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Differentiated Thyroid Cancer in Children and Adolescents: 12-year Experience in a Single Center

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What is already known on this topic?

Differentiated thyroid cancer has a good prognosis in the pediatric population even in the presence of metastatic disease. For this reason, an individualized risk-based approach is recommended to select patients for additional therapy. Lymphovascular invasion is usually not considered, despite being a well-known risk factor in the adult population.

What this study adds?

Our study describes the outcomes of a cohort of patients diagnosed at pediatric age and suggests that lymphovascular invasion may be associated with a higher risk of persistence/recurrence and should therefore be considered for decision making.

Abstract

Objective: Differentiated thyroid cancer (DTC) is the most common pediatric endocrine cancer but studies are scarce. Latest recommendations advocate for an individualized risk-based approach to select patients for additional therapy. Lymphovascular invasion is not considered, despite being a well-known risk factor in the adult population. The aim of this study was to describe the outcomes of a cohort of DTC patients diagnosed at pediatric age and to evaluate the impact of lymphovascular invasion on the risk of persistence/recurrence.

Methods: A retrospective study of patients diagnosed with DTC at pediatric age from 2010 to 2022 at a single center was performed. All patients had total thyroidectomy. Radioactive iodine therapy (RAI) was used in selected patients. The response to therapy and occurrence of persistent/recurrent disease were evaluated.

Results: A total of 21 DTC were diagnosed, mostly papillary thyroid carcinoma (PTC) (81.0%, n=17). Six patients (28.6%) had nodal involvement and one (4.8%) had lung metastasis at the time of the diagnosis. Lymphovascular invasion was present in 11 patients (52.4%). After surgery, 13 patients (61.9%) underwent RAI. The mean follow-up time was 5.7±3.1 years. In total, 6 patients (31.6%) experienced persistent/recurrent disease during the follow-up time. Among PTC patients, persistent/recurrent disease was more frequent in the presence of lymphovascular invasion [55.6% (5/9) vs. 0.0% (0/6), p=0.031].

Conclusion: An individualized risk-based approach is recommended. Our study suggests that lymphovascular invasion may be associated with a higher risk of persistence/recurrence and should therefore be considered for decision making in children and adolescents with PTC.

Keywords: Differentiated thyroid cancer, papillary thyroid cancer, children and adolescents, pediatric, lymphovascular invasion, persistence, recurrence

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Introduction

Differentiated thyroid cancer (DTC) is the leading cause of pediatric endocrine cancer, accounting for over 6% of all pediatric cancers (1). Among 15- to 19-year-old adolescents, thyroid cancer is the eighth most frequently diagnosed cancer and the second most common among girls (1,2). However, pediatric papillary thyroid cancer (PTC) is still a rare disease.

The most common presentation of DTC in children and adolescents is a thyroid nodule. However, DTC also frequently presents as cervical adenopathy with or without a palpable thyroid lesion or as an incidental finding after imaging or surgery for an unrelated condition (3). The most common subtype of DTC is PTC, accounting for 90% or more of all childhood cases (4,5). Follicular thyroid carcinoma (FTC) and oncocytic follicular Hürthle cell carcinoma (OFTC) are less frequent (4,5).

When compared to adult patients, children and adolescents with DTC are more likely to have regional lymph node involvement, extrathyroidal extension and distant metastasis, thereby requiring the use of more aggressive treatment (3,4,5,6,7,8,9). However, the pediatric population with thyroid cancer is at very low risk of death and at higher risk for long-term harm from aggressive treatment. (3,4,5,6,7,8,9). Thus, more conservative strategies, including lobectomy and less radioactive iodine therapy (RAI) use, have been advocated.

Due to the lack of clinical trials, treatment options remain controversial. The latest American Thyroid Association (ATA) guidelines advocate for an individualized risk-based approach to identify patients who are likely to benefit from additional staging and therapy, after accurate preoperative staging for regional disease and appropriate surgery (10). These guidelines define three Pediatric risk levels: "Low risk", "Intermediate risk" and "High risk" (Table 1) with a more conservative strategy with less RAI use in low-risk patients. The assignment of a pediatric risk level results from the pathologic findings and postoperative clinical data. Nevertheless, only the extension of the primary tumor and the presence of nodal involvement and distant metastasis (TNM classification) are considered. Lymphovascular invasion is not considered in these recommendations, despite being a well-known risk factor for recurrence in the adult population with PTC (11,12,13,14,15). Most recently, European guidelines for the management of DTC have been published (16). However, although these include risk stratification based on some histological characteristics and subtypes, they again do not take lymphovascular invasion into account. Furthermore, specific recommendations on prophylactic RAI are not included due to the scarce evidence.

