1*
T2N0M0 (n=6)	3	1	2	0
T2N1aM0 (n=2)	2	0	0	0
T3N1bM0 (n=1)	1	0	0	0

The case with T1bN1bM0 developed distant (lung) metastasis during follow-up.

Table 5. ATA pediatric risk classification and pediatric modified dynamic risk stratification following initial treatment response

Pediatric dynamic risk stratification (n)	ATA risk classification		
	Low (n=35)	Moderate (n=5)	High (n=1)
Excellent response (n=32)	30	2	0
Indeterminate response (n=4)	3	1	0
Biochemical incomplete response (n=4)	2	1	1
Structural incomplete response (n=1)	1	0	0

ATA, American Thyroid Association.

Table 6. Patients categorized as persistent and recurrent based on adult differentiated risk classification after initial treatment

Case	Follow-up duration (yr)	Family history of cancer	Family history of thyroid disease	Initial treatment	ATA nodule risk classification with FNA and USG	ATA pediatric thyroid cancer risk classification	AJCC/TNM Stage	De Groot staging	MACIS	Combined risk classification	DRS	Last treatment	Treatment year
I	5.5	Absent	Congenital hypothyroidism[†]	TT[‡]	Low	Moderate	T1aN1bM0	Stage 2	4.28	Low	Structural	RAI (150 mCi)	<2015
II	9.1	Absent	CLT	TT[‡]+LN dissection	High	Low	T1bN1aM0	Stage 2	3.62	Low	Biochemical	RAI (150 mCi)	<2015
III	14.7	Absent	CLT	TT	Moderate	Moderate	T1bN1bM0	Stage 2	4.46	Low	Structural	RAI (150 mCi)	<2015
IV	9.7	Absent	Absent	TT+LN dissection	High	Moderate	T1bN1bM0	Stage 4	8.46	High	Recurrence	RAI (200 mCi) in nuclear medicine and adult follow-up	<2015
V	7.1	Exist	CLT	Right lobectomy	Moderate	Low	T2N0M0	Stage 1	3.77	Low	Structural	TT, RAI (50 mCi)	<2015
VI	5.8	Absent	Absent	TT	High	Low	T2N0M0	Stage 1	3.7	Low	Biochemical	RAI (125 mCi)	<2015
VII	10.7	Absent	Absent	TT	High	Low	T2N0M0	Stage 1	3.85	Low	Structural	RAI (125 mCi)	<2015
VIII	3.1	Absent	CLT	TT	Moderate	Low	T1aN0M0	Stage 1	3.22	Low	Biochemical	Suppressive treatment is incompatible, screening and sTg are normal	>2015
IX	2.4	Exist	CLT	TT	Low	Low	T1bN0M0	Stage 1	3.43	Low	Biochemical	RAI (30 mCi)	>2015
X	2.9	Absent	CLT	TT+LN diseksiyonu	High	Low	T1bN1aM0	Stage 2	3.43	Low	Structural	CLND+RAI (100 mCi)	>2015
XI	1.3	Absent	Absent	TT+CLND	High	Moderate	T1bN1aM0	Stage 2	4.58	Low	Biochemical	RAI (150 mCi)	>2015
XII	1.1	Absent	Absent	TT+CLND	High	High	T1bN1bM0	Stage 1	5.49	High	Structural	Lateral LND+RAI (150 mCi)	>2015

FNA, fine-needle aspiration; USG, ultrasonography; ATA, American Thyroid Association; AJCC, the American Joint Committee on Cancer; MACIS, distant Metastasis, patient Age, Completeness of resection, local Invasion, and tumor Size; DRS, dynamic risk stratification; TT, total thyroidectomy; RAI, radioactive iodine; CLT, chronic lymphocytic thyroiditis; LN, lymph node; sTg, serum thyroglobulin; LND, lymph node dissection; CLND, central LND.
[†]Dishormonogenesis. [‡]Complementary total thyroidectomy.

