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Thyroid nodules and tumors in childhood

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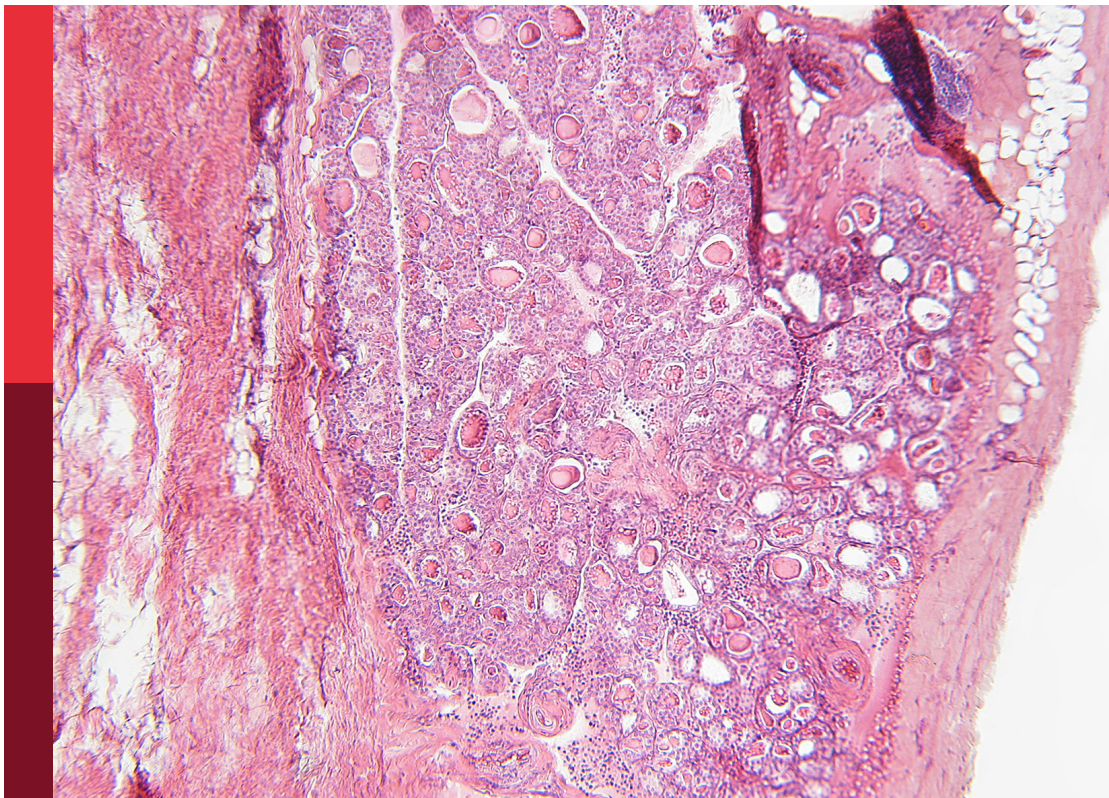

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Thyroid nodules and tumors in childhood

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Editorial: Thyroid nodules and tumors in childhood

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KEYWORDS

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Editorial on the Research Topic
Thyroid nodules and tumors in childhood

Nodular thyroid disease in pediatric age displays a lower prevalence than in adulthood, even if to date no literature data have been produced on the global incidence and prevalence of this condition in childhood. Although most thyroid nodules in childhood are benign, they carry a risk of malignancy up to five times greater than that in adults (1, 2). Most pediatric patients with differentiated thyroid cancer (DTC) present with an asymptomatic thyroid nodule found occasionally; not fully investigated are the association with autoimmune thyroiditis and the correlation with US changes over time (3). To standardize medical decisions and avoid unnecessary fine needle aspiration biopsy (FNAB), the European Thyroid Association and the American Radiology College have established guidelines for Thyroid Imaging, Reporting and Data System (EU-TIRADS and ACR-TIRADS). Based on cytological finding on FNAB, several classifications have been produced, of which the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) and the British Thyroid Association (BTA) are the most widely used. However, increasing evidence, using BSRTC and BTA (3), or other National cytological classifications (4), indicates the need for pediatric-specific data for the optimal management of thyroid nodules in children, which may differ from that of adult nodules with equivalent cytology. Furthermore, the broadening of knowledge of the oncogenic landscape supports the incorporation of oncogene testing to rule-in malignancy of nodules with indeterminate cytology. Finally, in patients with syndromes with genetic predisposition, a surveillance approach is necessary to promptly recognize a DTC occurrence.

Aim of this Research Topic was to collect evidence on epidemiology, diagnostic tools and pathways, as well as data on the management and long-term outcomes of "*Thyroid nodules and tumors in childhood*", with a focus also on possible correlation with autoimmune disease and rare genetic syndromes with predisposition to thyroid malignancies. The present Research Topic includes 1 *Systematic Review*, 6 *Original articles* and 2 interesting *Case reports* on rare diseases with genetic predisposition to thyroid malignancies, thus covering most of the current research in the specific field of thyroid nodules and malignancy in the pediatric age.

To estimate the overall incidence and prevalence of DTCs in the pediatric age and seek for differences between sub-types, i.e. the more frequent papillary thyroid carcinoma (PTC) and the rare follicular thyroid carcinoma (FTC), Moleti et al. conducted a systematic review of articles produced from 2000 to 2021 and two separate meta-analysis. They provide valuable data on the current global epidemiology of pediatric and adolescent DTC and indicate the need for a prospective international registry on pediatric DTC, based on standardized data collection, to implement relevant information on the clinical behavior of these rare diseases.

In an original article, Tuli et al. focused their research on the effectiveness of the EU-TIRADS and ACR-TIRADS scoring systems in risk stratification in a large pediatric population of 200 patients with thyroid nodules referred to a single Center over a 20-year period, adding new data on the performance and the limitations of these two important diagnostic tools used routinely in the clinical practice, also compared with the FNAB results.

Januś et al. provided two interesting papers from their Center; in the first, through a prospective follow-up study, they report their experience on the US evolution of the thyroid gland with autoimmune thyroiditis (AIT) before the development of PTC, in a population of 180 children referred to their Outpatient Endocrine Department for suspected thyroid disorder, confirming the fundamental role of thyroid US in the routine follow-up of patients with AIT, not only for the early detection of clinically-silent thyroid malignancies, but also for the possible influence on oncological therapy. In the second paper, through a retrospective analysis, they indicate their 22-year experience on the natural course and US, laboratory, and histopathological features on a cohort of 90 pediatric patients with PTC diagnosed through the EU-TIRADS scoring system, with and without AIT.

A similar issue was investigated by Jie et al., who compared the US, clinical, and pathological features of 52 children and adolescents with PTC, with and without Hashimoto's thyroiditis (HT), indicating HT as a possible independent risk factor in children and adolescents with PTC, which showed more aggressive features.

Sarli et al., through a multicenter survey, underline the possible risk of thyroid neoplasms in patients with rare disorders of the neck region, i.e. the 22q11.2 deletion and DiGeorge-like syndromes, conditions rarely associated with malignancies, for which no aggregate data exist, thus emphasizing the need for prolonged clinical and US follow up for these conditions.

In their rigorous manuscript van de Berg et al., within a retrospective analysis of nationwide population-based data, summarized the long-term oncological outcomes of the two subtypes of the DTC, the PTC and FTC, in the Dutch population aged <18 years, diagnosed between 2000 and 2016, with important advances on the knowledge of the trend over time of these 2 forms of DTC, of any risk factors for recurrence and of survival rate.

The Research Topic also contains 2 very peculiar *Case Reports* of great clinical value for the diagnostic pathway, the genotype-phenotype correlation and impact on family counseling.

The first, produced by Vincenzi et al., reports the occurrence of a multinodular goiter in a patient with Bannayan-Riley-Ruvalcaba syndrome associated with a PTEN variant and congenital hypothyroidism due to homozygous alterations of the TPO gene, arguing a possible synergic role of TPO and PTEN mutations, a gene known to predispose to thyroid cancer (5).

The second, reported by Stambouli et al., describes the appearance of a rare embryonal rhabdomyosarcoma in a patient found to harbor a germline DICER1 mutation, highlighting the need to look for DICER1 syndrome in the presence of rare and unusual tumors during childhood, in the presence of a family history of thyroid diseases in childhood or early adulthood.

In conclusion, this Research Topic contains original contributions that can enrich scientific knowledge and help improve daily clinical practice and follow-up of patients with nodular and tumor disorders of thyroid in childhood; it can also represent a food for thought and inspiration for new research in this area.

Author contributions

LS: Writing – original draft, Writing – review & editing. MW: Writing – review & editing. MV: Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Long-Term Oncological Outcomes of Papillary Thyroid Cancer and Follicular Thyroid Cancer in Children: A Nationwide Population-Based Study

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Introduction: Pediatric thyroid carcinoma is a rare malignancy and data on long-term oncological outcomes are sparse. The aim of this study was to describe the long-term oncological outcomes of pediatric papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) in a national cohort, and to identify risk factors for recurrence.

Methods: We conducted a nationwide, retrospective cohort study, in which we combined two national databases. Patients aged <18 years, diagnosed with PTC or FTC in the Netherlands between 2000 and 2016, were included. pT-stage, pN-stage, multifocality and angioinvasion were included in a Cox-regression analysis for the identification of risk factors for recurrence.

Results: 133 patients were included: 110 with PTC and 23 with FTC. Patients with PTC most often presented with pT2 tumors (24%) and pN1b (45%). During a median follow-up of 11.3 years, 21 patients with PTC developed a recurrence (19%). Nineteen recurrences were regional (91%) and 2 were pulmonary (9%). No risk factors for recurrence could be determined. One patient who developed pulmonary recurrence died two years later. Cause of death was not captured. Patients with FTC most often presented with pT2 tumors (57%). One patient presented with pN1b (4%). In 70%, no lymph nodes were collected. None of the patients with FTC developed a recurrence or died.

Conclusion: Pediatric PTC and FTC are two distinct diseases. Recurrence in pediatric PTC is common, but in FTC it is not. Survival for both pediatric PTC and FTC is very good.

Keywords: papillary thyroid cancer, follicular thyroid cancer, children, long-term oncologic outcomes, pediatric

INTRODUCTION

Pediatric thyroid cancer is rare and represents only 2.3% of all thyroid cancer diagnoses (1). In children, 85% of the cases are papillary thyroid carcinoma (PTC) and only 8% are follicular thyroid carcinoma (FTC) (2). Both types are a form of differentiated thyroid cancer (DTC) (2).

Pediatric PTC and pediatric FTC exhibit major clinical differences. Pediatric PTC is generally multifocal, bilateral and often presents with cervical lymph node metastases (3–5). Contrarily, pediatric FTC is generally unifocal and is more prone to hematogenous metastases, mainly to the lungs (3, 6). Cervical lymph node metastases are less common in children with FTC (6). In pediatric PTC, recurrence is very common, with rates ranging from 13% to 37% (4, 5, 7, 8). Conversely, long-term outcome data of pediatric FTC are very sparse. The limited data available suggest high survival rates and possibly lower to similar recurrence rates compared to pediatric PTC (6, 9).

Nevertheless, most previous studies regarding pediatric thyroid cancer included only patients with PTC or reported on patients with DTC indiscriminately, as FTC is exceedingly rare. In addition, most studies included children and adolescents up to 21 years of age.

Consequently, there is a lack of knowledge concerning the true long-term oncological outcomes of PTC and FTC, separately, in children younger than 18 years of age.

Therefore, this study aimed to describe the long-term oncological outcomes of pediatric PTC and pediatric FTC in a national cohort, and to identify risk factors for recurrence.

METHODS

This study was conducted as retrospective, nationwide, population-based cohort study and is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (10). This study has been approved by the institutional review board of Amsterdam UMC. Nationwide data of patients with differentiated thyroid carcinoma between 0 and 18 years of age, in the period from 2000 to 2016, were collected from the 'Netherlands Cancer Registry' (NCR). Recurrence data were collected by matching the cohort with data from the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands (PALGA) (11). Patients who did not match the PALGA-database were excluded, because there was no confirmation of pathology or recurrence data of these patients. Using the database of PALGA and in consultation with a pathologist, all patients were retrospectively reclassified in accordance with the staging criteria of the eighth edition of the TNM classification system (12). According to the Dutch National guidelines (13, 14), all children were treated in pediatric tertiary referral centers.

Synchronous metastases were collected from the NCR-database. Cytology- or pathology proven metachronous metastases were collected from the PALGA-database. Recurrence was defined as cytology- or pathology proven recurrence after an interval of six months or longer after initial surgery. Regional recurrence was defined as cytology- or pathology proven recurrence in lymphoid- or non-lymphoid tissue in one of the cervical lymph node levels of the neck. Distant recurrence was defined as recurrence outside of the cervical lymph node levels of the neck. Last date of follow-up for survival was January 31st 2021. Last date of follow-up for recurrence was March 15th 2021.

Primary outcome included the disease characteristics, treatment modalities and long-term oncological outcomes of children with PTC and FTC, separately. Secondary outcome included possible risk factors for recurrence for both PTC and FTC, separately. The following variables were included in the analysis for risk factors for recurrence: pT-stage, pN-stage, multifocality and angioinvasion. Extrathyroidal extension is already imbedded as pT3b in the eight edition of the TNM classification system (12). The aforementioned variables were chosen because previous literature suggests an effect on recurrence for these variables (5, 7, 15, 16) and because we expected these to be the most relevant.

Statistical Analysis

Patients were stratified according to tumor type. Categorical variables were expressed as numbers and percentages. Continuous variables were unanimously non-normally distributed and therefore expressed as median with interquartile range. Missing data were excluded from the analysis. A cox-regression plot was performed on recurrence data. For patients with multiple recurrences, the time to first recurrence was used. Patients without recurrence were censored at the last follow-up. Cox-regression analysis was applied on recurrence data to determine independent risk factors. Statistical significance was defined using a 2-sided $\alpha = .05$ and/or 95% Confidence Interval (CI). Statistical analysis was performed using SPSS 26.0 software.

RESULTS

The initial cohort consisted of 135 patients. Two patients were excluded: one patient because there was no match with the PALGA-database, another patient because of uncertainty about the diagnosis. In total, 133 patients were included in this study, of which 110 children with PTC and 23 children with FTC. For patients with PTC, median age at diagnosis was 15.8 years and the male to female ratio was 1: 2.8. Two patients had a history of radiotherapy for a non-thyroid malignancy. For patients with FTC, median age at diagnosis was 16.2 years and the male to female ratio was 1: 6.7.

Disease Characteristics

Disease characteristics are shown in **Table 1**. Most patients with PTC presented with a pT2 tumor (26 patients; 23.6%). Gross extrathyroidal extension invading strap muscle (pT3b) and gross extrathyroidal extension invading subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve (pT4a) was present in 19 patients (17.3%) and 12 patients (10.9%),

TABLE 1 | Disease characteristics of children with papillary thyroid carcinoma or follicular thyroid carcinoma.

Full cohort (N = 133 patients)		
Variables	**PTC (N = 110)**	**FTC (N = 23)**
Age, median (IQR)	15.8 (14.3 – 16.8)	16.2 (11.9 – 16.8)
Female, n (%)	81 (73.6)	20 (87.0)
History of radiotherapy, n (%)	2 (1.8)	0
Fine Needle Aspiration (FNA), n (%)	72 (65.5)	9 (39.1)
Bethesda classification, n (% of total FNA)		
Bethesda 1	2 (2.8)	–
Bethesda 2	2 (2.8)	–
Bethesda 3	4 (5.6)	3 (33.3)
Bethesda 4	9 (12.5)	3 (33.3)
Bethesda 5	9 (12.5)	3 (33.3)
Bethesda 6	46 (63.9)	–
FNA cervical lymph node, n (%)	16 (14.5)	1 (4.3)
Tumor positive, n (%)	15 (13.6)	1 (4.3)
No FNA of tumor or FNA of lymph node, n (%)	26 (23.6)	13 (56.5)
pT-stage, n (%)		
pT1a	21 (19.1)	2 (8.7)
pT1b	16 (14.5)	1 (4.3)
pT2	26 (23.6)	13 (56.5)
pT3a	13 (11.8)	5 (21.7)
pT3b	19 (17.3)	–
pT4a	12 (10.9)	2 (8.7)
pT4b	–	–
Missing values	3 (2.7)	
Multifocality, n (%)	43 (39.1)	1 (4.3)
Angioinvasion, n (%)	35 (31.8)	16 (69.6)
Tumor diameter, mm (IQR)	20 (10.3 – 39.5)	31.5 (24.8 – 44.0)
Missing values, n (%)	22 (20.0)	5 (4.6)
pN-stage, n (%)		
pN0	12 (10.9)	6 (26.1)
pN1a	19 (17.3)	–
pN1b	49 (44.5)	1 (4.3)
Nx	30 (27.3)	16 (69.6)
M1, n (%)	7 (6.4)	1 (4.3)
Cancer stage, n (%)		
Stage I	103 (93.6)	22 (95.7)
Stage II	7 (6.4)	1 (4.3)

Disease characteristics of children (younger than 18 years of age at diagnosis) with papillary thyroid carcinoma or follicular thyroid carcinoma.
PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; n, number of patients; IQR, interquartile range; FNA, Fine Needle Aspiration.

respectively. Multifocality of the tumor was present in 43 patients (39.1%). Angioinvasion was found in 35 patients (31.8%). Central lymph node metastases (pN1a) were present in 19 patients (17.3%) and lateral lymph node metastases (pN1b) in 49 patients (44.5%). In total, 7 patients with PTC (6.4%) presented with distant metastases.