The criteria for diagnosing vascular invasion in thyroid carcinomas are poorly defined. Vascular invasion has been used by histopathologists to describe venous invasion exclusively, but also to describe lymphatic invasion sometimes (11,12,13,17). Moreover, distinguishing venous invasion from lymphatic invasion is not always straightforward, making it sometimes impossible to provide a clear classification (18). Therefore, specific information on the type of vascular invasion presented is often absent from histopathology reports.

The aim of this study was to describe the outcomes of a cohort of DTC patients diagnosed at pediatric age. A secondary aim was to evaluate the impact of lymphovascular invasion on the risk of PTC persistence/recurrence in this population.

Methods

Patients

A retrospective study of patients diagnosed with DTC at pediatric age was conducted, covering the period from January 2010 to July 2022 at the Pediatric Hospital of Coimbra, Portugal. Patients included in this study needed to meet the following criteria: (1) histopathological confirmation of DTC, including PTC, FTC or OFTC; and (2) under the age of 18 years at diagnosis.

All the patients participating in this study underwent total thyroidectomy by experienced thyroid surgeons. Therapeutic central and lateral neck lymph node dissection was performed in case of malignant cytology and clinical

Table 1. ATA pediatric thyroid cancer risk levels (11)

ATA pediatric risk level	Definition
Low risk	Disease grossly confined to the thyroid with N0/Nx disease or patients with incidental N1a disease (microscopic metastasis to a small number of central neck lymph nodes)
Intermediate risk	Extensive N1a or minimal N1b disease
High risk	Regionally extensive disease (extensive N1b) or locally invasive disease (T4 tumors), with or without distant metastasis

"Risk" is defined as the likelihood of having persistent cervical disease and/or distant metastases after initial total thyroidectomy - lymph node dissection by an experienced thyroid surgeon and is not the risk for mortality, which is extremely low in the pediatric population.
ATA: American Thyroid Association

evidence of gross extrathyroidal invasion and/or locoregional metastasis on preoperative staging or intraoperative findings. Prophylactic neck dissections were not performed in any of the patients.

The tumor stage was classified according to the American Joint Committee on Cancer TNM (AJCC/TNM) staging system, 7th Edition. Patients with PTC were also classified according to the ATA pediatric thyroid cancer risk levels as "Low risk", "Intermediate risk" or "High risk". The tumor was also evaluated for multifocality, lymphovascular invasion and extrathyroidal extension. The term lymphovascular invasion was used to describe venous and/or lymphatic invasion.

RAI therapy was used in selected patients after multidisciplinary discussion, followed by iodine whole-body scan. No patients received chemotherapy or kinase inhibitor therapy. Thyroid stimulating hormone suppression therapy was performed in all patients for at least five years.

Follow-up and Clinical Outcomes

Follow-up visits were performed every 3-6 months for at least three years and then annually. Upon turning 18 years-old, care was transitioned to adult endocrinology. During the follow-up period, laboratory tests, including serum thyroglobulin (Tg) and Tg antibody measurement, and ultrasound of the neck were performed. Fine-needle biopsy was used in the presence of suspicious lymph nodes or nodules in the neck area.

The response to therapy was evaluated at 12 months after surgery and at the last follow-up visit and classified as "no evidence of disease" or "persistent/recurrent disease". The persistent/recurrent disease was defined as any evidence of structural disease on imaging with or without abnormal biochemical findings after initial surgery. Persistent/recurrent disease at any time during follow-up was also evaluated and classified as locoregional or distant disease. To evaluate the outcomes, patients with a follow-up of less than one year were excluded.

The protocol was approved by the Ethics Committee of Centro Hospitalar Universitário de Coimbra (OBS.SF.135-2022, 03.11.2022). Patient consent was waived by the Ethics Committee due to the retrospective nature of the study and full data anonymization.