The importance of risk stratification in clinical surveillance of pediatric thyroid cancers cannot be overstated. We evaluated the classifications based on individual risk profiles and observed instances of persistent and recurrent disease even in cases classified by the ATA 2015 guidelines as low risk (Table 6). This emphasizes the complexity of managing thyroid cancers in children compared with adults and indicates that the current risk assessment models for pediatric thyroid cancers may need refining.

Malignancy features were evident even in cases initially classified as benign based on the first FNAB result. This situation highlights the importance of continued monitoring and reevaluation of nodules in pediatric patients, as an initial benign appearance does not guarantee the absence of malignancy in the long term. Incorporating additional molecular markers or genetic testing specific to the pediatric population may improve the accuracy of risk stratification, as certain genetic alterations, such as RET/PTC rearrangements, are associated with high growth rates in benign thyroid nodules [18]. Due to the absence of molecular investigations in our cases, we were unable to demonstrate this relationship. However, the clinical features we observed provide guidance for further studies.

Pediatric thyroid cancers differ significantly from those in adults with respect to clinical presentation and molecular characteristics [19-22]. The variations in mutation patterns between pediatric and adult patients are associated with differences in tumor growth, treatment response, and long-term prognosis [23-25]. Pediatric patients more commonly present with multifocal disease, lymph node involvement, and distant metastasis at diagnosis [5]. The underlying reasons for these differences likely involve variations in the mutational profiles of thyroid tumors in pediatric and adult patients. As a result, relying solely on guidelines formulated based on adult data may not be appropriate for managing pediatric thyroid cancers. The differences in tumor biology and clinical behavior between pediatric and adult cases necessitate a more individualized approach to ensure optimal patient outcomes [1,26]. In our study, this relationship can explain the rates of recurrence observed in cases previously classified as low-risk despite appropriate treatment and monitoring.

Our study evaluated Tg, stimulated thyroglobulin (stTg) parameters, and persistent structural disease, as recommended in the DRS and ATA guidelines [1,11,12]. The ATA guidelines emphasize classifications before and after RAI treatment, with a recommended stTg threshold of 2 ng/mL, while the DRS uses a threshold of 1 ng/mL. However, no classification is tailored explicitly to pediatric patients [11, 12, 26]. Total thyroidectomy enhances the success of Tg and stTg measurements [1,11,12]. Zanella et al. [12] reported that factors associated with persistent disease include TNM, ATA risk, DRS classifications, and stTg levels. The use of stTg as a predictive marker of an excellent treatment response was particularly noteworthy. Elevated Tg levels after thyroidectomy and RAI therapy could indicate residual or recurrent disease. Monitoring Tg levels over time may provide valuable information regarding disease progression and help tailor treatment approaches to individual patients. However, due to the retrospective nature of our study, we were unable to conduct a correlation analysis regarding the cutoff levels of stimulated postoperative Tg.

The ATA guidelines regarding the management of DTC and the role of neck dissection and RAI therapy have been subjects of extensive discussion and debate. The ATA guidelines recommend central and/or lateral neck dissection in patients with DTC who undergo total thyroidectomy and experience pre-/perioperative lymph node metastasis. In cases without advanced tumor disease, lymph node dissection is not recommended [1]. However, the 2022 European Thyroid Association guidelines recommend prophylactic bilateral central neck dissection for patients undergoing total thyroidectomy without recent lymph node metastasis to identify occult metastases and improve disease staging [26]. However, the extent of neck dissection and the potential risks and benefits associated with the procedure are unclear [1,26,27]. Prophylactic central neck dissection aims to eliminate the micrometastases of DTC to optimize management [26]. Another reason for the variation in risk scores during follow-up could be the inability to predict micrometastases.