Most patients with FTC presented with a pT2 tumor (13 patients; 56.6%). Two patients (8.7%) presented with a pT4a tumor. Multifocality of the tumor was present in one patient (4.3%). Angioinvasion was found in 16 patients (69.6%). One patient (4.3%) with FTC presented with lateral lymph node metastases. In 16 patients (69.9%), no lymph nodes were collected (Nx). Distant metastases at presentation were found in one patient (4.3%).

Treatment Modalities

Treatment modalities are shown in **Table 2**. For patients with PTC, surgery was performed in 99.1%. Three patients (2.7%) received a hemithyroidectomy as definite surgery. All other patients received a total thyroidectomy in one or two tempi. Central- and lateral lymph node dissection was performed in 29.1%. In 9.1%, only central dissection was performed. Radioiodine remnant ablation (RRA) was given to 86.4% of the patients with PTC. Two patients solely underwent resection of a

TABLE 2 | Treatment modalities of children with papillary thyroid carcinoma or follicular thyroid carcinoma.

Full cohort (N = 133 patients)		
Variables	**PTC (N = 110)**	**FTC (N = 23)**
Surgery, *n (%)*	109 (99.1)	23 (100)
Total thyroidectomy in one tempo, *n (%)*	80 (72.7)	2 (8.7)
Total thyroidectomy in two tempi, *n (%)*	24 (21.8)	20 (87.0)
Hemithyroidectomy as only surgery, *n (%)*	3 (2.7)	1 (4.3)
Lymph node dissection, *n (%)*	42 (38.2)	1 (4.3)
Central lymph node dissection, *n (%)*	10 (9.1)	–
Central + lateral lymph node dissection, *n (%)*	32 (29.1)	1 (4.3)
RRA, *n (%)*	95 (86.4)	20 (87.0)
Other type of treatment, *n (%)*	2 (1.8)	-
No treatment, *n (%)*	1 (<1)	-

Treatment modalities of children (younger than 18 years of age at diagnosis) with papillary thyroid carcinoma or follicular thyroid carcinoma.
PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; n, number of patients; RRA, radioactive Iodine remnant ablation.

median neck cyst with an incidental finding of PTC. One patient with PTC received no treatment.

All patients with FTC received surgery. One patient (4.3%) received a hemithyroidectomy as definite surgery. Twenty patients (87.0%) underwent a total thyroidectomy in two tempi. Two patients (8.7%) directly underwent a total thyroidectomy. One patient (4.3%) received central- and lateral lymph node dissection. RRA was given to 87.0% of the patients with FTC.

Long-Term Oncological Outcomes

Long-term oncological outcomes are shown in **Table 3**. Median follow-up for patients with PTC was 11.3 years (IQR 7.2 – 14.9). During follow-up, 21 patients (19.1%) with PTC developed a recurrence. Of these patients, nineteen developed a regional recurrence (90.5% of total recurrences). Two patients (9.5%) developed a distant recurrence (both pulmonary). Median time to recurrence was 9 months (IQR 7.0 – 21.5). All recurrences occurred within 5 years after initial surgery. During follow-up, one male patient who was diagnosed with a pT1aN0Mx PTC at age 15 years died. He was treated with a hemithyroidectomy as definite surgery and developed a pulmonary recurrence 2.5 years after initial surgery. The patient died 4 years and 9 months after initial surgery, or 2 years and 3 months after the recurrence. Because only an overall survival was captured in this database, we

TABLE 3 | Long-term oncological outcomes of children with papillary thyroid carcinoma or follicular thyroid carcinoma.

Full cohort (N = 133 patients)		
Variables	**PTC (N = 110)**	**FTC (N = 23)**
Follow-up, median in years (IQR)	11.3 (7.2 – 14.9)	9.8 (7.3 – 12.3)
Recurrence, n (%)	21 (19.1)	0
5-year disease-free survival, %	80.9	100
Time to recurrence, median in months (IQR)	9 (7.0 – 21.5)	–
Location, n (% of total recurrences)		
Regional	19 (90.5)	–
Central lymph node	1 (4.8)	–
Lateral lymph node	14 (66.7)	–
Non-lymphoid tissue	4 (19.0)	–
Distant	2 (9.5)	–
Consecutive recurrences, n (%)		
1	17 (15.5)	–
2	3 (2.7)	–
3	–	–
5	1 (<1)	–
7	–	–
Death to all causes, n (%)	1 (<1)	0
5-year overall survival, %	99.1	100

Long-term oncological outcomes of children (younger than 18 years of age at diagnosis) with papillary thyroid carcinoma or follicular thyroid carcinoma.
PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; n, number of patients; IQR, interquartile range.

do not know the cause of death. The disease-free survival rate for PTC is shown in **Figure 1**.

Median follow-up for patients with FTC was 9.8 years (IQR 7.3 – 12.3). None of the patients with FTC developed a recurrence or died during follow-up.

Risk Factors for Recurrence

Risk factor analysis was performed for PTC only, as no recurrences occurred in patients with FTC. Possible risk factors for recurrence in PTC are shown in **Table 4**. Cox-regression analysis for risk factors of recurrence was performed on pT-stage, pN-stage, multifocality and angioinvasion. None of the variables included were identified as risk factors.

DISCUSSION

In this large nationwide study, we described the disease characteristics, treatment modalities and long-term oncological outcomes of pediatric PTC and FTC in The Netherlands, and attempted to determine risk factors for recurrence. Our main findings are that recurrence in pediatric PTC is common, but in FTC it is not. Nonetheless, overall survival is very good for both PTC and FTC. During a median follow-up of 11.3 years, 19.1% of the patients with PTC developed a recurrence. Median time to recurrence was 9 months. All patients developed their recurrence within five years after initial treatment. One patient (<1%) diagnosed with a pT1aNoMx PTC died two years and three months after a pulmonary recurrence. We do not know the cause of death, as this databases did not capture cause of death. For patients with FTC, no recurrence or death occurred during a median follow-up of 9.8 years. In a Cox-regression analysis including pT-stage, pN-stage, multifocality and angioinvasion, no risk factors for recurrence of PTC could be determined.

The results of this study, in which the nationwide databases of NCR and PALGA (11) were combined, add to the sparse data on the long-term oncological outcomes of pediatric PTC and, especially, FTC in the Netherlands. In addition, the results of this study provide more insights in the disease characteristics and the treatment management of pediatric PTC and FTC.

Our finding that 62% of the patients with PTC presented with lymph node metastases, is in line with previous studies, showing rates between 58% - 86% of lymph node metastases at presentation (4, 5, 8). However, in this study, only one patient with FTC (4.3%) presented with lymph node metastases. As pediatric FTC is exceedingly rare, there are only few studies on FTC in pediatric age and most are cases series (6, 9, 17, 18). In the two most recent studies including pediatric and adolescent patients with FTC (under 21 years of age), 1 of 20 patients (5%) and none of 30 patients presented with lymph node metastases, respectively (6, 9).

During a median follow-up of 11.3 years, the recurrence rate for patients with PTC was 19%. Previous reported recurrences rates of pediatric PTC vary widely from 13% to 37%, mainly due to differences in age distribution, different definitions of recurrence and varying duration of follow-up (4, 5, 7, 8). In this study, the median time to recurrence was 9 months and all recurrences occurred within five years after initial surgery. Interestingly, though, Hay et al. (4) and Sugino et al. (7), both reported a 10-, 20- and 30-year disease-free survival of pediatric PTC and found that recurrences occurred up to 30 years after initial treatment, underlining the indolent nature of the disease. Therefore, it is possible that even with our relative long median follow-up of 11.3 years, the reported recurrence rate of 19.1% might be an underestimation of the eventual recurrence rate for pediatric PTC.

Regional recurrences in pediatric PTC seem to have no effect on disease-specific survival (4, 19), but it does necessitate additional treatment, increasing the change of postoperative complications after surgery and even secondary malignancies after RRA (20). Distant spread seems to be associated with a lower disease-free survival (4, 7), but data are controversial (19, 21).

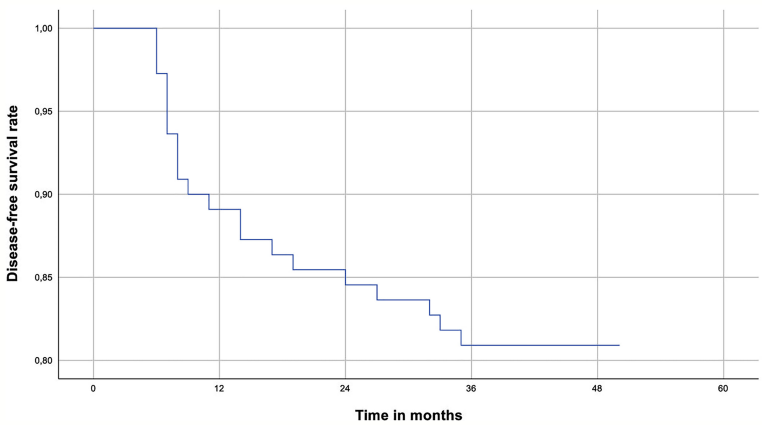

FIGURE 1 | The disease-free survival rate for children with papillary thyroid carcinoma. Cox-regression plot for the disease-free survival rate in children (younger than 18 years of age at diagnosis) with papillary thyroid cancer.

TABLE 4 | Risk factors for recurrence in children with papillary thyroid carcinoma.

Risk factors	Hazard ratio	*P* - value
pT1b	2.7 (0.4 – 16.9)	.278
pT2	1.3 (0.2 – 7.7)	.791
pT3a	2.0 (0.3 – 14.2)	.496
pT3b	2.0 (0.3 – 12.6)	.440
pT4a	5.6 (1.0 – 31.2)	.051
pN1a	1.3 (0.3 – 6.0)	.749
pN1b	2.1 (0.5 – 8.1)	.277
Multifocality	1.3 (1.0 – 1.7)	.093
Angioinvasion	0.8 (0.3 – 2.2)	.628

Cox-regression analysis for risk factors for recurrence in children (younger than 18 years at diagnosis) with papillary thyroid carcinoma.

To the best of our knowledge, only two previous studies reported long-term oncological outcomes of pediatric FTC. Enomoto et al. (6) reported outcomes of 20 children and adolescents (under 21 years old) with FTC with a median follow-up of 23.5 years and found a recurrence rate of 15% (3 of 20 children). These recurrences occurred at 6 years, 14 years and 24 years after initial surgery. The 30-year disease specific-survival was 100%. Contrarily, Spinelli et al. (9) reported outcomes of 30 children (aged younger than 19 years) with FTC with a mean follow-up of 6 years and found no recurrences and an overall survival of 100%. These results indicate that pediatric FTC, as well as pediatric PTC, is a very indolent disease. Consequently, it is possible that the follow-up of Spinelli et al. (9) and that of the present study are too short to report an accurate recurrence rate for pediatric FTC.

In the present study, we only attempted to determine risk factors for recurrence of PTC, as no recurrences occurred in patients with FTC. However, we could not determine any risk factors for recurrence of PTC (**Table 4**). This is in contrast with previous studies that found multifocality, extrathyroidal extension and lymph node metastases as risk factors for recurrence of pediatric PTC (5, 7, 15, 16). In addition, Wang et al. (16) and Rubinstein et al. (5) found younger age and non-Caucasian race as risk factors for recurrence, respectively. However, the aforementioned studies included pediatric and adolescents patients (under 21 years of age) or analyzed risk factors for DTC indiscriminately.

It is generally excepted that the clinical behavior of PTC in children is different from that of PTC in adults. Pediatric PTC tends to present with larger tumors and more often with regional or distant spread. Interestingly, 30-year cause-specific survival is better in children than in adults, despite the more advanced presentation (19). In this study, we reported high rates of regional and distant spread and high recurrence rates of pediatric PTC, which add to the belief that PTC in children might have a different clinical behavior than in adults. As FTC is very rare, studies that directly compare children with adults do not exist. However, studies of adult patients with FTC show similar patterns of metastasis compared to children, as FTC rarely metastasize to the cervical lymph nodes, but more often hematogenous to bones and lungs (22–24).

There are some limitations to this study. Firstly, Thyroglobulin levels were not captured in this database, nor were Iodine scans. Therefore, it is possible that we missed some patients that presented with biochemical recurrences or distant recurrences, which are not always confirmed with histopathology. In that case, the recurrence rate of 19.1% would be an underestimation. In addition, it is possible that some patients with an early recurrence presented with persistent disease rather than recurrent disease. We could not differentiate between an early recurrence or persistent disease, as we had no Tg-values or Iodine scans to define a period of no evidence of disease. However, it is expected that any residual disease is treated within six months of diagnosis. Secondly, cause of death was not captured in this database. Therefore, we cannot make a definite statement about the cause of death of the patient that died two years and three months after a pulmonary recurrence of PTC. Thirdly, our long follow-up of 11.3 years for PTC and 9.8 years for FTC, respectively, might not be sufficient to determine all recurrences and mortality, as pediatric PTC and FTC are very indolent diseases. However, it is expected that only a very small proportion of the patients develops a recurrence or dies after 10 years of follow-up, as all recurrences and mortality in this study occurred during the first 5 years after initial surgery.

CONCLUSION

In conclusion, the results of this nationwide study show that pediatric PTC and FTC are two very distinct diseases with different long-term oncological outcomes. Recurrence is very common in children with PTC. Contrarily, during follow-up, no recurrences occurred in children with FTC. Both pediatric PTC and FTC have a very high survival rate. Only one patient with PTC died to any cause two years and three months after a pulmonary recurrence. In this study, no risk factors for recurrence could be determined. Based on our results, we propose that pediatric PTC and FTC should not be grouped together as DTC indiscriminately when determining long-term oncological outcomes. More research with a follow-up longer than 10 years should be conducted to reveal the oncological outcomes of pediatric FTC. As the survival rate in pediatric PTC is very high, future research should focus on the factors differentiating between patients at risk for recurrence and patients not at risk. Conducting these studies could lead to more a personalized treatment of both pediatric PTC and FTC,

thereby improving the oncological outcomes of our high risk patients while reducing overtreatment of our low risk patients.

AUTHORS CONTRIBUTIONS

CD and JD collected the data from IKNL for this study. DB, AK, CD, JD collected the data from PALGA for this study. DB performed the analyses under supervision of AK and JD. DB took the lead in writing the manuscript. AE, CD, HS, ST, AT, CM, MV and EN all critically reviewed and improved the manuscript. All authors agreed with the publication of the manuscript in its current form.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medisch Ethische Toetsings Commissie AMC. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

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Evaluation of the efficacy of EU-TIRADS and ACR-TIRADS in risk stratification of pediatric patients with thyroid nodules

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Background: Pediatric thyroid nodules have a lower prevalence but a higher rate of malignancy (ROM) than those in adults. Ultrasound features suspected of malignancy lead to fine needle aspiration biopsy (FNAB) and subsequent cytological determination, upon which management is decided. Based on the characteristics of ultrasound, to standardize clinician decisions and avoid unnecessary FNAB, the European Thyroid Association and the American Radiology College have established guidelines for Thyroid Imaging, Reporting and Data System (EU-TIRADS and ACR-TIRADS) for ROM stratification of thyroid nodules. The aim of this study is to evaluate the diagnostic performance of ACR-TIRADS and EU-TIRADS in pediatric age.

Materials and methods: Subjects younger than 18 years of age with thyroid nodules greater than 0.5 cm observed in the 2000-2020 period were included.

Results: Data from 200 subjects were collected. The overall ROM was 13%, rising to 26% if nodules with a diameter >1 cm were considered. Patients with a malignant nodule were more likely to have a higher EU-TIRADS score (p=0.03). Missed cancer diagnoses were 26.9%. Using the EU-TIRADS system, 40% of FNABs could have been avoided, while this scoring system would have resulted in FNAB being performed in 12% of cases where the assessment of ultrasound features would not recommend FNAB. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 73.1%, 57.1%, 73.1%, and 50%, respectively. Even considering the ACR-TIRADS, a higher score correlated with a higher ROM (p<0.001). This system missed 6 diagnoses of cancer (23.1%). Using the ACR-TIRADS system, 45.3% of FNABs could have been avoided, while FNAB should have been performed in 12% of cases where it was not recommended by ultrasound characteristics. Sensitivity, specificity, PPV and NPV were 76.9%, 50%, 76.9%, and 42.9%, respectively.

Conclusion: The present study confirms the correspondence of the EU-TIRADS and ACR-TIRADS categories with respect to malignancy but indicates

not entirely satisfactory performance compared to FNAB alone. However, the use of the two TIRADS systems should be encouraged in multicentre studies to increase their performance and establish paediatric-specific points in the scoring criteria.

KEYWORDS

thyroid nodule, pediatric age, ACR-TIRADS, EU-TIRADS, diagnostic performance, thyroid nodules outcome

Introduction

Nodular thyroid disease in paediatric age has a lower prevalence (0.2-5.1%) than in adulthood (1-10%) (1–3), but the main difference between paediatric and adult age lies in the rate of malignancy (ROM) (16-26% vs 5-10%) (4–6). The most important risk factors for the development of thyroid cancer include underlying thyroid disease, radiation exposure, previous malignancy, family history, young age, male gender, and genetic predisposition (1–21).

Nodule size >1 cm, hypoechoic pattern, intranodal vascularization or microcalcifications, irregular edges and neck lymph nodes are the main ultrasound features that indicate malignancy (5, 22–29). Once suspicious ultrasound features are present, fine needle aspiration biopsy (FNAB) is required to determine the cytological category, identified based on the most widely used cytological classifications, namely the Bethesda System for Reporting Thyroid Cytopathology (BSRTC), the British Thyroid Association (BTA) and, in Italy, the Guidance of the Italian Society of Anatomic Pathology and Cytology (SIAPEC) (30–32). The cytological category assignment leads to different clinical management that includes clinical-radiological follow-up or surgery, with some differences between these classifications. Despite the differences, all agree on a higher ROM in paediatric age for all categories, especially for indeterminate nodules (6, 33, 34).