Statistical Analysis

Statistical analysis was conducted using Statistical Package for Social Sciences software version 27.0 (IBM Inc., Armonk, NY, USA). For continuous quantitative variables, distribution normality was tested through histogram observation and kurtosis and skewness analysis. The results are presented as mean ± standard deviation or median (interquartile range).

The goodness of fit χ^2-test was used to compare frequencies between the groups with and without persistent/recurrent disease. Student's t-test for independent variables and Mann-Whitney test were used to compare continuous variables with normal and non-normal distribution between the two groups, respectively. A two-sided p value < 0.05 was considered statistically significant.

Results

Sample Characteristics

During the study period, a total of 21 DTCs were diagnosed at pediatric age. The median age at initial diagnosis was 16 [14-16] years (minimum-maximum: 8-17 years). The majority of patients were female (85.7%, n = 18). The clinicopathologic characteristics of the patients are presented in Table 2.

Table 2. Clinicopathologic characteristics of the patients

	n = 21
Age (years)	16 [14-16]
Female gender (%, n)	85.7% (18/21)
History of any cancer in first degree relatives (%, n)	23.8% (5/21)
Reason for diagnosis (%, n)	
Indeterminate or suspicious thyroid nodule on fine needle aspiration cytology[a]	76.2% (16/21)
Atypia of undetermined significance	9.5% (2/21)
Follicular neoplasm	23.8% (5/21)
Malignant	42.9% (9/21)
Incidental diagnosis[b]	23.8% (5/21)
Thyroidectomy for benign multinodular goiter	14.3% (3/21)
Thyroidectomy for PTEN syndrome	4.8% (1/21)
Thyroidectomy for Grave's disease	4.8% (1/21)
Surgery (%, n)	
Total thyroidectomy	100% (21/21)
Central lymphadenectomy	19.0% (4/21)
Lateral lymphadenectomy	9.5% (2/21)

Table 2. Continued

	n = 21
Histopathology (%, n)	
PTC	81.0% (17/21)
Classic variant	61.9% (13/21)
Follicular variant	19.0% (4/21)
FTC (minimally invasive)	14.3% (3/21)
OFTC	4.8% (1/21)
Multifocality (%, n)	23.8% (5/21)
Largest size of the dominant tumor (mm)	16 [12-32]
Lymphovascular invasion (%, n)	52.4% (11/21)
Extrathyroidal extension (%, n)	33.3% (7/21)
Minimal	23.8% (5/21)
TNM classification[c] (%, n)	
T	
T1a	14.3% (3/21)
T1b	23.8% (5/21)
T2	28.6% (6/21)
T3	23.8% (5/21)
T4a	9.5% (2/21)
N	
Nx	52.4% (11/21)
N0	19.0% (4/21)
N1a	4.8% (1/21)
N1b	23.8% (5/21)
M	
Mx	38.1% (8/21)
M0	57.1% (12/21)
M1	4.8% (1/21)
ATA pediatric thyroid cancer risk levels[d] (%, n)	
Low risk	64.7% (11/17)
Intermediate risk	11.8% (2/17)
High risk	23.5% (4/17)
RAI after surgery (%, n)	61.9% (13/21)

Data are presented as median, 25th and 75th percentiles. [a]Fine needle aspiration cytology according to the criteria of the Bethesda System for Reporting Thyroid Cytopathology; [b]No identifiable nodules on thyroid ultrasound or previous benign cytology; [c]American Joint Committee on Cancer TNM (AJCC/TNM) stating system, 7th edition; [d]Applied to children and adolescents with PTC.

PTC: papillary thyroid carcinoma, FTC: follicular thyroid carcinoma, OFTC: oncocytic follicular Hürthle cell carcinoma, ATA: American Thyroid Association, RAI: radioactive iodine therapy

An indeterminate or suspicious thyroid nodule on fine needle aspiration cytology was the most frequent reason that led to diagnosis (76.2%, n = 16). All patients received total thyroidectomy. Therapeutic central and lateral neck lymph node dissection were performed in 4 (19.0%) and 2 (9.5%) patients, respectively.