Including patients treated before guideline implementation adds an intriguing dimension to our study. This situation allows a comparison of outcomes and management strategies between patients treated according to the current guidelines and those managed differently based on previous practices. We calculated DRS in patients 6 to 24 months postoperatively and after RAI treatment. Although RAI treatment is recommended for patients in the intermediate and high-risk groups, our study included some low-risk patients who underwent RAI prior to current guideline establishment (Table 6). In addition, not all patients who had evidence of disease received RAI ablation. In contrast to the 2015 ATA guidelines, the 2022 guidelines recommend iodine-131 therapy for all children after total thyroidectomy [26]. The use of RAI therapy in patients without lymph node or distant metastasis is debatable. While RAI has shown efficacy in ablating residual thyroid tissue, targeting distant metastases, reducing recurrence rates, and improving survival, routine use in low-risk patients without significant tumor burden could cause potential side effects on growth, fertility, and secondary malignancies [28]. There is also growing awareness of the long-term effects of RAI therapy, particularly in pediatric patients, which has raised concerns about potential adverse effects. Any decision to administer RAI therapy should be carefully evaluated by case.

MACIS, De Groot, and TNM staging can be used to determine a patient's condition in a cross-sectional manner, while ATA and DRS scoring are more dynamic. Our research indicates that all risk stratifications should be considered in patient follow-up. Despite the potential benefits of using DRS in pediatric DTC patients, the evidence supporting its application in the pediatric population is limited. Children should not be treated as miniature adults, and management of pediatric DTC should differ from that of adults. The validity and effectiveness of DRS in predicting outcomes in pediatric patients may not

entirely align with its application in adults.

It is important to acknowledge the potential limitations of our study design, including its retrospective nature and relatively small sample size. Consequently, only descriptive statistics could be analyzed. We provide a detailed description of the follow-up course for pediatric thyroid cancer patients, covering their management from diagnosis through treatment and long-term follow-up. We recognize that this descriptive approach may focus narrowly on the observational aspects of patient care. The retrospective nature of our study restricted our ability to perform extensive statistical analyses and to fully verify postoperative risk stratification. Despite this limitation, we were able to highlight key observations and insights from our patient cohort. While the study encompassed all patients managed at our tertiary center, there is need for national studies and prospective cohorts to validate and generalize our findings. Notably, our study underscores the potential effectiveness of RAI therapy in managing persistent disease in low-risk groups over the long term. The findings suggest that RAI treatment could help address persistent disease in patients with low-risk profiles, potentially enhancing disease management and improving patient outcomes. Despite concerns about RAI side effects, our patient cohort did not report any serious side effects, such as secondary malignancies.

Overall, while our study provides valuable insights into the long-term management of pediatric thyroid cancer patients, larger, prospective studies are needed to confirm these findings and to explore the broader applicability of RAI therapy in this context. In conclusion, this study emphasizes the complexity of managing pediatric thyroid cancers and the importance of risk stratification. The pediatric ATA guidelines are adequate for the management of patients with DTC. Additionally, DRS can identify risk factors in the diagnosis and follow-up of DTC cases. For example, persistent disease in patients classified as low risk according to the ATA guidelines was resolved after RAI treatment.

Notes

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References

1. 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: the American Thyroid Association guidelines task force on pediatric thyroid cancer. Thyroid 2015;25:716-59.
2. Dermody S, Walls A, Harley EH Jr. Pediatric thyroid cancer: an update from the SEER database 2007–2012. Int J Pediatr Otorhinolaryngol 2016;89:121-6.
3. Önder A, Aycan Z. Approach to thyroid nodules in children and adolescents. Turk J Pediatr 2014;56:219-25.
4. Lim-Dunham JE, Toslak IE, Alsabban K, Aziz A, Martin B, Okur G, et al. Ultrasound risk stratification for malignancy using the 2015 American Thyroid Association management guidelines for children with thyroid nodules and differentiated thyroid cancer. Pediatr Radiol 2017;47:429-36.
5. Dinauer CA, Breuer C, Rivkees SA. Differentiated thyroid cancer in children: diagnosis and management. Curr Opin Oncol 2008;20:59-65.
6. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 1990;71:414-24.
7. Powers PA, Dinauer CA, Tuttle RM, Francis GL. The MACIS score predicts the clinical course of papillary thyroid carcinoma in children and adolescents. J Pediatr Endocrinol Metab 2004;17:339-43.
8. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Taskforce. Thyroid 2006;16:109-42.
9. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association Management Guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
10. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classi-