Based on the ultrasound features, the European Thyroid Association and the American Radiology College have established guidelines for Thyroid Imaging, Reporting and Data System (EU-TIRADS and ACR-TIRADS respectively) for risk stratification of malignancy of thyroid nodules. Once the TIRADS category is assigned, both guidelines determine whether to perform FNAB or adopt an active surveillance strategy, depending primarily on the size of the nodule (35, 36). The main reasons that led to the definition of these guidelines were the need to standardize the ultrasound description of thyroid nodules as much as possible, provide selection criteria to perform FNAB, avoid unnecessary procedures, and provide clinicians with an additional tool for the management of thyroid nodules, especially in the category of the indeterminate cytology.

Most existing studies evaluating ACR-TIRADS in adulthood have established that the score is useful for managing thyroid nodules and reducing the number of unnecessary FNAB procedures, while there are some concerns about its reliability for the evaluation of nodules with indeterminate cytology (37–51). Among the different TIRADS classification systems, ACR-TIRADS has been indicated as the most accurate classification system for identifying high-risk nodules and preventing most unnecessary FNABs (35, 36, 52–60), although in 10.2- 96 20% of cases a failure to diagnose malignancy has been reported (46, 55, 61).

To improve the diagnostic performance of ACR-TIRADS, some Authors have indicated additional nodules features or PET activity as risk factors (61, 62). Many efforts have been made to evaluate the diagnostic performance of ACR-TIRADS also in paediatric age (63). Its performance has been mostly defined as suboptimal, with a higher rate of cancers missed than in adulthood, up to 25% of cases (63, 64), suggesting that FNAB should be performed in all the 4 and 5 ACR-TIRADS categories (65–71). EU-TIRADS has also been considered a useful tool for physicians managing adults with thyroid nodules, although its performance should be improved and a FNAB should be performed in all nodules assessed as EU-TIRADS ≥4 (50, 72–75). Considering the EU-TIRADS, the rate of missed diagnosis of cancer is higher than that found in ACR-TIRADS, reaching up to 37.7% of cases (55, 72–79).

The purpose of this retrospective study is to evaluate the diagnostic performance of ACR-TIRADS and EU-TIRADS in risk stratification of paediatric thyroid nodules and determine whether extensive use of these tools can help the paediatric endocrinologist better manage thyroid nodules in pediatric age.

Materials and methods

The study included all subjects under the age of 18 with thyroid nodules greater than 0.5 cm followed at the Tertiary Center of Paediatric Endocrinology of the Regina Margherita Children's Hospital in Turin in the period 2000-2020. Patients

with nodules less than 0.5 cm in diameter and with suspicious characteristics were also initially considered. However, none of these were then included in the study as no malignant features were found in any of these nodules. After approval by the Institute's Ethical Committee, clinical, laboratory and radiographic data were collected from electronic medical records. All patients underwent thyroid ultrasound evaluation, which assessed the diameter of the nodule and the ultrasound pattern; they were therefore classified as anechoic, hypoechoic, isoechoic, hyperechoic, or mixed nodules. All lymph node changes were then recorded, such as rounded swollen shape, irregular margins, increased size, absence of echogenic hilum, heterogeneous echo pattern, presence of calcifications or cystic areas, and irregular vascularization. Patients undergoing multiple ultrasound monitoring were considered as a single case. In patients with multiple nodules, the largest nodule was considered.

All ultrasound evaluations were performed in the same institution and the images were retrospectively evaluated by two independent radiologists blinded for the outcome. The TIRADS category was indicated according to both EU-TIRADS and ACR-TIRADS. Patients with inadequate ultrasound images to correctly assess the TIRADS category were excluded. In case of nodules >1 cm or suspicious features of malignancy on ultrasound evaluation, a cytological sample was obtained by fine needle aspiration biopsy (FNAB) within one month of the ultrasound finding. Histological specimens were also obtained from subjects undergoing lobectomy or total thyroidectomy. All specimens were evaluated by a single pathologist.

Statistical analysis and graphs construction were performed using Graphpad 7 (GraphPad Software, La Jolla, CA, USA). Sensitivity (number of true positives divided by the sum of true positives and false negatives), specificity (number of true negatives divided by the sum of true negatives and false positives), positive predictive value (number of true positive divided by the sum of true positive and false positive), negative predictive value (number of true negative divided by the sum of true negative and false negative) and diagnostic accuracy (sum of true positives and true negatives divided by the samples' number) were calculated based on the results of patients undergoing both FNAB and surgery. Differences between groups were established by t test to compare mean values of continuous variables. The calculations were considered statistically significant when the P-value was <0.05. Cohen's kappa coefficient was calculated to measure the inter-rater reliability among the radiologists assigning the TIRADS score.

Results

We collected clinical, laboratory and ultrasound retrospective data from 200 subjects (119 females and 81 males) aged less than 18 years with thyroid nodules (Table 1). The observed overall rate of

TABLE 1 Clinical, biochemical and US features of all subjects (N=200) with thyroid nodules.

Clinical, biochemical and US features		All (n = 200)	Benign (n = 174)	Malignant (n = 26)	p
Age at diagnosis (years)		12 (2–18)	12 (2-18)	12.9 (7-17.1)	0.22
Gender (M/F)	M	81	70	11	0.65
	F	119	104	15	
Thyroid disease familiarity		108	96	12	0.66
Radiation exposure		28	22	6	0.1
TSH (mcUI/ml)		2.01 (0.1-5.3)	1.94 (0.1-4.9)	2.56 (0.8-5.3)	**0.01**
fT4 (pg/ml)		11.5 (1.05-134)	11.5 (1.05-13.4)	12 (7.3-15.3)	0.55
fT3 (pg/ml)		4.05 (2.3-5.8)	4 (3.06-5.8)	4.09 (2.3-4.6)	0.18
Thyroid antibodies positivity		69	53	16	0.8
Nodule localization	Left lobe	91	86	5	**0.01**
	Right lobe	92	75	17	
	Bilateral	17	13	4	
Major nodule diameter (mm)		9 (8-60)	8 (8-10)	24 (7-60)	**<0.0001**
Echoic pattern	Hypoechoic	121	101	20	0.24
	Hyperechoic	14	14	0	
	Isoechoic	20	18	2	
	Anechoic	17	17	0	
	Mixed	28	24	4	
Intranodal vascularity		61	46	15	**0.003**
Intranodal calcifications		23	15	8	**0.009**
Lymph node involvement		11	1	10	**<0.0001**

Bold is for statistical significant.

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malignancy (ROM) was 13% (26/200 malignant nodules), which rose to 26% if nodules with a diameter >1 cm were considered. The mean age at diagnosis was 11.6 years (range 2-18), with a mean follow-up of 8.6 years. The ratio of female to male was 1.47 and dropped to 1.27 considering the malignant nodules.

Regarding risk factors such as age, gender, family history of thyroid diseases, positive thyroid antibodies and radiation exposure for cancer previously treated with radiotherapy, no difference was observed between benign and malignant nodules.

All subjects had normal levels of fT4 and fT3, but the TSH level was significantly lower in subjects with a benign nodule than in subjects with a malignant nodule *(p=0.01)*.

Bilateral and right lobe involvement was associated with a higher malignancy rate than left lobe localization (23.6% vs 18.5% vs 5.5% malignancy rate, respectively, *p=0.01*), as also observed for intranodal vascularization and calcification (*p=0.003* and *p=0.009*, respectively), and lymph node involvement (*p<0.0001*). A larger nodule diameter was significantly more present in the malignant nodule than in the benign nodule group (mean diameter 24 mm vs 8 mm, respectively, *p=<0.001*). The echogenic pattern was not related to ROM.

FNAB was performed based on nodule size and ultrasound features in 75/200 (37.5%) of subjects, including 7 TIR1 (9.3%), 4 TIR1c (5.3%), 22 TIR2 (29.3%), 14 TIR3a (18.7%), 9 TIR3b (12%), 3 TIR4 (4%) and 16 TIR5 (21.4%).

Surgery was performed in 40/200 (20%), with a total malignancy rate of 65% (0% for the TIR1-TIR3a, 77.8% for the TIR3b and 100 % for the TIR4-TIR5 categories) as shown in Table 2.

Cohen's kappa coefficient among the radiologists assigning the TIRADS score was 0.85. The correlation between cytological categories after FNAB and the EU-TIRADS score is represented in Table 3. Patients with a malignant nodule were more likely to have a higher EU-TIRADS score ***(p=0.03)***. If all nodules are considered, the most frequently assigned category was EU-TIRADS 4 (53%, ROM 16.9%), followed by EU-TIRADS 2 (18.5%, ROM 0%), EU-TIRADS 3 (18%, ROM 8.3%) and EU-TIRADS 5 (10.5%, ROM 23.8%). Nodules with cytological determination were mainly assigned to EU-TIRADS 4 (46.7%), with ROM up to 48.6%, followed by EU-TIRADS 3 (30.1%, ROM 21.7%), EU-TIRADS 2 (14.7%, ROM 0%) and EU-TIRADS 5 (8%, ROM 83.3%).

The correlation between the FNAB categories and the ACR-TIRADS system score is represented in Table 4. Higher scores correlated with higher ROMs *(p<0.001)*. Most nodules were classified as ACR-TIRADS 4 (54.5%, ROM 15.6%), followed by ACR-TIRADS 3 (24.5%, ROM 4.1 %), ACR-TIRADS 1 (10%, ROM 0%), ACR-TIRADS 5 (6.5%, ROM 53.8%) and ACR-TIRADS 2 (4.5%, ROM 0%). When only nodules with cytological determination were considered, the category assigned in most cases was ACR-TIRADS 4 (42.7%, ROM 75%), followed by ACR-TIRADS 5 (17.3%, ROM 53.8 %), ACR-TIRADS 3 (16%, ROM 16.7%), ACR-TIRADS 1 (13.3%, ROM 0%) and ACR-TIRADS 2 (10.7%, ROM 0%).

Based on the EU-TIRADS score, missed cancer diagnoses would have occurred in 7 cases (26.9%), with 5 nodules classified in category 3 and 2 nodules in category 5 (Table 5). All nodules in category 3 were < 20 mm and in category 5 < 10 mm. All missed diagnoses were assigned to the TIR5 cytological category. Using the EU-TIRADS system, 40% (30/75) of the FNABs performed could have been avoided, while this scoring system would have led to perform a FNAB in 12% (15/125) of the cases in which the assessment of the ultrasound features would not have recommended FNAB. Sensitivity, specificity, positive predictive value, and negative predictive value based on

TABLE 2 Cytological, histological data, malignancy rate and FNAB accuracy for each cytological category.

SIAPEC category	Nr	Surgery	Outcome	ROM	FNAB Accuracy
TIR1	7 (9.3%)	–	All benign	0%	–
TIR1C	4 (5.3%)	1	All benign 1 ST for cystic nodule and dysphagia	0%	100%
TIR2	22 (29.3%)	5	All benign 5 TTs for important MNS	0%	100%
TIR3a	14 (18.7%)	1 TT 5 ST	6 patients with benign histology 8 patients still undergoing ultrasound/FNAB follow-up	0%	100%
TIR3b	9 (12%)	7 TTs 2 STs	All subjects underwent surgery 7 patients with malign histology 2 STs with NS histological diagnosis	77.8%	77.8%
TIR4	3 (4%)	3 TTs	All malign PTC histological diagnosis in all subjects	100%	100%
TIR5	16 (21.4%)	16 TTs	All malign PTC histological diagnosis in all subjects	100%	100%
Total	75	40		65%	95%

ROM, rate of malignancy; ST, subtotal thyroidectomy; TT, total thyroidectomy; MNS, multinodular struma; NS, nodular struma; PMC, papillary micro carcinoma; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma.

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TABLE 3 Correlation between cytological categories and EU-TIRADS score.

All nodules

	All (n = 200)	Benign (n = 174)	Malign (n = 26)	ROM	p
EU-TIRADS 2	37	37	–	0%	p=0.03
EU-TIRADS 3	36	33	3	8.3%	
EU-TIRADS 4	106	88	18	16.9%	
EU-TIRADS 5	21	16	5	23.8%	

Nodules with cytologic determination

		SIAPEC cytologic category after FNAB						ROM	Score accuracy on ROM
		TIR 1/1C (n=11)	TIR 2 (n=22)	TIR 3a (n=14)	TIR 3b (n=9)	TIR 4 (n=3)	TIR 5 (n=16)		
EU-TIRADS 2 (n=11)	FNAB	–	–	–	–	–	–	0%	100%
	NO FNAB	4	3	4	–	–	–		
EU-TIRADS 3 (n=23)	FNAB	4	1	6	–	–	–	21.7%	78.2%
	NO FNAB	–	3	4	–	–	5		
EU-TIRADS 4 (n=35)	FNAB	–	8	–	8	3	7	48.6%	100%
	NO FNAB	3	6	–	–	–	–		
EU-TIRADS 5 (n=6)	FNAB	–	1	–	1	–	2	83.3%	66.7%
	NO FNAB	–	–	–	–	–	2		

histological outcome were 73.1%, 57.1%, 73.1%, and 50% respectively.

With the ACR-TIRADS system, cancer diagnosis would have been lost in 6 cases (23.1%), with 2 nodules assigned to ACR-TIRADS category 3 and 4 nodules to ACR-TIRADS category 4. All missed diagnoses were classified cytologically as TIR5. Using the ACR-TIRADS system, 45.3% (34/75) of the FNABs performed could have been avoided; on the other hand, a FNAB was indicated in 12% (15/125) of cases in which it was not recommended by the evaluation of the ultrasound features. Sensitivity, specificity, positive predictive value, and negative predictive value based on histological outcome were 76.9%, 50%, 76.9%, and 42.9%, respectively. The sensitivity and specificity of FNAB based on histological outcome for all categories were

TABLE 4 Correlation between cytological categories and ACR-TIRADS score.

All nodules

	All (n = 200)	Benign (n = 174)	Malign (n = 26)	ROM	p
ACR TIRADS 1	20	20	–	0%	p<0.0001
ACR TIRADS 2	9	9	–	0%	
ACR TIRADS 3	49	47	2	4.1%	
ACR TIRADS 4	109	92	17	15.6%	
ACR TIRADS 5	13	6	7	53.8%	

Nodules with cytologic determination

		SIAPEC cytologic category after FNAB							Score accuracyon ROM
		TIR 1/1C (n=11)	TIR 2 (n=22)	TIR 3a (n=14)	TIR 3b (n=9)	TIR 4 (n=3)	TIR 5 (n=16)	ROM	
ACR-TIRADS 1 (n=10)	FNAB	–	–	–	–	–	–	0%	100%
	NO FNAB	5	4	1	–	–	–		
ACR-TIRADS 2 (n=8)	FNAB	–	–	1	–	–	–	0%	100%
	NO FNAB	2	4	1	–	–	–		
ACR-TIRADS 3 (n=12)	FNAB	–	–	1	–	–	–	16.7%	83.3%
	NO FNAB	3	5	1	–	–	2		
ACR-TIRADS 4 (n=32)	FNAB	–	4	4	9	3	3	75%	87.5%
	NO FNAB	1	3	1	–	–	4		
ACR-TIRADS 5 (n=13)	FNAB	–	2	2	–	–	7	53.8%	100%
	NO FNAB	–	–	2	–	–	–		

TABLE 5 Risk stratification performance of EU-TIRADS and ACR-TIRADS in paediatric age.

	Sensibility	Specificity	PPV	NPV	Accuracy on ROM	Missed cancer	Avoided FNAB	AddictiveFNAB
EU-TIRADS	73.1%	57.1%	73.1%	50%	90.7%	7/26	30/75	15 (12%)
ACR-TIRADS	76.9%	50%	76.9%	42.9%	92%	6/26	34/75	15 (12%)
SIAPEC FNAB	100%	85.7%	92.9%	100%	95%	–	–	–

100% and 85.7%, respectively, while PPV and NPV were 92.9% and 100%, respectively. Considering the high ROM of the nodules within the TIR3b category, all nodules classified in TIR3b were considered cytologically malignant. Compared to FNAB, ROM accuracy was lower for both EU-TIRADS and ACR-TIRADS (95% vs 90.7% and 92% respectively).

Discussion

Thyroid nodules in paediatric age have a lower prevalence than in adulthood, but greater ROM (1–7). Considering only nodules >1 cm, the ROM rate of our cohort was 26%, in line with previous published studies. The overall ROM rate was 13%, probably underestimated as most patients did not have suspicious ultrasound features leading to FNAB.

The behaviour of pediatric thyroid cancer is different from that of adults, with higher rates of extrathyroid extension and disease recurrence, but much better prognosis and survival rates; to date their management therefore remains challenging. Giving the invasiveness of FNAB, to avoid unnecessary procedures and anxiety for children and their parents, the best follow-up strategy should include this procedure only when strictly necessary, in presence of certain clinical and ultrasound features. The most important, reported by the current guidelines for adults, is the size of the nodule greater than 1 cm. Other features include intranodal calcification or vascularization, lymph node involvement, marked hypoechoic pattern, bilateral or right lobe localization of the nodule, poorly defined nodule margins and some clinical risk factors, particularly radiation exposure for cancer treatment, increased TSH values, young age and male gender. In our cohort, TSH levels were correlated to malignancy, as previously reported (6, 26). Considering the child's body size and the presence of microcarcinomas, in presence of multiple risk factors FNAB should be performed even if the nodule size is smaller than 1 cm (1–7).