On histopathology, the most frequent subtype of DTC was PTC (81.0%, n = 17), mostly classic variant (61.9%, n = 13). No high-risk variants were observed. Five patients (23.8%) had multifocal PTC. Three patients (14.3%) were diagnosed with minimally invasive FTC, and one (4.8%) with OFTC. The median size of the largest dominant tumor was 16 [12-32] mm. Four patients (19.0%) had microcarcinoma. Lymphovascular invasion was present in 11 (52.4%) and extrathyroidal extension in 7 (33.3%) patients. Six patients (28.6%) had nodal involvement at the time of the diagnosis. One patient (4.8%) had N1a disease and 5 patients (23.8%) N1b disease. Among patients with reported lymphovascular invasion, 6 (54.5%) had nodal involvement. The others were classified as Nx since it was not possible to evaluate regional lymph nodes on histopathology. According to the ATA pediatric thyroid cancer risk levels, the majority of the patients with PTC (64.7%, 11) had low risk of having persistent cervical disease and/or distant metastases after initial total thyroidectomy/lymph node dissection. After surgery, 13 patients (61.9%) underwent RAI. Iodine whole-body scan revealed cervical lymph node metastasis in 7 patients (33.3%) and lung metastasis (M1) in one (4.8%). RAI tended to be used more frequently in ATA intermediate and high-risk groups ["low risk" 45.5% (5/11), "intermediate risk" 100% (2/2), "High risk" 100% (4/4), p = 0.05].

Clinical Outcomes of the Cohort

Two patients had been recently diagnosed with PTC at the time of the study and were excluded from the follow-up analysis. The mean follow-up time in the remainder

was 5.7 ± 3.1 years, ranging from 13 months to 10 years. Twelve months after surgery, the majority (78.9%, 15) had no evidence of disease, while 4 (21.1%) had persistent/recurrent disease. At the last follow-up visit, only 3 (15.8%) had persistent/recurrent disease. Overall, 6 DTC patients (31.6%) experienced persistent/recurrent disease during the follow-up time, all but one of them with PTC. Their characteristics are summarized in Table 3. Four of them had persistent locoregional disease after initial surgery and RAI; one patient underwent supplementary neck dissection and additional RAI and was disease-free by the end of seven years of follow-up; another exhibited no evidence of disease after a single additional RAI. The latter patient had minimally invasive FTC and it was not clear if the persistent tissue was malignant or not. Two patients received additional RAI and achieved stable disease by the end of the follow-up, at 13 months and 10 years. One patient had persistent locoregional and pulmonary disease after initial surgery and RAI. Supplementary neck dissection and additional RAI were performed. By the end of the follow-up (5 years), the patient had no evidence of locoregional disease and stable pulmonary disease. Despite an undetectable level of Tg, one patient presented with a suspicious lymph node in the neck area two years after initial treatment. Supplementary neck dissection confirmed recurrent locoregional disease with a PTC. At the time of the study (9 years follow-up), there was no evidence of disease. In conclusion, at the last follow-up visit, 16 patients (84.2%) had no evidence of disease, 2 patients (10.5%) had stable locoregional disease and 1 patient (5.3%) had stable pulmonary disease, despite adequate treatment according to evidence-based guidelines. None of the patients had a persistent elevated Tg level without structural disease. The clinical outcomes of the follow-up are presented in Table 4.

Table 3. Clinical characteristics of the patients that experienced persistent/recurrent disease during the follow-up

Sex	Age at diagnosis	Tumor and stage[a]	Lymphadenectomy[b]	Lymphovascular invasion	Initial treatment	Persistence/ recurrence	Diagnosis	Additional treatments	Last-follow-up visit
Female	15	PTC T2Nx	No	Yes	Surgery + RAI	Persistent disease	Neck RAI avid disease after initial RAI	Surgery + RAI	No evidence of disease (7 years)
Female	8	FTC T1bNx	No	Yes	Surgery + RAI	Persistent disease	Neck RAI avid disease after initial RAI	RAI	No evidence of disease (11 years)
Female	16	PTC T2N1a	No	Yes	Surgery + RAI	Persistent disease	Neck RAI avid disease after initial RAI	RAI	Stable locoregional disease (1 year)
Female	12	PTC T2Nx	No	Yes	Surgery + RAI	Persistent disease	Neck RAI avid disease after initial RAI	RAI	Stable locoregional disease (10 years)
Female	9	PTC T4aN1b	Yes	Yes	Surgery + RAI	Persistent disease	Neck and pulmonary RAI avid disease after initial RAI	Surgery + RAI	No evidence of locoregional disease and stable pulmonary disease (5 years)
Male	13	PTC T3N1b	Yes	Yes	Surgery + RAI	Recurrent disease	Cytology diagnosis of locoregional disease after suspicious neck ultrasound, despite undetectable level of Tg, 2 years after surgery	Surgery	No evidence of disease (9 years)