fication of malignant tumours. Oxford: Wiley Blackwell; 2017.
11. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid 2010;20:1341-9.
12. Zanella AB, Scheffel RS, Nava CF, Golbert L, Laurini de Souza Meyer E, Punales M, et al. Dynamic risk stratification in the follow-up of children and adolescents with differentiated thyroid cancer. Thyroid 2018;28:1285-92.
13. Avram AM, Giovanella L, Greenspan B, Lawson SA, Luster M, Van Nostrand D, et al. SNMMI procedure standard/EANM practice guideline for nuclear medicine evaluation and therapy of differentiated thyroid cancer: abbreviated version. J Nucl Med 2022;63:15N-35N.
14. Howard SR, Freeston S, Harrison B, Izatt L, Natu S, Newbold K, et al. Paediatric differentiated thyroid carcinoma: a UK National Clinical Practice Consensus Guideline. Endocr Relat Cancer 2022;29:G1-33.
15. 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;49:619-28.
16. Ali SZ, Baloch ZW, Cochand-Priollet B, Schmitt FC, Vielh P, VanderLaan PA. The 2023 Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2023;33:1039-44.
17. Pace-Asciak PZ, Payne RJ, Eski SJ, Walfish P, Damani M, Freeman JL. Cost savings of patients with a MACIS score lower than 6 when radioactive iodine is not given. Arch Otolaryngol Head Neck Surg 2007;133:870-3.
18. Sapio MR, Guerra A, Marotta V, Campanile E, Formisano R, Deandrea M, et al. High growth rate of benign thyroid nodules bearing RET/PTC rearrangements. J Clin Endocrinol Metab 2011;96:E916-9.
19. Cherella CE, Angell TE, Richman DM, Frates MC, Benson CB, Moore FD, et al. Differences in thyroid nodule cytology and malignancy risk between children and adults. Thyroid 2019;29:1097-104.
20. Sugino K, Nagahama M, Kitagawa W, Ohkuwa K, Uruno T, Matsuzu K, et al. Distant metastasis in pediatric and adolescent differentiated thyroid cancer: clinical outcomes and risk factor analyses. J Clin Endocrinol Metab 2020;105:e3981-8.
21. Cordioli MI, Moraes L, Alves MT, Delcelo R, Monte O, Longui CA, et al. Thyroid-specific genes expression uncovered age-related differences in pediatric thyroid carcinomas. Int J Endocrinol 2016;2016:1956740.
22. Paulson VA, Rudzinski ER, Hawkins DS. Thyroid cancer in the pediatric population. Genes (Basel) 2019;10:723.
23. 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;15:320-5.
24. Kumagai A, Namba H, Saenko VA, Ashizawa K, Ohtsuru A, Ito M, et al. Low frequency of BRAF T1796A mutations in childhood thyroid carcinomas. J Clin Endocrinol Metab 2004;89:4280-4.
25. Mostoufi-Moab S, Labourier E, Sullivan L, LiVolsi V, Li Y, Xiao R, et al. Molecular testing for oncogenic gene alterations in pediatric thyroid lesions. Thyroid 2018;28:60-7.
26. Pacini F, Fuhrer D, Elisei R, Handkiewicz-Junak D, Leboulleux S, Luster M, et al. 2022 ETA Consensus Statement: what are the indications for post-surgical radioiodine therapy in differentiated thyroid cancer? Eur Thyroid J 2022;11:e210046.
27. Chen L, Wu YH, Lee CH, Chen HA, Loh EW, Tam KW. Prophylactic central neck dissection for papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes: a systematic review and meta-analysis. World J Surg 2018;42:2846-57.
28. Clement S, Peeters R, Ronckers C, Links T, Van Den Heuvel-Eibrink M, Van Dijkum EN, et al. Intermediate and long-term adverse effects of radioiodine therapy for differentiated thyroid carcinoma–a systematic review. Cancer Treat Rev 2015;41:925-34.