For both the paediatric and adult populations, numerous efforts have been made to improve the selection criteria that lead clinicians to perform FNAB. To standardize the ultrasound description of thyroid nodules as much as possible and better select candidates for FNAB, the European Thyroid Association and the American Radiology College have established guidelines for Thyroid Imaging, Reports and Data System. Despite several limitations of both scoring system, previous studies in paediatric and adult cohorts have encouraged their use to increase the available data that can improve their performance. EU-TIRADS categories have been observed to be related to thyroid nodules malignancy, although the performance of such system should be improved and therefore a FNAB is currently recommended in all EU-TIRADS ≥4 nodules (50, 72–75), as cancer underdiagnosis rate rises to 37.7% (55, 72–80). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of EU-TIRADS in adulthood are between 70.6-83.5%, 51.2-94.1%, 11.8-76.1% and 85.4-94.9%, respectively (62, 73–75, 77, 78). The performance of EU-TIRADS in paediatric age has been evaluated in a few studies that showed lower efficacy than in adults, with sensitivity, specificity, PPV and NPV ranging between 41.7-100%, 25-75.9%, 41.7-44%, 75.9-100% respectively (63, 78, 79). The data from our study confirm the significant correlation of the EU-TIRADS category with malignancy. Sensitivity, specificity, PPV and NPV were 73.1%, 57.1%, 73.1% and 50 %, respectively, showing an underestimation of malignant lesions and a low ability to detect histologically determined benign nodules, which do not require FNAB. Lost cancer diagnoses in our cohort were 26.9%, while 40% of FNABs could have been avoided and 12% of patients who were not selected for needle-biopsy should have undergone FNAB.

Most existing studies evaluating ACR-TIRADS in adulthood have determined that the system score is useful for managing thyroid nodules and reducing the number of unnecessary FNAB, while some concerns remain about its reliability in evaluating nodules of indeterminate cytology (37–51). Among the different TIRADS, ACR-TIRADS was ranked as the best performing classification for identifying high-risk nodules and unnecessary FNABs (35, 36, 52–60), although a missed malignancy diagnosis occurred in 10.2-20% of cases in which ACR-TIRADS have not indicated the need for FNAB (46, 55, 61). The combined sensitivity and specificity of ACR-TIRADS in adults were 89% and 70%, respectively (61). Many efforts have been made to evaluate the diagnostic performance of ACR-TIRADS also in paediatric age (63), mostly defined as suboptimal, with a rate of up to 25% of undiagnosed cancers, higher than that of adulthood (63, 64), which suggests performing FNAB in all ACR-TIRADS categories 4 and 5 (65–71). Sensitivity, specificity, PPV and NPV in the paediatric age group vary between 70-75%, 64-92.3%, 21.8-83.3% and 64-97.2%, respectively (65, 67–71). In our study, the performance of ACR-TIRADS was similar to that

indicated by the literature for sensitivity, but the specificity was lower, and the cancer underdiagnosis rate higher (23.1%). Using ACR-TIRADS, 45.3% of FNAB could have been avoided, while 12% of unselected patients would have had to undergo FNAB.

Considering the two scoring systems, ACR-TIRADS performed better than EU-TIRADS as also observed in previous studies (52–60). The number of potentially avoidable FNABs was substantial, although malignant nodules were underestimated and the performance of both scores to avoid FNAB in definitive benign nodules was not satisfactory. The interpretation of FNAB results according to the SIAPEC classification has a significantly greater risk stratification capacity, with a sensitivity of 100%. This is mainly due to the interpretation of the indeterminate category TIR3b as cytologically malignant, with consistently high ROM (77.8%), while the ROM observed in the indeterminate category TIR3a was 0%. This result differs from the BSRTC system which assigns similar ROMs in the indeterminate grouped categories Bethesda III and IV.

Despite the limitations of TIRADS scores, we confirm that their use should be encouraged to improve their performance and have an additional tool in the management of paediatric thyroid nodules. The main limitation of TIRADS in children is the criterion of the size as a determinant for the execution of FNAB. We must be aware that the current guidelines have been established for adults and are not at all suitable for children, especially considering their body size. The EU-TIRADS score does not include lymph node involvement in the score but indicates the need for FNAB in case of suspicious ultrasound features; intranodal vascularization, described as a risk factor for malignancy, is also not included in the EU or in the ACR-TIRADS. Bilateral and right lobe localization should also be considered in the final score. To improve the diagnostic performance of ACR-TIRADS, some authors have indicated additional characteristics as risk profiles or PET activity (61, 62). The association of ultrasound data with clinical data could be an additional aid to performance improvement. The final score could also include an age <10 years, male gender, previous radiation exposure for cancer treatment, a higher TSH level, as well as a familial history or genetic predisposition to thyroid cancer (1–5).

The present study has several limitations. The retrospective nature of the study limits the statistical power of the data analysis. The number of histologically and cytologically determined malignant nodules is limited due to the low prevalence of pediatric thyroid nodules and restrictive criteria for FNAB, which can lead to underestimation, despite the case series being recruited in a tertiary centre of Paediatric Endocrinology over a 20-years period.

In conclusion, in the present study the correlation of the EU-TIRADS and ACR-TIRADS categories with malignancy was confirmed, even if their performance was not entirely satisfactory compared to FNAB alone. However, their use should be encouraged within multicentre studies, to increase the performance of both TIRADS systems and to allow for an update of the scoring criteria, including pediatric-specific points.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the City of Health and Science University Hospital of Turin. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

GT and JM contributed to the study concept, the statistical analysis and to the first draft of manuscript. MS contributed to the data collection and literature research. FQ and LS contributed to the study concept and the revision con the final version of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Ultrasound evolution of parenchymal changes in the thyroid gland with autoimmune thyroiditis in children prior to the development of papillary thyroid carcinoma – a follow-up study

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Background: Follicular cell-derived thyroid carcinoma represents the vast majority of paediatric thyroid cancers (TCs). Papillary thyroid carcinoma (PTC) accounts for over 90% of all childhood TC cases, and its incidence in paediatric patients is increasing. The objective of this follow-up study was to present the outcome of ultrasound (US) and laboratory monitoring of paediatric patients with autoimmune thyroiditis (AIT) prior to the development of PTC.

Patients and methods: This prospective study included 180 children and adolescents (132 females; 73.3%) with a suspicion of thyroid disorder referred to the Outpatient Endocrine Department. The patients were divided into four groups: 1) 28 patients with a mean age of 10.7 [standard deviation (SD), 3.1] y, in whom PTC was detected during the active surveillance of AIT [AIT(+), PTC(+) follow up (F)]; 2) 18 patients with a mean age of 12.8 (SD, 3.4) y, in whom PTC and AIT were detected upon admission (A) [AIT(+), PTC(+) A]; 3) 45 patients with a mean age of 13.0 (SD, 3.4) y, in whom PTC was detected upon admission and AIT was excluded [AIT(-), PTC(+) A]; and 4) an age- and sex-matched control group of 89 patients with AIT and with a mean age of 9.4 (SD, 3.0) y. The analysis included clinical, US, and laboratory assessment results of children on admission (groups 1–4) and during follow-up (groups 1 and 4) in the Paediatric Endocrine Outpatient Department.

Results: Upon admission of those in group 1, the US evaluation revealed a hypoechogenic thyroid gland in 12 and an irregular normoechogenic gland in 16 patients. US monitoring revealed an increase in thyroid echogenicity and an increased irregularity of the thyroid structure during the follow-up period of all of the patients from group 1. Such changes were not noticed in group 4. PTC was

diagnosed at the mean time of 3.6 y (3 mo–9 y) since AIT confirmation in group 1. The mean maximum PTC diameter as per the US was significantly smaller in group 1 than in groups 2 and 3 [13.2 (10.8) mm vs. 22.2 (12.8) and 22.05 (15.4) mm]. Fewer patients in group 1 were referred to 131I than in groups 2 and 3 (71.4% vs. 94.4 and 93.3%). Interestingly, significant differences were observed in the thyroglobulin antibody (TgAb)/thyroid peroxidase antibody (TPOAb) ratio between groups 2 and 3, as opposed to group 4, at the beginning of observation [15.3 (27.6) and 3.5 (8.8] vs. 0.77 (1.9)]. In group 1, after the follow-up, an increase in the TgAb/TPOAb ratio was observed [1.2 (9.8) to 5.2 (13.5)]. There were no significant differences between groups 1–3 in labeling index Ki67, lymph nodes metastasis, extrathyroidal extension, and angioinvasion. There were no associations between thyroid-stimulating hormone, TgAb, and the extent of the disease.

Conclusion: The use of thyroid US focused on the search for developing tumours in the routine follow-up of patients with AIT may not only help in the early detection of thyroid malignancies that are not clinically apparent but may also influence the invasiveness of oncological therapy and reduce the future side effects of 131I therapy. We propose that the repeat evaluation of TPOAb and TgAb warrants further exploration as a strategy to determine TC susceptibility in paediatric patients with AIT in larger multicentre studies.

KEYWORDS

autoimmune thyroiditis, papillary thyroid carcinoma, ultrasonography of thyroid gland, TgAb/TPOAb ratio, hypoechogenic thyroid nodules

1 Introduction

Follicular cell-derived thyroid carcinoma represents the vast majority of paediatric thyroid cancers (TCs) (1). Papillary thyroid carcinoma (PTC) accounts for over 90% of all childhood TC cases (2). The most recent statistical data presented by Siegel et al. estimate that TC accounts for 12% of cancers in adolescents and 2%, in children below 14 y of age (3). TC ranks the fourth most common type of cancer in adolescents and the seventh most common in children in the United States (3). According to the data of the Polish National Cancer Registry, new cases of TC in patients below 19 y of age constitute 2.3% of all TCs diagnosed, every second solid neoplasm in girls, and every eighth solid neoplasm in boys (2).

The prevalence of chronic autoimmune thyroiditis (AIT) has been assessed as up to 2% in children and almost 10% in adolescents, depending on the populations studied (4, 5). The disease has female sex predominance, and although it can be diagnosed from infancy, its peak is observed after puberty (6). AIT is responsible for approximately 55–65% of all pediatric euthyroid goiters (7, 8). In 1955, Dailey et al. suggested for the first time that AIT might be considered a premalignant lesion, as chronic inflammation contributes to the development of cancer in many tissues (9–12). Chronic autoimmune inflammation of the thyroid may cause functional and/or structural thyroid disorders leading to an estimated one-third of patients to develop a nodular rebuilding of the thyroid gland (13–20).

In the paediatric population, the incidence of thyroid nodules is lower (0.5–2%) than in those with AIT (3.5–31.5%) (13–23). In recent years, there has been an increase in the coincidental occurrence of AIT and PTC in children and adolescents (7, 14, 16, 23). According to the current paediatric guidelines, neck US in children with autoimmune thyroid disease (AITD) should be performed at least annually (2, 24).The practicality of this approach was presented by our group in the study evaluating parenchymal changes in the thyroid gland with diffuse AIT in children prior to the development of PTC (25). In 2022, Siegel et al. in Cancer Statistics revealed that in the adult population in the United States, after decades of increase, TC incidence rates have now been declining partly because of recent changes in clinical practice designed to reduce overdetection. However, in a more recent analysis in 2023, Huang et al. found that the incidence rate of TC increased in most countries among individuals irrespective of age groups (3, 26). Additionally, the incidence rate increased in populations aged <40 y in several countries, including Poland (26). Because the presentation of PTC in children is more severe than in adults, the extent of surgery is larger, and therapy also includes 131I therapy, leading to potential future therapeutic side effects. On the other hand, overall survival in children is excellent (24, 27, 28). Therefore, it is important to focus the research on the early detection of malignancies with the aim to reduce future side

effects of oncological therapy for PTC in children with long life-expectancy (24, 27, 28).

The present study provides an expansion of previous work from our centre related to the monitoring of patients with thyroid disorders (25). The aim of this study was to prospectively present the outcome of US follow-up in children with AITD who developed PTC and to characterize the US and laboratory variables prior to the development of PTC that might be useful in selecting the PTC risk group within the large population of paediatric patients with AIT.

2 Patients and methods

This prospective study included 180 children and adolescents (132 females; 73.3%) referred to the Outpatient Endocrine Department. The patients were recruited since 2010 till 2023. Patients were divided into four groups: 1) 28 patients with a mean age of 10.7 [standard deviation (SD), 3.1] y, in whom PTC was detected during the active surveillance of AIT [AIT(+), PTC(+) follow up (F)]; 2) 18 patients with a mean age of 12.8 (SD, 3.4) y, in whom PTC and AIT were detected upon admission (A) [AIT(+), PTC(+) A]; 3) 45 patients with a mean age of 13.0 (SD, 3.4) y, in whom PTC was detected upon admission and AIT was excluded [AIT (–), PTC(+) A]; and 4) an age- and sex-matched control group of 89 patients with AIT and with a mean age of 9.4 (SD, 3.0) y.

The prospective analysis of medical records included the evaluations of thyroid function status, US, and cytological and histopathological variables in patients with PTC. All hormonal and immune assessments were routinely performed at the Department of Biochemistry at the University Children's Hospital in Krakow, Poland and were determined using a single fasting blood sample. Thyroid-stimulating hormone (TSH), fT3, and fT4 levels were measured using immunochemistry with an ADVIA Centaur machine, and thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TgAb), and thyroid hormone receptor antibody (TRAb) levels were assessed using the radioimmunoassay method with a Brams machine. TSH, fT3, fT4, TPOAb, and TgAb assessments were performed upon admission to the Department (on first visit) and prior to therapy with levothyroxine or antithyroid methimazole when it was needed. TPOAb and TgAb were additionally examined if US analysis revealed a nodule (prior to surgery). TRAb was controlled only in patients with thyrotoxicosis. TSH, fT3, and fT4 were controlled routinely every 3, 4, and 6 mo in all of the patients. Either TPOAb or TgAb were assessed in all patients. Most of the patients underwent all of the assessments of TPOAb and TgAb. In group 1, TPOAb and TgAb were both assessed in 23 of the 28 patients. In group 2, TPOAb was assessed in all 18 and TgAb, in 10 of the 18 patients. In group 3, TPOAb was assessed in 33 and TgAb, in 25 of the 45 patients. In group 4, TPOAb was assessed in 85 and TgAb, in 69 of the 89 patients. Therefore the TgAb/TPOAb ratio could only be assessed in all 23 patients in group 1, 10 out of 18 patients in group 2, 23 out of 45 patients in group 3, and 66 out of 89 patients in group 4.

AIT was diagnosed based on the typical features of chronic AIT seen during thyroid US assessment as previously described, on increased TPOAb and/or TgAb and/or TRAb antibodies levels, and after histopathological confirmation in all of the patients after thyroidectomy (groups 1 and 2) (16, 25). In group 4 the diagnosis of AIT was based on positive TPOAb and/or TgAb and ultrasound.

Thyroid US was performed on all of the patients at the time of thyroid dysfunction diagnosis and annually since then. US of the thyroid gland was performed at the University Children's Hospital by paediatric endocrinologists and surgeons with experience in paediatric US (DJ and AT >20 y and AKW and MW >15 y). Thyroid US was performed using a high-resolution Voluson 730 GE Medical System (8- to 12-MHz linear-array transducer), Philips Epiq5 (L12-5 linear transducer), Philips iE22 (L11-3 linear transducer), and Samsung HS40 (LA3-16AD transducer). The US examination was performed in the longitudinal and transversal planes. Normal thyroid parenchyma (normoechogenic background) was defined as demonstrating homogenous echogenicity and relative hyperechogenicity compared with the adjacent sternohyoid, sternothyroid, omohyoid, and sternocleidomastoid muscles as described previously (16, 25). The analysis included US features of the thyroid gland according to the EU-TIRADS PL 2022 classification (Polish update of EU-TIRADS 2017) and of the lymph nodes (29, 30).

The patients presenting a nodule containing suspicious features, such as hypoechogenicity, a hyperechogenic 'border' between a nodule and thyroid parenchyma, poorly defined margins, irregular shape, microcalcifications, solid composition, presence of chaotic vascularity as detected *via* Doppler flow, and/or pathological lymph nodes were referred to paediatric oncologic surgeons for fine needle aspiration biopsy (FNAB).

FNAB results were classified according to Bethesda criteria (31). In the patients with PTC, total thyroidectomy with a histopathological verification of the lateral and central lymph nodes was performed. Histopathological evaluation was performed in the Department of Pathology of University Children's Hospital in Krakow.

The hematoxylin and eosin (HE)-stained tissue slides (deparafinnated, cut with 3.5-um thickness) were scanned with the NanoZoomer SQ Hamamatsu (x400 magnification) after a routine diagnosis of thyroid nodules. The pictures were taken from the scans, with the scale placed on the bottom left.

This study was approved by the relevant institutional review board (The Bioethics Committee of the Jagiellonian University; opinion number:1072.6120.288.2021). Written informed consent was obtained from all of the participants and/or their parents. Written informed consent was obtained from the individual(s) and minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

2.1 Statistics

We summarised baseline and demographic characteristics using descriptive statistics. Categorical variables were expressed as percentages. We assessed the distribution of continuous variables using the Shapiro-Wilks test and described continuous variables using mean and SD when appropriate. We used the non-parametric Kruskal-Wallis and U-Mann Whitney tests to compare the groups

of patients. For the assessment of correlations, we used the Spearmann test. A two-tailed p<0.05 was considered statistically significant. All of the analysis were performed with STATISTICA, version 13 (TIBCO Software Inc., Palo Alto, CA 94304 United States).

3 Results

Clinical, hormonal and histopathological assessment of the patients in the four groups are presented in Table 1 and Table 2.

Females predominated in all of the groups. However, a female sex prevalence was more visible in the AIT groups (Table 1).

Interestingly, in group 1, there were more cases with a positive family history of thyroid disorders (nodular goiter, AIT, and PTC) than in groups with PTC detected upon admission. In group 3, this percentage was only 13.3%, and it may explain why these patients presented with a more advanced disease stage upon the first referral (Table 1).

3.1 Admission

The causes of referral were as follows: in group 1, there were abnormal US features of the thyroid gland in over 70% of the patients, whereas goiter dominated in groups 2 to 4 (Table 1)

There were no significant differences in age upon admission between the groups (Table 1).