[a]American Joint Committee on Cancer TNM (AJCC/TNM) stating system, 7th edition; [b]Central and/or lateral lymphadenectomy in addition to total thyroidectomy.
PTC: papillary thyroid carcinoma, FTC: follicular thyroid carcinoma, RAI: radioactive iodine therapy, Tg: thyroglobulin

Risk Factors of Persistent/Recurrent Disease in PTC

Among PTC patients, there were no significant differences of persistent/recurrent disease between ATA risk groups ["Low risk" 22.2% (2/9), "Intermediate risk" 50.0% (1/2), "High risk" 50.0% (2/4), p = 0.44]. Comparison between PTC patients with and without lymphovascular invasion showed that persistent/recurrent disease was more frequent in patients with lymphovascular invasion [55.6% (5/9) vs. 0.0% (0/6), p = 0.031] (Figure 1). Similarly, the comparison between PTC patients with and without persistent/recurrent disease showed that lymphovascular invasion was more frequent in the persistence/recurrence group ["Persistent/recurrent disease" 100% (5/5), "No evidence of disease" 40.0% (4/10), p = 0.031]. Additionally, this group tended to be younger at diagnosis, although the difference was not significant ["Persistent/recurrent disease" 13 (12-15) years, "No evidence of disease" 16 (15-17) years, p = 0.075]. There were no differences regarding gender, multifocality, size of the tumor, extrathyroidal extension, lymphadenectomy, nodal involvement, RAI use after surgery or follow-up time (Table 5). Due to the sample size, a logistic regression model was not possible to perform.

Table 4. Follow-up clinical outcomes of the patients with DTC

	n = 19
Follow-up time (years)	**5.7 ± 3.1**
Response to therapy (%, n)	
12 months after surgery	
No evidence of disease	78.9% (15/19)
Persistent/recurrent disease	21.1% (4/19)
At the last follow-up visit	
No evidence of disease	84.2% (16/19)
Persistent/recurrent disease	15.8% (3/19)
Persistent/recurrent disease at any time of the follow-up (%, n)	31.6% (6/19)
Type	
Persistent disease	26.3% (5/19)
Recurrent disease	5.3% (1/19)
Location	
Locoregional disease	26.3% (5/19)
Locoregional and distant disease (pulmonary)	5.3% (1/19)

Data are presented as mean ± standard deviation.
DTC: differentiated thyroid cancer

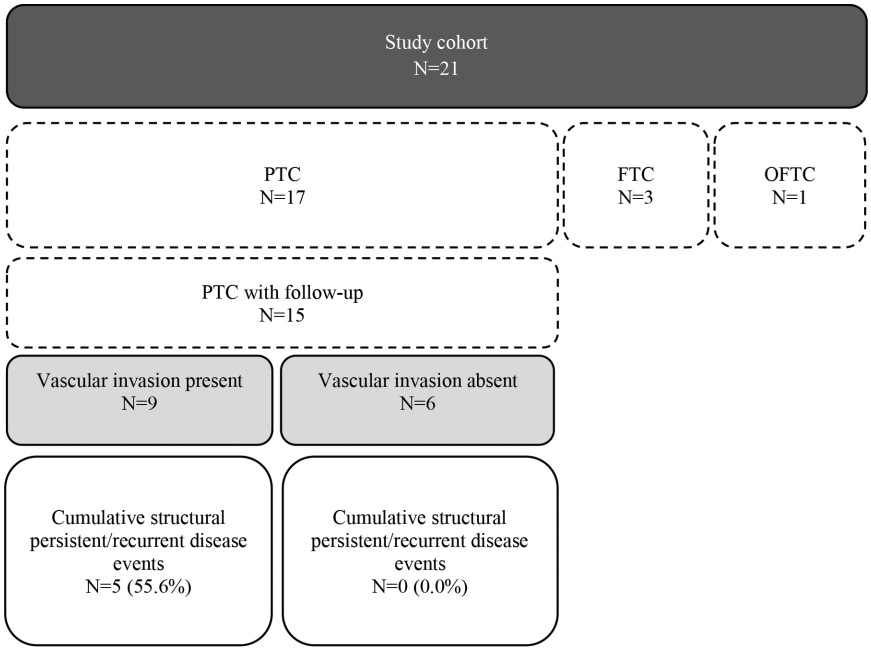

Figure 1. Comparison between patients with and without lymphovascular invasion

PTC: papillary thyroid carcinoma, FTC: follicular thyroid carcinoma, OFTC: oncocytic follicular Hürthle cell carcinoma