At AIT diagnosis, the mean thyroid volume was above the reference ranges for Polish patients and, according to WHO reference ranges, in all groups (32, 33). However, in groups 2 and 3, this was not statistically significantly bigger than in the other groups (Table 1).

There were significant differences between TSH, TPOAb, and TgAb between group 4 and the other groups as there were more cases of overt hypothyroidism in this group (Table 1).

In group 1, TSH ranged from 0-26, in group 2 from 0-6.2, in group 3 from 0.7-5.1, and in group 4 from 0-692.3 μIU/ml.

Hypothyroid patients from three groups started receiving levothyroxine: 22 patients in group 1 (4 with overt hypothyroidism and 18 with subclinical hypothyroidism), 4 patients in group 2 (all with subclinical hypothyroidism) and 60 patients in group 4 (55 with overt hypothyroidism and 5 with subclinical hypothyroidism).

Prior to surgery, three patients from group 2 were treated with the antithyroid drug methimazole due to thyreotoxicosis.

Interestingly, the TgAb/TPOAb ratio was significantly lower in group 4 [0.77 (1.9)] versus group 3 [3.5 (8.8)] and not significantly different versus group 2 [15.3 (27.6)] (Table 1).

TABLE 1 AIT-confirmation –first visit.

parameters	AIT confirmation-first visit			AIT control group	p value
	(1) AIT(+) PTC(+) F	(2) AIT(+) PTC(+) A	(3) AIT (–) PTC(+) A	(4) AIT(+) PTC(-)	
n	28	18	45	89	
female n [%]	23 [82.1]	14 [77.8]	31 [68.9]	64 [71.9]	p=0.1
Family history of thyroid diseases n [%]	21 [75]	7 [38.9]	6 [13.3]*	47 [52.8]*	p=0.047
Cause of referral n [%] USG Goiter	 22 [78.6] 2 [21.4]	 7 [38.9] 11 [61.1]	 17 [37.8] 28 [62.2]	 9 [10.1] 80 [89.9]	 p=0.1 p=0.2
Age at AIT diagnosis (years) mean [SD]	10.7 [3.1]	12.8 [3.4]	13.0 [3.4]	9.4 [3.0]	p=0.1
Thyroid volume (ml) mean [SD]	18.4 [17.0]	25.1 [15.3]	27.2 [18.7]	19.9 [18.1]	p=0.2
TSH at AIT diagnosis (μIU/ml N:0.4-4.0) mean [SD]	8.6 [4.9]	4.8 [7.9]	2.5 [1.3]*	44.3 [115.6]*	p=0.02
TPOAb at AIT diagnosis (IU/ml N<30) mean [SD]	2134.9 [3780.7]*	888.8 [2093.9]*	19 [13.5]*	4628.7 [3533.2]*	p=0.01
TgAb at AIT diagnosis (U/ml N<30) mean [SD]	449.8 [476.9]	1059.8 [2467.5]	14.47 [8.5]*	1176.3 [2374.8]*	p=0.01
TgAb/TPOAb mean [SD]	1.2 [9.8]	15.3 [27.6]	3.5 [8.8]*	0.77 [1.9]*	p=0.04

Clinical, hormonal and histopathological assessment of patients in four groups: 1- PTC detected during active surveillance of AIT [AIT(+) PTC(+) F], 2- PTC and AIT detected on admission [AIT(+) PTC(+) A], 3- PTC detected on admission, AIT excluded [AIT (–) PTC(+) A], 4- Age-, and gender matched control group of pediatric patients with AIT. Legend: AIT-autoimmune thyroiditis, PTC-papillary thyroid carcinoma, significant differences between the groups are marked with asterix for p<0.05. Significantly higher TPOAb levels were found in group 4 than in other groups.

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TABLE 2 PTC diagnosis.

parameters	PTC follow-up	PTC on admission		AIT control group	p values
	(1) AIT(+) PTC(+) F	(2) AIT(+) PTC(+) A	(3) AIT(-) PTC(+) A	(4) AIT(+) PTC(-)	
n	28	18	45	89	
Time to PTC detection since referral in group 1 and time of follow-up in group 4 (years) mean [range]	3.6 [0.3-9]	–	–	4.3 [0.2-12.6]	p=0.4
Age at PTC diagnosis (years) mean [SD]	14.5 [3.3]	12.8 [3.4]	13.0 [3.4]	13.7 [3.1]	p=0.4
Thyroid volume at PTC diagnosis (ml) mean [SD]	17.05 [14.9]	25.1 [15.3]	27.2 [18.7]	14.5 [5.8]	p=0.4
PTC largest diameter (mm) mean [SD]	13.2 [10.8]*	22.2 [12.8]*	22.05 [15.4]*	–	p=0.04
unifocal n[%]	13 [46.4]	4 [22.2]	15 [33.3]	–	p=0.3
multifocal & bilateral n[%]	15 [53.6]	14 [77.8]	30 [66.7]	–	p=0.2
LNM largest diameter (mm) mean [SD]	4.6 [7.5]	7.9 [8.8]	5.03 [7.8]	–	p=0.2
LNM central n [SD]	5.0 [11.3]	6.3 [9.8]	3.2[5.1]	–	p=0.3
LNM lateral n [SD]	2.0 [4.9]	4.9 [6.1]	2.4 [4.9]	–	p=0.4
LI Ki67 mean [SD]	9.6 [4.6]	10.15 [4.9]	9.7 [5.2]	–	p=0.4.
ETE n[%]	10 [35.7]	6 [33.3]	21 [46.6]	–	p=0.4
AI n[%]	11 [39.3]	8 [44.4]	25 [55.5]	–	p=0.3
TSH at PTC dgn (μIU/ml N:0.4-4.0) mean [SD]	3.9 [5.2]	4.8 [7.9]	2.5 [1.3]	2.7 [3.9]	p=0.4
TPOAb at PTC dgn (IU/ml N<30) mean [SD]	957.9 [2025.3]*	888.8 [2093.9]*	19 [13.5]*	3966.1 [2978.2]*	p=0.01
TgAb at PTC dgn (U/ml N<30) mean [SD]	758.9 [1567.0]	1059.8 [2467.5]	14.47 [8.5]*	853 [1265.8]*	p=0.01
TgAb/TPOAb mean [SD]	5.2 [13.5]	15.3 [27.6]	3.5 [8.8]*	0.21 [0.4]*	p=0.04
^{131}I n [%]	20 [71.4]	17 [94.4]	42 [93.3]	–	p=0.4
PTC subtypes n					
classic	14	7	24	–	
follicular	4	3	8		
c,f	4	-	4		
c,f,s	4	3	3		
cs	1	2	-		
columnar	1	-	-		
ds	-	1	1		
fs	-	1	1		

(Continued)

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TABLE 2 Continued

parameters	PTC follow-up	PTC on admission		AIT control group	p values
	(1) AIT(+) PTC(+) F	(2) AIT(+) PTC(+) A	(3) AIT(-) PTC(+) A	(4) AIT(+) PTC(-)	
c,f,s,c/m	-	1	-		
c,f,s,t,c/m	-	-	1		
ds,s,f	-	-	1		
c,f,s,o,g	-	-	1		
s,anaplastic	-	-	1		

Clinical, hormonal and histopathological assessment of patients in four groups: 1- PTC detected during active surveillance of AIT [AIT(+) PTC(+) F], 2- PTC and AIT detected on admission [AIT(+) PTC(+) A], 3- PTC detected on admission, AIT excluded [AIT(-) PTC(+) A], 4- Age-, and gender matched control group of pediatric patients with AIT. Legend: AIT-autoimmune thyroiditis, PTC-papillary thyroid carcinoma, LNM-lymph node metastasis, LN-lymph nodes, C LNM- central lymph nodes metastasis, L LNM-lateral lymph nodes metastasis, ETE-extrathyroidal extension, AI- angioinvasion, PTC subtypes: c-classic, f-follicular, s-solid, ds-diffuse sclerosing, c/m-cribriform morular, t-tall cell, g-glomerular, o-oncocytic; F-follow up, A-admission, AI-angioinvasion, ETE-extrathyroidal extension; significant differences between the groups are marked with asterix for $p<0.05$. Significantly larger PTC diameters were found in groups 2 and 3 than in group 1. Significantly higher TPOAb levels were found in group 4 than in other groups.

3.2 PTC diagnosis

PTC was diagnosed at the mean time of 3.6 y (3 mo to 9 y) from AIT confirmation in group 1 (Table 2).

Significantly larger PTC diameters were found in groups 2 and 3 than in group 1 (Table 2). However, the localization of lesions (unifocal or multifocal and bilateral), number of lymph nodes with central or lateral PTC metastasis [lymph nodes metastasis (LNM)], maximum length of the largest metastatic lymph node, labelling index Ki67, extrathyroidal extension, and angioinvasion were similar in all groups 1-3 (Table 2).

After follow-up we have seen a decrease of mean TSH in group 1 and 4, however the mean thyroid volume decreased more in group 4 than in group 1. The mean (SD) TSH levels in group 1 and 2 were close to upper normal range and in the middle of the normal range in group 4.

TPOAb was significantly higher in group 4 than in the other groups. Interestingly, the TgAb/TPOAb ratio was significantly lower in group 4 [0.21 (0.4)] than in groups 3 [3.5 (8.8)] and 1 [5.2 (13.5)] (Table 2). This observation can be explained by a decrease of TPOAb level and increase in TgAb titers as seen in some children in group 1, whereas in the AIT group, we observed a decrease in both TPOAb and TgAb levels. Unfortunately, our small sample size enabled a more detailed analysis.

Histological assessment revealed more aggressive subtypes of PTC in group 2 and mostly in group 3: tall cells, diffuse sclerosing, and solid and more mixed subtypes, including the solid/anaplastic subtype (Table 2).

In group 1, only 71.4% were referred for 131I therapy. Meanwhile, this percentage was higher in group 2 (94.4%) and group 3 (93.3%) (Table 2).

3.3 US assessment

US and corresponding histopathological features of the thyroid gland from representative patients from group 1 are presented in Figures 1–3.

Upon admission, in group 1, the US evaluation revealed a hypoechogenic thyroid gland in 12 and irregular normoechogenic gland in 16 patients. US monitoring showed an increase in thyroid echogenicity during the follow-up period in all of the patients in group 1; an increasing irregularity of the thyroid structure was also seen. Such changes were not noticed in the patients in group 4 with hypoechoic thyroid glands typical for diffuse thyroiditis during the study period. In groups 2 and 3, with PTC detected upon admission, the US of the thyroid gland represented nodular rebuilding in all of the patients at the background of irregular normoechogenicity of the thyroid gland.

The malignant lesion was hypoechoic in all of the patients, though we observed three US patterns. The first was seen in 18 out of 28 patients in group 1, 10 out of 18 patients in group 2, and all 45 in group 3; here, we noted the nodular, lobulated composition of the lesion (Figure 1). Histopathological assessment revealed small malignant lesions separated by fibrosis (Figure 1). The second pattern was seen in only seven patients only in group 1. The lesion was circumscribed by a hyperechogenic layer, which was histopathologically confirmed to be fibrosis with psammoma bodies (Figure 3). This pattern was characteristic in patients with diffuse thyroiditis and hypoechoic parenchyma with hyperechogenic layers of fibrosis seen in the background. The third pattern included hypoechogenic nodules later described by pathologists to be lesions with spiculated, irregular margins surrounded by fibrotic parenchyma with multiple areas of lymphocytic infiltration in patients with goiter. This pattern was seen in 3 out of 28 patients in group 1 and 8 out of 18 patients in group 2 (Figure 2).

We found that the majority of detected nodules showed a fast growth rate over time, with volumes that doubled or even tripled within 2–8 mo of observation before FNAB was performed. This pattern of growth has already been described in our previous report (25).

3.4 Pathology

After FNAB based on the Bethesda criteria was conducted, total thyroidectomy with lymph node dissection where appropriate was performed in all of the patients (31). The recurrences were observed only in group 3, in five patients who were subsequently subjected to lateral lymph node dissection.

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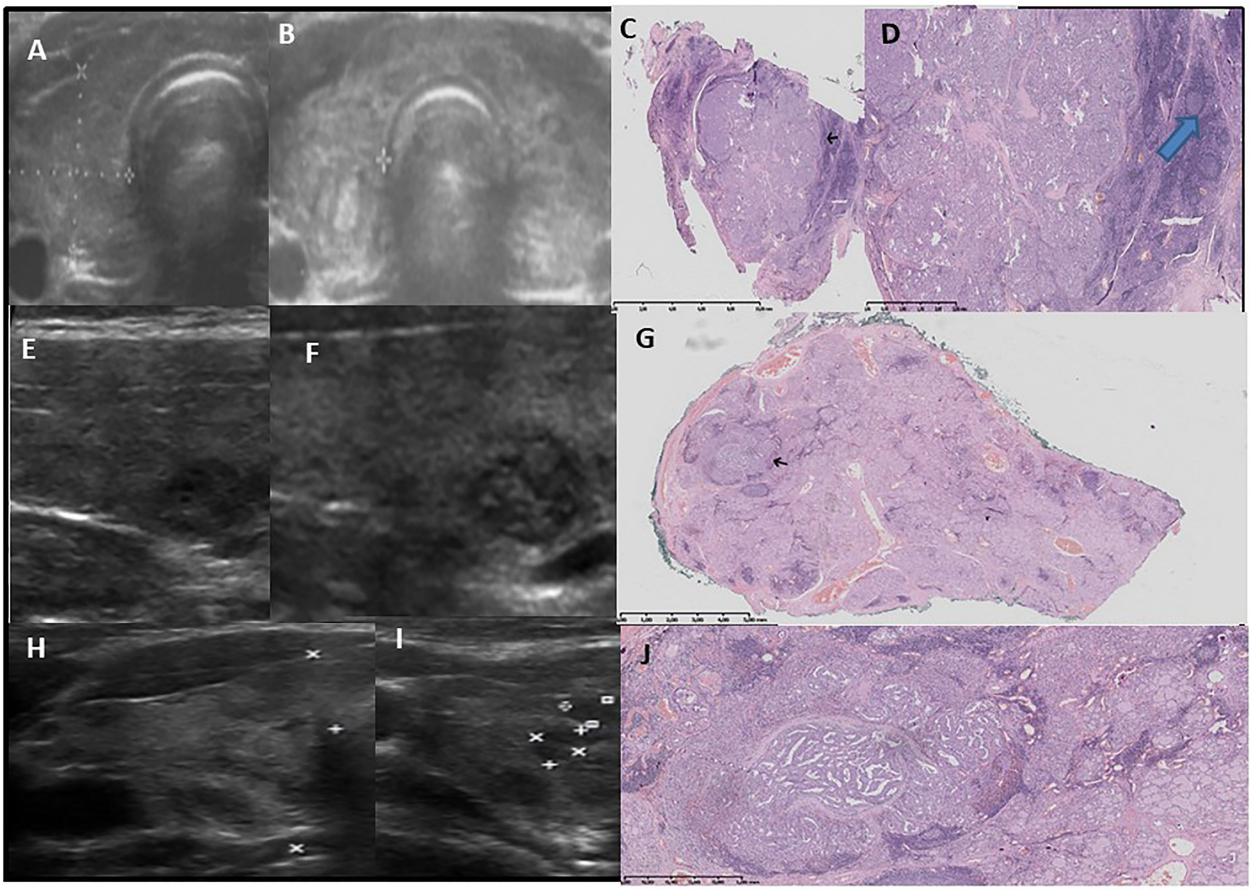

FIGURE 1
Pattern 1 - a lobulated nodule on US seen as few small malignant lesions- separated by fibrosis and surrounded by lymphocytic inflammation in histology. Ultrasound -pathology correlations. 1st row **(A–D)**: Development of lobulated nodule with nodular hyperechogenic solid composition after 5 years since the confirmation of autoimmune thyroiditis and first thyroid ultrasound. Increase in background echogenicity is visible. Female patient, age 17 years old, classic PTC, 10 mm, multifocal, bilateral **(A)**-before, **(B)**-after.**(C)** Lobulated tumour radiates from a central scar, pushing into thyroid H&E x1, **(D)** thin fibrotic capsule partially visible. Outside the tumour chronic lymphocytic infiltration with formation of germinal centers, fibrosis is visible H&E x10, black arrow – tumour, blue arrow – germinal center in lymphocytic inflammation. 2nd and 3rd row **(E–J)**: Development of lobulated nodule with nodular hyperchogenic solid composition after 4 years since the confirmation of autoimmune thyroiditis and first thyroid ultrasound. Female patient, 18 years old, with classic, follicular PTC, 5 mm, multifocal, bilateral **(E, H)** -before, **(F, I)**-after). **(G)** Lobulated tumour with fibrotic layers inside, pushing into thyroid H&E x1, black arrow – tumour. **(J)** light-pink fibrotic capsule is partially visible in a small, central compartment with purely papillary composition. Tumour invades capsule and the outer part of whole cancer has more compact papillary-follicular composition surrounded by a dark-blue lymphocyte inflammation. The pink, thin, long fibrosis is present in non-tumoural thyroid. Angioinvasion (+). H&E x20.

There was no correlation between the PTC subtype and the pattern of a nodule seen on US, though our sample may have been too small to observe the differences.

A histopathological assessment revealed that the malignant lesions were not encapsulated. Fibrotic capsules, if partially visible, were infiltrated by the branches of the lesions. In all of the patients, the lymphocytic infiltration around the tumor was visible. In patients with a normoechoic background, the infiltration was less advanced in the surrounding thyroid tissue than in patients with a hypoechoic background, where massive inflammation with germinal centres infiltrated by tumors was visible (Figures 1–3).