Table 5. Comparison of the clinical characteristics of PTC patients with and without persistent/recurrent disease during the follow-up time

	Persistent/recurrent disease	No evidence of disease	p
Age (years)	13 [12-15]	16 [15-17]	0.075
Female gender (%, n)	80.0% (4/5)	80.0% (8/10)	1.000
Multifocality (%, n)	40.0% (2/5)	10.0% (1/10)	0.242
Largest size of the dominant tumor (mm)	32 [26-35]	22 [8-33]	0.254
Lymphovascular invasion (%, n)	100.0% (5/5)	40.0% (4/10)	**0.031**
Extrathyroidal extension (%, n)	40.0% (2/5)	40.0% (4/10)	1.000
Lymphadenectomy (%, n)	40.0% (2/5)	20.0% (2/10)	0.560
Nodal involvement (%, n)	60.0% (3/5)	30.0% (3/10)	0.329
RAI after surgery (%, n)	100.0% (5/5)	60.0% (6/10)	0.231
Follow-up time (years)	6.4 ± 3.6	4.5 ± 2.7	0.270

Data are presented as mean ± standard deviation or as median, 25th and 75th percentiles.
RAI: radioactive iodine therapy, PTC: papillary thyroid carcinoma

Discussion

Since pediatric DTC is a rare disease, published data are scarce and from retrospective cohorts. To the best of our knowledge, there are no randomized controlled clinical trials for the treatment of children and adolescents with DTC. Nevertheless, retrospective studies of therapeutic options have led to reconsideration of the former concept that all children with DTC should be similarly treated (10). Although children and adolescents are more likely to have aggressive disease, pediatric thyroid cancer is associated with a very low risk of death (3,4,5,6,7,8,9,10). The challenge is to provide aggressive therapy when warranted and to limit overtreatment of those who are unlikely to benefit (3,4,5,6,7,8,9,10).

The latest ATA guidelines advocate for an individualized, risk-based approach combining histopathological findings and postoperative clinical data to identify patients who are likely to benefit from additional staging and therapy (10). Current ATA recommendations are founded on well-accepted approaches to therapy in adults, as well as personal experience in certain pediatric practices (10,19,20). However, the pediatric risk stratification considers only the extension of the primary tumor, the presence of nodal involvement and distant metastasis (TNM classification) (10). Other factors, such as lymphovascular invasion and minimal extrathyroidal extension are not considered, despite being well-known risk factors of recurrence in the adult population with PTC (11,12,13,14,15). Recently, European guidelines for the management of DTC in children and adolescents were published. However, they also do not take lymphovascular invasion into account for risk stratification (16).

Our retrospective study described the outcomes of a DTC cohort of children and adolescents diagnosed and treated in a pediatric reference center in Portugal, with a median follow-up of 6 years. In accordance with the literature, our cohort was essentially constituted by adolescents and female patients (3,4,5,6,7,8,9,10). As expected, PTC was the most frequent subtype (3,4,5,6,7,8,9,10). At the last follow-up visit, the majority had no evidence of disease and none had died from thyroid cancer, confirming the good prognosis of DTC in children and adolescents (3,4,5,6,7,8,9,10). Overall, six patients experienced persistent/recurrent disease during the follow-up. However, only three patients had active, but stable disease at the last follow-up visit.

All children and adolescents in our series underwent total thyroidectomy and the majority (62%) received RAI. However, central and lateral neck lymph node dissection were less commonly performed in our series (19%), compared to other studies, where lymphadenectomy was performed in more than 80% of the patients (21,22). Furthermore, only about a third of the patients in our series had nodal involvement at the time of the diagnosis, compared to 53-98% of the patients in other studies. (22,23,24,25,26,27). However, our cohort presented with a higher persistence/recurrence rate during follow-up in comparison with other studies (31.6% vs. 17-30%), suggesting that other factors must be considered for risk determination in addition to nodal involvement (10,22). Furthermore, according to the ATA pediatric risk groups, two of the PTC patients with persistent/recurrent disease in our series would have been classified as "Low risk", possibly delaying further staging and treatment. This highlights the importance of considering other factors for persistence/recurrence risk determination in this population.