3.5 Correlations

There were no correlations between TSH, TgAb, and the extent of the disease. The only determined associations involving the extent of the disease were with age and PTC nodule diameter. The patients' ages correlated negatively with PTC mm (r: -0.3, p=0.01), LNM mm (r: -0.38, p=0.048), number of central and lateral LNM (r: -0.36; r: -0.32, p=0.01), extrathyroidal extension (ETE) (r: -0.37, p=0.01), and angioinvasion (AI) (r: -0.3, p=0.02). Negative correlations were found between thyroid peroxidase (TPO) and PTC mm (r: -0.29, p=0.011) and AI (r: -0.26, p=0.011). The diameter of PTC in mm correlated positively with LNM mm (r: 0.39, p=0.02), number of central and lateral LNM (r: 0.29; r: 0.36, p=0.01), LI Ki67 (r: 0.32, p=0.012), ETE (r: 0.36, p=0.01), and AI (r: 0.3, p=0.02).The TgAb/TPOAb ratio correlated with AI (r: 0.26, p=0.01).

4 Discussion

In the present follow-up study thyroid malignancies were detected early *via* US before they were clinically apparent. A

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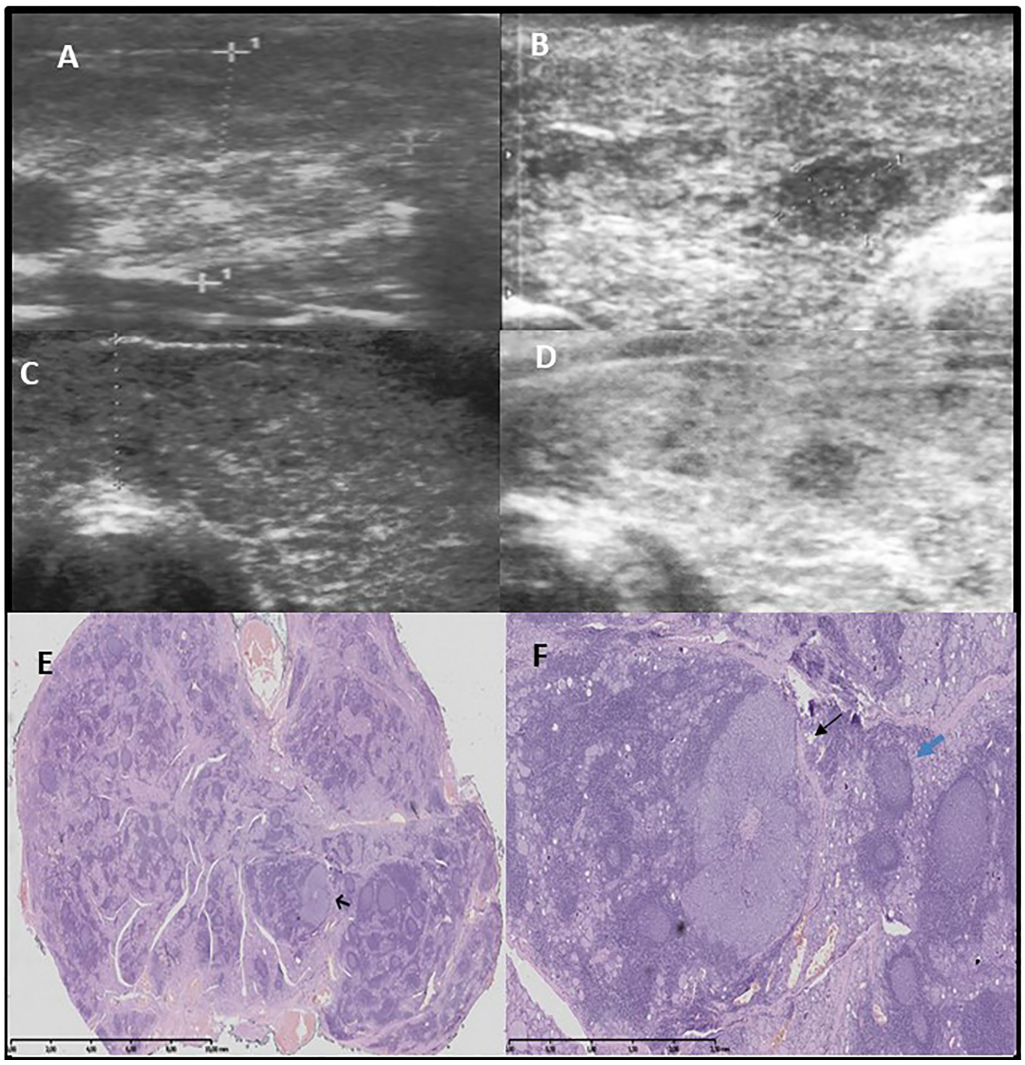

FIGURE 2
Pattern 3 - hypoechogenic nodule, histologically unencapsulated and with irregular margin. Row **(A, B)**: Development of hypoechogenic lesion surrounded by hyperechogenic fibrotic parenchyma after 1 9/12 years since the confirmation of autoimmune thyroiditis and first thyroid ultrasound. Female patient 11 years old, classic PTC, 6.7 mm, unilateral **(A)** before, **(B)** after Row **(C–F)**: Development of hypoechogenic lesion surrounded by hyperechogenic fibrotic parenchyma after 4 years since the confirmation of autoimmune thyroiditis and first thyroid ultrasound. Female patient 17.5 years old, classic, follicular PTC, multifocal, bilateral **(C)** before, **(D)** after, **(E)** The thyroid with AITD and goiter seen as a mixture of normal thyroid with colloid production, intense lymphocytic infiltration, as well as oblong and irregular fibrotic bands. In one large area of intense lymphocytic infiltration an irregular demarcated tumour is present (black arrow). H&E x1, **(F)** irregular classic PTC with lymphocytic background adhere on the right to fibrotic band (black arrow). The tumour is surrounded by large lymphocytic aggregation on the left. In the central part of the tumour, small, irregular, oval area of fibrosis is seen. H&E x10, blue arrow germinal center.

surgical work-up of all of the patients confirmed malignancies, and there were no surgical complications and unnecessary surgeries. We found that the majority of detected nodules showed a fast growth rate over time, with volume that doubled or even tripled within 2–8 mo of observation before FNAB was performed. This pattern of growth has already been described in our previous report (25).

In the present study, we observed that paediatric PTC is fast-growing and aggressive as even with the regular monitoring and detection of small lesions after thyroidectomy, over 70% of children in group 1 were referred for 131I therapy due to multifocality and bilaterality and LNM, a known observation in paediatrics (2, 6, 13, 24). However, this percentage was over 90% in other groups; thus, active surveillance might reduce the need for 131I therapy. Additionally, the diameter of the nodules was significantly lower in the actively surveilled group. Interestingly, we observed more aggressive and mixed PTC subtypes in groups detected upon admission (referred with goiter or nodules already found during US assessment). Furthermore, the percentage of those with a family history of thyroid disorders was much smaller in group 2 and especially in group 3 than in group 1; therefore, the children in these groups were referred relatively late to endocrinologists. The poor awareness of thyroid diseases by parents without familiarity with thyroid problems could impact late referrals. This finding is not surprising, but it may underline the need for a thorough check-up of family thyroid history in paediatric patients, as well as thyroid US checks in cases of neck goiter even if this history is negative.

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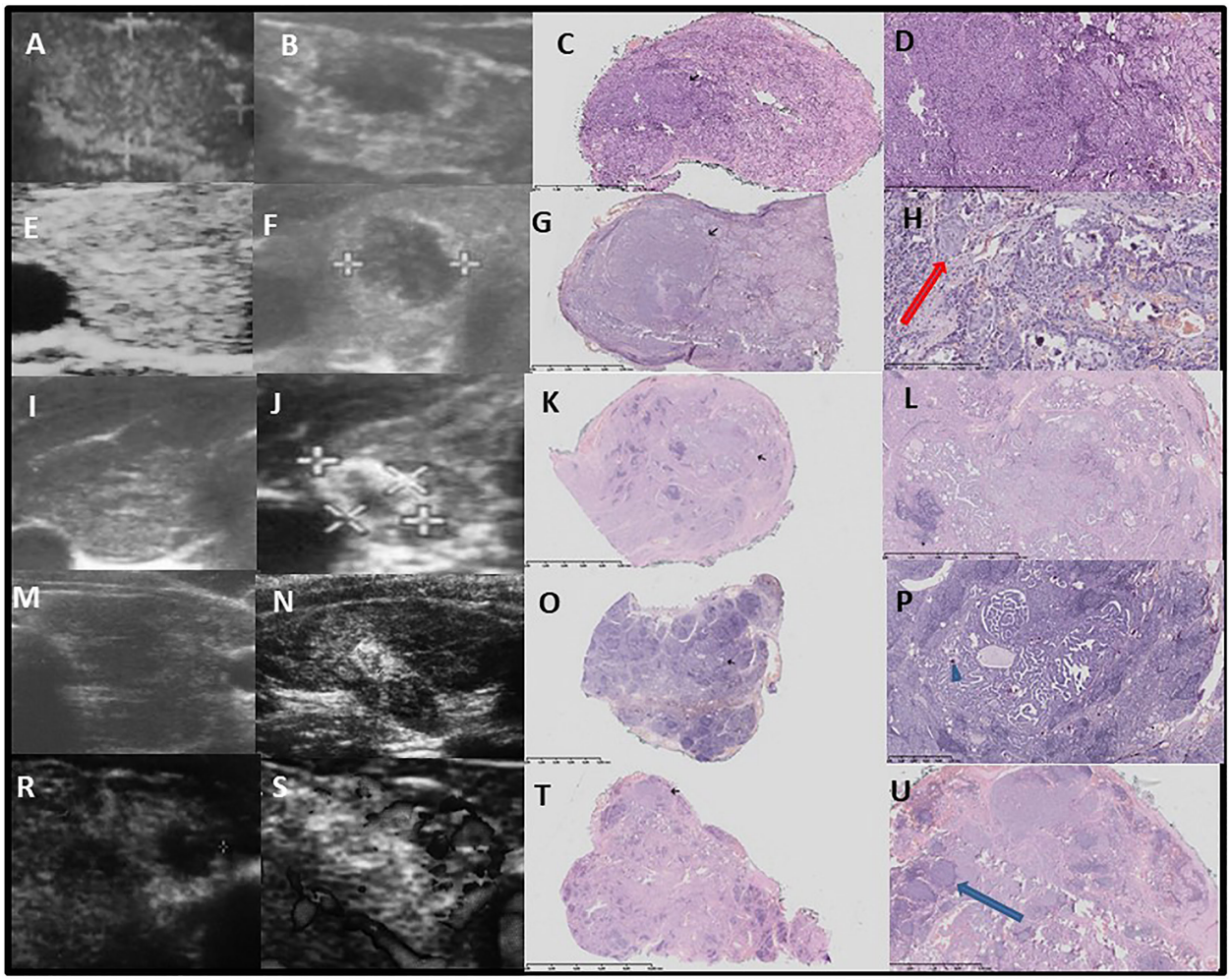

FIGURE 3
Pattern 2 – well circumscribed hypoechogenic lesion surrounded by a hyperechogenic thick layer and further, hypoechogenic parenchyma with hyperechogenic fibrosis. Thick layer is histologically seen as a tumour surrounded by fibrosis and psammoma bodies, and with diffuse thyroiditis in the background. Ultrasound -pathology correlations. Row **(A–D)**: Development of hypoechogenic nodule surrounded by hyperechogenic fibrotic layer after 4 7/12 years since the confirmation of autoimmune thyroiditis and first thyroid ultrasound. Female patient, 14 years old, classic, follicular, solid PTC, 7 mm and 2 mm, multifocal, bilateral **(A)**-before, **(B)**-after. **(C)** The tumour infiltrates into surrounding thyroid on histology, correlated with blurred margin on ultrasound, no angioinvasion H&E x1, black arrow – tumour. **(D)** thin fibrotic capsule around classic PTC subtype is visible (upper part of the tumour). Outside the tumour chronic lymphocytic infiltration (dark blue) and fibrosis with few psammoma bodies (small, purple bodies which generate oblong artefacts resembling jagged tissues) is visible H&E ×40. Row **(E–H)**: Development of hypoechogenic nodule surrounded by hyperechogenic fibrotic layer after 4 years since the confirmation of autoimmune thyroiditis and first thyroid ultrasound. Female patient, 13 years old, classic, follicular, solid PTC, 9 mm, unilateral **(E)** before, **(F)** after. **(G)** The 'mushroom-shaped' tumour, predominantly papillary in upper part, and follicular and solid in lower part which infiltrates into surrounding thyroid (histology) what correlates with blurred margin on ultrasound. Angioinvasion is present. Inside the solid part of the tumour oblong, irregular fibrosis and desmoplasia are visible. Tumour infiltrates its capsule (a thin capsule is seen in upper part of the tumour, which in this part is quite well demarcated and oval). H&E x1, black arrow – tumour. **(H)** High magnification of the PTC enriched with multiple psammoma bodies and a foci of squamous epithelial metaplasia (red arrow). H&E ×100. Row **(I–L)**: Development of hypoechogenic nodule surrounded by hyperechogenic fibrotic layer on the background of hypoechoic thyroid, after 4 11/12 years since the confirmation of autoimmune thyroiditis and first thyroid ultrasound. Female patient, 17.5 years old, classic, follicular, solid PTC, 9.8 mm, multifocal, bilateral **(I)** before, **(J)** after). **(K)** The tumour is infiltrating into surrounding thyroid on histology, angioinvasion is absent. H&E ×1, black arrow - tumour. **(L)** a biphasic (central – dense and solid, while outer – papillary and follicular) tumour infiltrates its capsule (herein a thin capsule demarcate upper part of the tumour). Outside the tumour chronic lymphocytic infiltration and irregular fibrosis is visible H&E ×10. Row **(M–P)**: Development of hypoechogenic nodule surrounded by hyperechogenic fibrotic layer on the background of hypoechoic thyroid, after 2 years since the confirmation of autoimmune thyroiditis and first thyroid ultrasound. Female patient, 8.8 years old, classic PTC, 6.7 mm, unilateral **(M)**-before, **(N)**-after). **(O)**-The tumour is not encapsulated and infiltrates the thyroid. Outside and inside the tumour massive lymphocytic infiltration with formation of germinal centres. H&E x1, black arrow – tumour. **(P)**-Papillary tumour with a few psammoma bodies (blue arrowhead) and fibrosis (surrounds the lower part and sides of the tumour as well as occurs between lymphocytic infiltration), H&E x40. Row **(R–U)**: Development of hypoechogenic nodule surrounded by hyperechogenic fibrotic layer after 4 years since the confirmation of autoimmune thyroiditis and first thyroid ultrasound. Female patient 17 years old, follicular PTC, 10 mm, multifocal, bilateral **(R)** before, **(S)** after). **(T)** Extensive fibrosis and lymphocytic infiltration of thyroid with less fibrosis in a tumour. H&E x1, black arrow – tumour. **(U)** Follicular tumour interspersed with thin bands of fibrous tissue. A few small psammoma bodies (which give oblong artefacts) are seen in lower part of the tumour. Lymphocytic germinal centers within the tumour (blue arrow) H&E x40.

This study is an expansion of our previous work presenting the follow-up of patients with AIT who did not appear to have nodules on the first US check-up, which was performed during the first referral visit, but who later developed nodules, as seen during subsequent visits (25). The patterns observed and described in our previous work and presented to all members of our team enabled an increase in the detection of PTC in our departments. In the present study, the mean time to PTC detection was 3.6 y. These data are consistent with those of the Italian study by Rizzo et al., demonstrating that the lag time between AIT diagnosis and PTC detection was approximately 5 years (34). The increase in the number of thyroid nodules during follow-up, but not PTC, has also been reported by Radetti et al. in a large study of paediatric patients with AIT (13). This difference could be related to the small size bias in our group of selected patients.

The US evaluation of thyroid nodules detected during follow-up revealed three patterns of a nodule. To our knowledge, this is the first study describing different patterns of a developing nodule in paediatric patients. The first, which was more common, was of a lesion with a nodular, lobulated, solid composition. The second was of a lesion circumscribed by a hyperechogenic layer, which was histopathologically confirmed to be fibrosis with psammoma bodies. This pattern was characteristically seen in patients with diffuse thyroiditis and hypoechogenic parenchyma with hyperechogenic layers of fibrosis seen in the background. The third pattern included hypoechogenic nodules later described by pathologists as lesions with spiculated, irregular margins surrounded by fibrotic parenchyma in patients with goiter. These observations require much larger groups of paediatric patients in multicentre studies for confirmation and the determination of molecular associations.

A histopathological assessment revealed that malignant lesions were not encapsulated. Fibrotic capsules, if partially visible, were infiltrated by the branches of the lesions. This was in contrast to usually encapsulated PTC nodules in adults (24, 27). In all of the patients, the lymphocytic infiltration around the tumour was visible. However, in patients with a normoechoic background, it was less advanced in the surrounding thyroid tissue than in patients with a hypoechoic background, where massive lymphocytic infiltration, with the formation of germinal centres within the tumour, was visible.

Oppenheimer et al. found that the subset of patients with nodular AIT who had normal background parenchyma is a particularly interesting group to consider in further research and proposed that these patients may not carry a preexisting clinical diagnosis of AIT (22). Therefore, it was suggested by other research groups that an autoimmune reaction might be secondary to developing PTC (35–38). In a study by Paparodis et al., patients with less destructive AIT were described to have a higher risk for differentiated TC than were patients with a clear destructive AIT (21). However, in our study, we were able to notice the formation of a nodule on a hypoechoic background in several patients. As reported by Lee et al., a sonographic AIT diagnosis is made based on the hypoechogenicity and heterogenicity of the thyroid gland (7). Thyroidal parenchymal stiffness takes place in patients with AIT due to the lymphocytic infiltration, fibrosis, and follicular destruction in the thyroid gland during the disease process. This can be seen on US as increased parenchymal echogenicity with time (39, 40). We suggest that we should search for lesions that are circumscribed by a fibrotic layer in these paediatric patients.

Another point of interest in this study is the observation that although all hypothyroid patients in group 1 received levothyroxine treatment and presented decreased thyroid volumes and TSH levels, this therapy failed to provide any protection from nodule development. However, in the group 1 that developed AIT we have not seen similar decrease of mean thyroid volume as in AIT control group 4. Corrias et al. and Mussa et al. presented that progressive increase in nodule diameter under levothyroxine therapy is a factor which seems to be significantly associated with the risk of malignancy, an observation reported also by other researchers (13, 14, 25, 41).

After follow-up we have seen a decrease of mean TSH in group 1 and 4. The mean TSH levels in group 1 were close to upper normal range and in the middle of the normal range in group 4. Mussa et al. and Zirilli et al. presented that persistently elevated TSH levels play an independent role as predictors of the likelihood of TC, in children and in adults (41, 42). Interestingly Mussa et al. presented that serum TSH in the upper normal range was consistently associated wih thyroid cancer in children (41). It has to be emphasized that there are no current guidelines related to the level of TSH suppression in AIT treatment in children, as a possible TC prevention, and our study was not designed to provide them. Recent studies presented however, that TSH suppressive therapy for TC is associated with increased cardiovascular risk and has a negative impact on cognition in children (43–45), therefore in our AIT patients we aimed at TSH within the normal range.

An interesting observation was related to the TPOAb and TgAb assessments. TgAb is generally used as a prognostic marker of PTC only after total thyroidectomy, but its preoperative value in patients with PTC with concomitant AIT is still unclear (46). The role of thyroid antibodies in inducing malignant transformation of the thyroid tissue, regional lymph node invasion, and even long-term disease-free survival is controversial (47–51). Jia et al. and Kim et al. have reported for the first time that positive serum TgAb is an independent predictive marker for thyroid malignancy in patients diagnosed with thyroid nodules, regardless of the presence of AIT (52, 53). Interestingly, in our study, the TgAb/TPOAb ratio was significantly lower in children with AIT than in children in whom PTC was diagnosed upon admission, independently with regards to AIT. However, in patients with PTC who were not diagnosed with AIT, both TgAb and TPOAb levels were below the lower norm. Interestingly, in the group that was actively surveilled, the TgAb/TPOAb ratio increased since the beginning of the observation period and was higher than in patients with AIT. This observation can be explained by a decrease of TPOAb level and increase in TgAb titers as seen in some children in this group, whereas in the AIT group, we observed a decrease in both TPOAb and TgAb levels.

Recent studies by Hosseini et al. and Grani et al. have also suggested the use of preoperative TgAb levels as a marker for PTC (54, 55). The causal relationship between AIT and PTC is not yet clear, and it is uncertain whether TgAb is generated by the same

pathological process in both AIT and PTC. It was found that the pattern of Tg recognition differs in patients with and without AITD (35, 56, 57). The Tg epitopic regions in patients without AITD were more variable than in those with AITD. Moreover, the pattern of recognition of TgAb in patients with both PTC and AIT was more similar to that observed in those with AIT, as compared to patients with PTC (35, 56, 57).

Min et al. observed an association between high serum TgAb levels and C LNM in patients with PTC and AIT, suggesting that it can be useful in predicting LNM in these patients (51). Similarly to our observation in paediatric patients that the TgAb/TPOAb ratio is associated with angioinvasion, Min et al. identified that the TgAb/TPOAb ratio were significantly associated with the extent of the disease once the ratio index was higher than 2 in adult patients (51). Unfortunately, a small sample size precluded a more detailed analysis in our study; therefore, multicentre paediatric research is necessary to confirm this observation.

Xu et al. have reported that larger PTC lesions and LNM were significantly associated with higher TgAb, and an increasing preoperative TgAb level of up to 2000 IU/mL was associated with shorter recurrence-free survival (46). According to Li et al., although preoperative positive TPOAb and TgAb are independent predictive markers for PTC, they are also associated with milder clinicopathological features of PTC (58). In our study, however, we found that AIT was observed in 50% of operated children, but we could not confirm the association of AIT with the PTC stage in relation to LNM or ETE. The only association involving the extent of the disease was found in relation to the age, tumour diameter, and TPOAb, similarly as observed in other recent paediatric studies (59–61). In paediatric patients, Huang et al. found that preoperative positive TgAb and TPOAb were protective factors for recurrence in younger age groups but not in older patients (62).

Unlike adults, children with differentiated TC may present with more advanced disease and have a higher local recurrence and distant metastases, even though their prognosis is favourable with overall 10-y survival rates of over 90% (24). Children have a longer posttreatment life expectancy and, thus, have more time for recurrence or potential treatment side-effects to manifest (1). Recent studies also confirmed that 131I therapy is associated with an increased risk for the development of second malignancies as well as with an increase in overall mortality for patients with PTC, especially for those who were treated in childhood (63). On the other hand, inadequate treatment of the initial cancer is linked to recurrent or persistent disease, and subsequent surgeries are much more difficult and prone to complications (1). Therefore, PTC prognostics is at present an area of intense research in the field of oncology (53).

Several limitations existed in our study. Due to the rarity of PTC incidence in young patients, our sample was small and had no power to establish statistical significance. Additionally, not all of the patients had repeated all of the tests, which influenced the result.

However, strengths included the fact that at the time of writing, the authors are clinical doctors and are involved in the diagnostic and therapeutic process. Additionally, patterns of nodule recognition described by our group are of practical value in every day US practices. Similarly to adult studies, we found that the preoperative TgAb/TPOAb ratio could likely serve as a novel prognostic factor for predicting PTC in children, though this needs confirmation in multicentre studies.

5 Conclusion

The use of thyroid US focused on the search for developing tumours in the routine follow-up of patients with AIT may not only help in the early detection of thyroid malignancies that are not clinically apparent but may also influence the invasiveness of oncological therapy and reduce the future side effects of 131I therapy. We propose that the repeat evaluation of TPOAb and TgAb warrants further exploration as a strategy to determine TC susceptibility in paediatric patients with AIT in larger multicentre studies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the relevant institutional review board (The Bioethics Committee of the Jagiellonian University; opinion number:1072.6120.288.2021). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

Study design: DJ. Study conduct: DJ, AT-N, AK-W, MK, MW, WG. Data collection: DJ, MK, AT-N, AK-W, MW. Data analysis: DJ, MW, MK. Data interpretation: DJ, MW, MK, AT-N, AK-W. Drafting manuscript: DJ, MW. Revising manuscript content: DJ, MW, WG, JS. Approving final version of manuscript: DJ, MW, JS, WG. DJ takes responsibility for the integrity of the data analysis.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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DICER1 syndrome and embryonal rhabdomyosarcoma of the cervix: a case report and literature review

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Background: Embryonal rhabdomyosarcomas (ERMS) of the uterine cervix and corpus are rare pediatric tumors usually associated with a late age of onset and frequent somatic DICER1 mutation. It may also develop in the context of a familial predisposition such as DICER1 syndrome requiring specific medical care for children and young adults at risk for a broad range of tumors.
Case presentation: This is a case of a prepubescent 9-year-old girl who was presented to our department for metrorrhagias due to a vaginal cervical mass, initially classified as a müllerian endocervical polyp on negative myogenin immunostaining. The patient subsequently manifested growth retardation (-2DS) and learning disabilities leading to genetic explorations and the identification of a germline pathogenic *DICER1* variant. The family history revealed thyroid diseases in the father, aunt and paternal grandmother before the age of 20.
Conclusion: Rare tumors such as cervical ERMS associated with a family history of thyroid disease during infancy could be related to DICER1 syndrome. Identifying at-risk relatives is challenging but necessary to detect early DICER1 spectrum tumors in young patients.

KEYWORDS

DICER1 syndrome, cervical embryonal rhabdomyosarcoma, thyroid pathologies, surveillance recommendations, genetic testing

Introduction

DICER1 syndrome is a rare autosomal dominant genetic disorder which predisposes to the development of a wide range of both benign and malignant tumors. This syndrome has been linked to pathogenic germline mutations of the *DICER1* gene which encodes an endoribonuclease involved in the maturation of microRNAs (miRNAs) and therefore the regulation of gene expression (1). DICER1 acts as a tumor suppressor where mutations in one gene allele lead to an increased risk of tumor development and the necessity of a somatic mutation in the second allele to produce a malignant phenotype. The majority of germline mutations are located throughout the entire gene, whereas somatic mutations have been found in the regions that encode the RNase III domains.

DICER1 syndrome is strongly suspected when typical DICER1-associated tumors such as lung cysts, pleuropulmonary blastoma (PPB), cystic nephroma, ovarian sex-cord stromal tumor and multinodular goiter develop in the early stages of childhood (2, 3). Recently a list of less commonly observed tumors including embryonal

rhabdomyosarcoma (ERMS) of the bladder, uterine cervix or fallopian tubes have also been described (4–6).

Incomplete penetrance of germline pathogenic *DICER1* variant and the low risk for relatives of developing a tumor before the age of 10 complicate care recommendations which have been recently discussed (7). Although DICER1 syndrome remains a rare entity it often leads to a delay in medical care for the proband with a high risk of malignant tumor development.

This is a case report of a female child incidentally diagnosed with rare *DICER1*-associated ERMS of the cervix after multiple investigations.

Case report

The female patient was born at term with a history of intrauterine growth restriction (IUGR; s:46 cm; w:2,550 g, hc: 34 cm) and neonatal dysmorphia, leading to neonatal urinary glycosaminoglycans (GAGs) analysis for screening of mucopolysaccharidosis with inconclusive results. She is a first child born at 39 weeks of amenorrhoea after normal pregnancy and delivery (mother's age: 24 yrs). At the age of 9 the girl was referred to our pediatric gynecology department for metrorrhagias. Clinical and physical examination revealed no sign of pubertal development but retrieved a cervically protruding vaginal mass corresponding to multiple polyps of 0.5 to 2 cm length. After surgical resection, the histopathological analysis indicated benign müllerian endocervical polyps with variable cellularity, mild atypia, squamous-like epithelium and diffuse Smooth Muscle Actin but negative Myogenin immunostaining. Serum tumor markers alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and human chorionic gonadotropin (hCG) were negative.

A year later, during clinical follow-up, the patient presented a decline in growth rate with growth retardation (-2 SD) (**Figure 1A**). A physical examination revealed prognathism, macroglossia and brachymetacarpia with no other remarkable factors. Isolated partial growth hormone (GH) deficiency was diagnosed on stimulation tests. Imaging tests, including hand and wrist x-ray, thyroid echography and pituitary magnetic resonance imaging (MRI) were all normal. Further cytogenetic and molecular testing showed normal karyotype (46XX) and no *SHOX* deficiency. Complementary hormonal results ([thyroid stimulating hormone (TSH), free thyroxine (FT4), parathyroid hormone (PTH), adrenocorticotropic hormone (ACTH), cortisol, prolactin, estradiol, anti-müllerian hormone (AMH), insulin-like growth

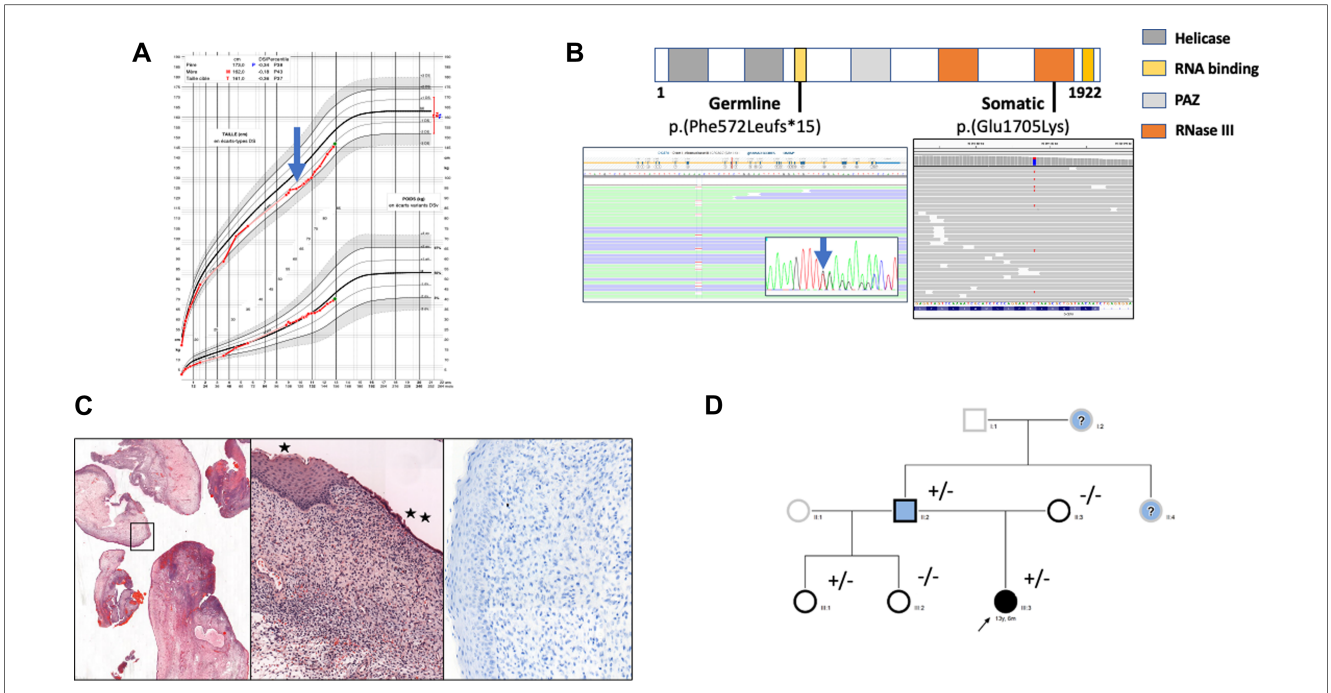

FIGURE 1
(A) growth curve of the female child. At 10 years old growth retardation (-2 SD) was noted (blue arrow) and synthetic growth hormone treatment was started. (B) Localization of identified somatic and germline variants. Germline heterozygous T deletion (c.1716del, p.(Phe572LeufsTer15)) and somatic heterozygous substitution c.5113G > A, p.(Glu1705Lys) were detected by next generation sequencing (Illumina, custom metabolic disorders panel) in exon 10 and 27 respectively of the *DICER1* gene (LRG_492, NM_177438.3; Sequencing depth was 874 x and 756 x respectively (Integrative Genomic Viewer Software). The germline variant was confirmed by Sanger sequencing (blue arrow). (C) Histologic and immunohistochemical examination of cervical tissue samples. Edematous congestive polyp fragments, hematoxylin and eosin (HE) staining, original magnification×25 (left panel); Surface squamous (*) or mucinous (**) epithelium without atypia, the underlaying proliferative cells are monotonous without atypia or mitosis, HE×100 (middle panel); Myogenin staining showing no myogenin expression,×200 (right panel). (D) Family pedigree. Individuals screened for *DICER1* germline variant are indicated by a black border. Clinical phenotypes are represented by black filling for ERMS, blue for thyroid disease and white for asymptomatic. The proband is marked with an arrow. "+" and "-" indicate the mutation status. Question marks correspond to symptomatic patients whose *DICER1* mutational status is unknown.

TABLE 1 Clinical and hormonl features for the index case and her mother.

			Reference range
Maternal features			
Age (yrs)	24		
Size (cm)	162		
Neonatal features			
Size (cm)	46		
Weight (g)	2.551		
Head Circonference (cm)	34		
At 9 yrs		At 12 yrs	
Before GH treatment		During GH treatment	
TSH	1.6	1.3	0.5–5 µIU/ml
FT4	14.7	14.3	8.6–25 pg/ml
PTH	22		6–50 pg/ml
ACTH	16		10–50 pg/ml
Cortisol 8 h	5.88		5–23 µg/dl
Prolactin	169		85–325 µUI/ml
Estradiol	23	22	< 35 ng/L
AMH	1.3		0.2–2.8 ng/ml
IGF	191	436	111–990 ng/ml
IGF-BP3	4.05	4.99	2.4–10 mg/L
LHRH test			
LH peak (mIU/ml)	2.1		
FSH peak (mIU/ml)	8.7		
At 10 yrs—before GH treatment			
Clonidine test- GH peak (ng/ml)	6		
L-DOPA test -GH Peak (ng/ml)	2.4		
Bone age (hand and wrist x-ray)	9 years 10 months		

factor 1 (IGF1), insulin-like growth factor binding protein-3 (IGF-BP3)]) before synthetic GH treatment (initial dose: 0.3 mg/kg/week) were all normal (details in Table 1).

At the age of 12, due to scholastic difficulties and learning disabilities associated with facial dysmorphism and a history of screening for mucoploysaccharidosis, a more comprehensive genetic exploration was performed using a broad gene panel for rare pediatric disorders combined with next-generation sequencing (NGS)(for complete panel see additional Supplementary Material Table S1). After obtaining written informed consent for genetic testing, no variant in mucopolysaccharidosis-related genes could be identified while an heterozygous pathogenic frameshift variant in exon 10 of the *DICER1* gene (NM_177438.3) designated as c.1716del; p.(Phe572LeufsTer15) was found. This variant leads to a premature stop codon in the P-loop containing the nucleoside triphosphate hydrolase-domain of the protein. The mutation was confirmed on a second blood sample.

The identification of this *DICER1* germline mutation led us to perform a molecular analysis on the endocervical mass. We found a second-hit somatic missense variation on the other *DICER1* gene allele designated c.5113G > A; p.(Glu1705Lys) in exon 24 (allele frequency: 27%) corresponding to the known genetic hotspot for somatic mutations in the ribonuclease III domain (Figure 1B).