In the present study, persistent/recurrent disease was more frequent in PTC patients with lymphovascular invasion (56% vs. 0%). This suggests that lymphovascular invasion may

be associated with a higher risk of persistence/recurrence and should therefore be considered for decision making in children and adolescents with PTC. Moreover, patients with persistent/recurrent disease tended to be younger, although the difference was not significant. Further research is needed to clarify whether younger age portends greater risk for extensive and recurrent disease, as suggested by other studies (4,8,28,29). In contrast to other studies, no significant differences were found regarding multifocality and the size of the tumor, probably due to the small size of our cohort (10).

In addition, our study contrasts with Redlich et al. (25), a German multicenter study, in which multivariate analysis revealed ATA high-risk level as a significant negative prognostic factor for event-free survival in pediatric patients with DTC. The small size of our cohort may explain this discrepancy. However, we have to consider the possibility that the risk of recurrence/persistence is underestimated in our cohort. The less aggressive strategy adopted in our sample, with lymph node dissection performed in a minority of cases, may have underestimated nodal involvement, and thus ATA risk prediction. Francis et al. (10) reported that "Low risk" patients may still be at risk for residual cervical disease, especially if the initial surgery did not include a central lymph node dissection, as seen in the "Low risk" patients that experience persistent disease in our cohort. The reduced rate of lymphadenectomy in our sample may explain the higher persistence/recurrence rate, compared to other studies. Therefore, other prognostic factors, such as lymphovascular invasion, can be particularly useful in the setting of a more conservative strategy, where nodal involvement may not be fully assessed.

Study Limitations

This study has some limitations. Unfortunately, due to the retrospective nature of the study, it was not possible to specify whether the lymphovascular invasion described in each case was venous, lymphatic or both. Furthermore, we did not have control over the preoperative and postoperative staging and management. Our series is based on a non-stratified approach in which all children underwent total thyroidectomy and variable extent of lymph node dissection and the majority received RAI. This contrasts with recent studies showing that more conservative strategies, including lobectomy and less RAI among children and adolescents, are safe and effective (10,22). Moreover, the small nature of our study limits the analysis, not allowing the performance of a logistic regression model to evaluate independent predictors of recurrent/persistent disease in PTC patients. Another limitation of the study is the relatively short follow-up time since pediatric patients may experience a recurrence 20-40 years after initial therapy (30,31).

Conclusion

In conclusion, our retrospective study describes the outcomes of a cohort of DTC patients diagnosed and treated at pediatric age in a reference center in Portugal. Children and adolescents with DTC were more likely to have more severe stages of disease. An individualized stratified risk-based approach is recommended to identify patients who are likely to benefit from additional staging and therapy. However, current recommendations consider only the extension of the primary tumor, the presence of nodal involvement and distant metastasis. Our study suggests that lymphovascular invasion may be associated with a higher risk of PTC persistence/recurrence in children and adolescents, especially in the setting of a more conservative strategy, where nodal involvement may not be fully assessed, and should therefore be considered for risk determination and decision making in this population. Further research is needed to confirm our results.

Ethics

Ethics Committee Approval: The protocol was approved by the Ethics Committee of Centro Hospitalar Universitário de Coimbra (OBS.SF.135-2022, 03.11.2022).

Informed Consent: Patient consent was waived by the Ethics Committee due to the retrospective nature of the study and full data anonymization.

Authorship Contributions

Surgical and Medical Practices: Joana Serra Caetano, Rita Cardoso, Isabel Dinis, Alice Mirante, Concept: Francisca Marques Puga, Laura Correia, Inês Vieira, Joana Serra Caetano, Rita Cardoso, Isabel Dinis, Alice Mirante, Design: Francisca Marques Puga, Laura Correia, Inês Vieira, Joana Serra Caetano, Rita Cardoso, Isabel Dinis, Alice Mirante, Data Collection or Processing: Francisca Marques Puga, Laura Correia, Inês Vieira, Analysis or Interpretation: Francisca Marques Puga, Literature Search: Francisca Marques Puga, Writing: Francisca Marques Puga.

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