In light of *DICER1* gene germline and somatic mutations, a pathological reassessment of the cervical resection was performed in a reference center, allowing reclassification from benign müllerian polyps to embryonal rhabdomyosarcoma with immunostaining focally positive for desmin and still negative for myogenin and myoD1 (Figure 1C). Together, all these results led to a diagnosis of DICER1 syndrome and the appropriate medical care for the patient and her family.

Family screening revealed that the father carried the same nucleotide deletion, which is consistent with thyroidectomy at the age of 16 for a multinodular goiter. A history of benign thyroid nodules in the father's mother and sister was also reported (Figure 1D). No other DICER1-related pathologies have been described in the family especially no PPB over three generations. Furthermore, extended genetic counseling was suggested for the father's family, in particular the proband's half-sisters. The youngest, who was 2 years old, carried the same familial deletion but presented no clinical or imaging manifestations at screening.

Discussion

DICER1 syndrome is associated with a panel of benign and malignant tumoral manifestations, which, in terms of unusual phenotypes, has not yet been completed. Our case is consistent with a double-hit tumorigenic process: the germline pathogenic variant being a frameshift caused by a deletion and the somatic variant found in the cervical tumor being a missense mutation c.5113G > A; p.(Glu1705Lys) in the catalytic domain of the protein, previously described in DICER1-related tumors (8). Concerning the germline variant c. 1716del, it was previously described in an infant with a PPB at the age of 0.8 years, corresponding to the youngest child in the series of 11 PPB-families (9).

ERMS is the most common subtype of rhabdomyosarcoma, with a high prevalence in the head and neck region as well as in the genitourinary tract, usually characterized by a positive immunohistochemistry for desmin, myogenin and MyoD1 (10, 11). The "botryoid" variant is a particular form of ERMS found in mucosa, typically presenting as a polyp. However, ERMS of the uterine cervix and corpus are particularly rare affections and, in our case the primary analysis showed no such typical immunostaining profile, which led to an inaccurate diagnosis of benign müllerian polyps. Moreover, *DICER1*-associated ERMS occurs most frequently in pubertal and post-pubertal adolescent girls and young women (mean 10–20 years). A recent study including five cervical and four uterine ERMS showed *DICER1* pathogenic variants in all the uterine lesions whereas these variants were absent in the urinary tract ERMS. The authors suggest that *DICER1*-associated ERMS could be qualified as a distinct subtype in future classifications, especially when related to a specific DNA methylation profile (12).

Growth retardation was an important feature in this case, but is not usually related to DICER1 syndrome. In their exploration of

pituitary development in families with the *DICER1*-truncating variant *Zhang* et al. showed that changes in miRNAs level could be the cause of clinical pituitary disorders but no evidence of a direct relation with growth hormone deficiency was noted (13). However, in a recent study on unusual symptoms of the DICER1 syndrome, *Venger* et al. described developmental delay and facial dysmorphism in a family carrying a *DICER1* frameshift variant (6). Considering the higher risk of cancer development for pediatric patients receiving GH treatment, this young girl carrying a germline *DICER1* pathogenic variant should benefit from reinforced sureveillance relative to current guidelines (14).

Family history is an important aspect in evaluating the risk of DICER1 syndrome. In this case, the association of a childhood tumor, although initially considered to be benign, and a familial history of multinodular goiter should alert the clinician to initiate genetic testing for *DICER1* (ideally included in a NGS gene panel). In addition, screening and surveillance recommendations differ based on age and gender. Therefore, chest imaging is recommended from birth until 12 years of age since PPB is the main lung expression of DICER1 syndrome, whereas thyroid and pelvic ultrasound (US) are only recommended as of 8 years of age throughout life (7, 15). For this young girl who became pubertal in accordance with the standard timelines, follow-up was initiated and included regular physical exams, yearly pelvic and abdominal US until the age of 40, and thyroid US every 3 years. Fine needle aspiration biopsy (FNAB) could be used when focal changes in the thyroid gland appeared but due to the 16 to 18-fold increased risk of differentiated thyroid cancer especially in female *DICER1* carrier, thyroidiectomy should be rapidly considered (16, 17). This was also the case for all the relatives' female children who were carriers of *DICER1* deletion. The initial treatment was surgical resection alone (no additional treatments), and four years later any local or distant recurrences were monitored.

This case report highlights that DICER1 syndrome should be suspected in the presence of early typical DICER1-related tumors as well as in case of unusual tumors during childhood, especially when there is a family history of thyroid diseases during infancy or young adulthood.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

AS: physician manuscript writing AC and IOP: physicians, diagnosis, follow up, genetic counselling and taking care SE and EM: pathologists, expertise on ERMs and somatic molecular analysis. FS and ST: germinal molecular analysis and manuscript design. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1150418/full#supplementary-material.

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Ultrasound, laboratory and histopathological insights in diagnosing papillary thyroid carcinoma in a paediatric population: a single centre follow-up study between 2000-2022

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Background: Papillary thyroid carcinoma (PTC) often coincides with autoimmune thyroiditis (AIT); whether this association is incidental or causal remains debated.

Objective: To evaluate the ultrasonographic, laboratory, and histopathological features of PTC in paediatric patients with and without AIT and its relationship to puberty.

Design: A retrospective cohort study.

Patients and methods: A retrospective analysis of medical records of 90 patients (69; 76.7% females). The mean age at PTC diagnosis was 13.8 years [range 6-18]. All patients were evaluated ultrasonographically before thyroid surgery. Thyroid nodules were categorised using the European Thyroid Imaging Reporting and Data System (EU-TIRADS PL), and cytopathology was assessed using Bethesda criteria. Neck ultrasound results and thyroid and autoimmune status were correlated with histopathological PTC assessment.

Results: The coexistence of PTC and AIT was found in 48.9% (44/90) of patients. The percentage of AIT was increasing with age; AIT was present only in 1/3 of prepubertal, close to 50% in pubertal, and over 60% in adolescent patients. The youngest patients (aged <10 years old) presented more often with goitre and

lymphadenopathy and less often with AIT than adolescents (15-18 years of age). There were no differences in TPOAb, TgAb, and TSH levels between the age subgroups. Presurgical TgAb levels were higher than those of TPOAb in the youngest patients. Histopathological analysis revealed that the solid subtype was observed more often in prepubertal children and diffuse sclerosing in children below 14 years of age, whereas the classic subtype dominated in late pubertal. Univariate and multivariate analyses revealed that lymph nodes metastases (LNM) were associated with PTC diameter and fT4 level, whereas extrathyroidal extension with age and angioinvasion with PTC diameter and age. The correlations between age and fibrosis, and the presence of psammoma bodies in malignant tissues were close to significant. We did not observe an association between TSH levels and the presence of autoimmunity and PTC variables.

Conclusions: In paediatric patients the natural course of PTC may be less aggressive in adolescent patients than in younger children (especially < 10 years of age). We suggest that pre-operative evaluation of paediatric patients with thyroid nodules could include apart from assessment of thyroid hormones, evaluation of TPOAb, TgAb, and TRAb together with comprehensive neck ultrasonography.

KEYWORDS

autoimmune thyroiditis, papillary thyroid carcinoma, ultrasonography of thyroid gland, PTC subtypes, prepubertal PTC, pubertal PTC, adolescent PTC

Introduction

The most common aetiology of acquired thyroid disease is autoimmune thyroiditis (AIT), reported in ~5-6% of paediatric patients, (0.3-2% of children and 4-9.6% of adolescents) (1–3). Thyroid carcinoma accounts for 12% of cancers, and in terms of incidence ranks seventh in children below 14 years, and fourth in adolescents (15-18 years) (4). The first report on the coincidence of thyroid cancer and AIT was presented by Dailey et al. in 1955, which suggested that AIT might be considered a precancerous lesion, as chronic inflammation contributes to the development of cancer in many tissues (5–8). Cell-mediated autoimmune inflammation of the thyroid may cause functional and/or structural disorders (9).

In adults with nodular AIT, the incidence, extent, and multifocality of papillary thyroid carcinoma (PTC) are increased (10–14). The correlation between AIT and PTC in paediatric patients is still under discussion. Thyroid nodules are more common in children with AIT (3.5%–31.5%) than in those without (0.5–2%) (15–22). In children with thyroid nodules, the risk of PTC is estimated to be 19-39%, and in nodular AIT, the risk of PTC ranges from 5% to 25%; however, the incidence of PTC in AIT cohorts is lower (0.67% to 9.6%) (9, 15–18, 23–25). A higher association between AIT and PTC has been reported in surgical series, ranging between 6.3-43% in paediatric patients with PTC (16, 26–32). Based on a review of reports published in 2000–2020, Sur et al. concluded that the development of PTC in children with AIT appeared to be higher than that in the healthy population (33). In contrast, Radetti et al. found that AIT contributes to the development of thyroid nodules but not cancer in children and adolescents (15). Similar observations have been reported by Ben-Skowronek et al. (34) and Borysewicz-Sanczyk et al. (35). These discrepancies might be related to how AIT was verified, whether by presurgical confirmation of autoimmunity in blood tests and typical ultrasound images, or by those two variables combined with histopathological assessment after thyroidectomy.

The clinical, molecular, and pathological presentations of paediatric PTC differ from those of adult PTC (36, 37). From a histopathological standpoint, paediatric PTC presents more often as a lesion in the thyroid tissue, rather than a single encapsulated nodule seen more frequently in adult PTC (37). Paediatric PTC is also characterized by large lesions, multifocality, bilaterality, and multiple satellite malignant lesions spread unilaterally or bilaterally, extrathyroidal extension (ETE) beyond the thyroid capsule, neck lymph node metastases (in over 80% of patients, even if the main malignant lesion is < 1cm), and lung metastases (present in 10–20% of the cases) (36). This severe presentation, particularly in children below 10 years of age, may be related to late diagnosis or an aggressive course (38). Despite this presentation, paediatric PTC has an excellent prognosis; the five-year survival is > 99% (4, 39–44).Treatment consists of thyroidectomy with radioactive iodide, used to treat metastatic or high-risk tumours (36). The most common genetic alterations in paediatric PTC are *RET-PTC* and *NTRK* fusions, whereas mutations in *BRAF, V600E*, and *RAS* are less frequent than in adults (45, 46).

Nonetheless, the paediatric population is not homogeneous, considering the influence of puberty (36, 37, 45, 47, 48). Few studies have compared differences in the biology of paediatric PTC between age groups. In two large paediatric studies, the authors reported significant differences between early childhood and adolescent PTC but did not relate the differences to thyroid autoimmunity (47, 48).

Although PTC is a rare cancer in children, its prevalence has increased in recent years. One of the causes is more frequent ultrasound (US) assessments and active ultrasound surveillance of thyroid disorders; however, many new patients present with advanced disease (4, 39, 40). Therefore, because of the potential link between AIT and PTC, careful follow-up of patients with AIT is necessary, and Polish recommendations state that children with AIT should undergo thyroid US screening at least once a year (49). In AIT, the ultrasound appearance of the thyroid gland varies depending on the phase and severity of the chronic inflammation (18, 50). Typical sonographic features include diffuse heterogeneity and nodular structures (18, 50). The ultrasound features of thyroid nodules suggestive of malignancy are solid composition (usually hypoechoic), irregular shape and margins, taller-than-wide shape, presence of microcalcifications, intranodular vascularity greater than peripheral vascularity, and cervical lymph node enlargement (51). In children and adolescents, any focal lesion found on US should be subjected to ultrasound-based malignancy risk stratification (36, 51). In this study, we used the EU-TIRADS-PL score, which is a modified EU-TIRADS score (51, 52).

The aim of the present study was to evaluate the ultrasonographic, laboratory, and histopathological variables of PTC in paediatric patients with and without AIT, and in relation to puberty.

Subjects and methods

Subjects

258 pediatric patients were referred for thyroid surgery between 2000 and 2022 in the major tertiary pediatric center in South-Eastern Poland (University Children's Hospital in Krakow). Ninety patients out of this group (34.9%), all with confirmed PTC, with a mean age of 13.8 years (age range 6-18 years, 69 [76.7%] girls) were further evaluated and presented in the study.

Methods

The retrospective analysis of medical records included the evaluation of thyroid function status and ultrasound, cytological, and histopathological variables in patients with PTC. All hormonal and immune assessments were routinely performed at the Department of Biochemistry at the University Children's Hospital in Krakow, Poland and were determined in a single fasting blood sample. TSH, fT3, and fT4 levels were measured using immunochemistry with an ADVIA Centaur machine, and TPOAb, TgAb, and TRAb levels were assessed using a radioimmunoassay method with a Brams machine. All assessments were performed before inclusion in the study and prior to therapy with levothyroxine or antithyroid thiamazole, when needed. Molecular analyses were routinely performed for suspected genetic syndromes.

AIT was diagnosed based on typical features of chronic autoimmune thyroiditis on thyroid ultrasound assessment, as described previously, and increased TPOAb and/or TgAb and/or TRAb antibody levels, as well as after histopathological confirmation in all patients after thyroidectomy (18).

Thyroid ultrasound was performed for all patients at the time of thyroid dysfunction diagnosis. At our institution, thyroid ultrasound is routinely performed as active surveillance once a year in patients with thyroid dysfunction and as a screening in all patients newly referred for endocrine assessment. Ultrasonography (US) of the thyroid gland was performed at the University Children's Hospital by paediatric endocrinologists and surgeons with experience in paediatric US (DJ, AT > 20 years and AKW, MW > 15 years). Thyroid US was performed using a high-resolution Voluson 730 GE Medical System (8–12-MHz linear-array transducer), Philips Epiq5 (L12-5 linear transducer), Philips iE22 (L11-3 linear transducer), and Samsung HS40 with elastography (LA3-16AD transducer). US was performed in axial and longitudinal planes. The analysis included ultrasound features of the thyroid gland according to the EU-TIRADS PL 2022 classification (Polish update of EU-TIRADS 2017) (51, 52), lymph nodes, and elastography.

Fine needle aspiration biopsy (FNAB) results were classified according to Bethesda criteria (53). Patients underwent total thyroidectomy with central and, if necessary, lateral lymph nodes dissection. Histopathological evaluation was performed at the Department of Pathology of University Children's Hospital in Krakow. Postoperative staging was performed based on the tumour, nodes and metastases (TNM) system proposed by the American Joint Committee on Cancer (54).

This study was approved by the relevant institutional review board (The Bioethics Committee of the Jagiellonian University opinion number:1072.6120.288.2021). Written informed consent was obtained from all participants and/or their parents. Written informed consent was obtained from the individual(s) and minor(s) legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Statistics

The baseline and demographic characteristics were summarised using descriptive statistics. Categorical variables are expressed as percentages. We assessed the distribution of continuous variables using the Shapiro–Wilk test and described continuous variables using median or mean and standard deviation as appropriate. The sensitivity, specificity, and positive and negative predictive values of ultrasonography of thyroid and lymph nodes were calculated in relation to the histological results. We assessed the absence of hyperechoic hilum, echogenicity of nodules, microcalcifications, and increased chaotic vascularisation in lymph nodes (combined). We used the non-parametric tests to compare groups PTC (+) AIT

+/- and LNM+/- with PTC variables. We used the non-parametric tests to compare PTC(+) AIT+/- and LNM+/- groups with control groups [PTC(-) AIT(+)]. We used the Spearman test to search for correlations between clinical parameters and histological variables. A two-tailed p-value of <0.05 was considered statistically significant. The association of subject characteristics (female sex, age, familial history, AIT, TSH, fT4) and tumour diameter with cancer characteristics (fibrosis, angioinvasion, lymph node infiltration, multifocality, ETE, psammoma bodies) was evaluated using univariate and multivariate logistic regression. Characteristics with p<0.1 in univariate analysis were included in the multivariate logistic regression as p<0.1 is considered as a trend, p<0.05 as significant. All analyses were performed using STATISTICA version 13 (TIBCO Software Inc., Palo Alto, CA 94304 United States).

Results

Patients characteristics

258 pediatric patients were referred for thyroid surgery between 2000 and 2022 in the major tertiary pediatric center in South-Eastern Poland (University Children's Hospital in Krakow). Histopathological diagnoses were updated according to the 2022 WHO Classification of Thyroid Tumours (37). Eighty-four patients had thyroid follicular nodular disease, 21 had Graves disease unresponsive to therapy, two had non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), two had well-differentiated tumour of uncertain malignant potential (WDUMP), 11 had follicular tumour of uncertain malignant potential (FTUMP), four had oncocytic adenoma, 25 had follicular adenoma, four had thyroid cysts, 89 had papillary thyroid carcinoma, one had invasive encapsulated follicular variant of PTC (IEFVPTC), three had follicular thyroid carcinoma (FTC), one had oncocytic carcinoma, two had poorly-differentiated thyroid carcinoma, and nine had medullary thyroid carcinoma (MCT) (37). One patient was diagnosed with Gardener syndrome and columnar subtype of PTC, two with DICER1 and thyroid follicular nodular disease, and one with Cowden syndrome and oncocytic carcinoma. Nine patients received radiotherapy of central nervous system, CNS (ALL) or chest (Hodgkin Lymphoma, Neuroblastoma, Wilms tumor) at a mean of 8.8 (range 2-14) years before PTC confirmation.

Ninety patients out of this group (34.9%), all with confirmed PTC, with a mean age of 13.8 years (age range 6-18 years, 69 [76.7%] girls) were further evaluated and presented in the study.

Patients with PTC were divided into four groups depending on the presence (+) or absence (-) of autoimmune thyroiditis (AIT) and lymph node metastasis (LNM): the PTC AIT (+) LNM (+) group included 26 patients with a mean age of 13.8 years (range 7-18 years, 84.6% girls); the PTC AIT (+) LNM (-) group included 18 patients with a mean age of 15.3 years (range 8.8-18 years, 94.4% girls); the PTC AIT (-) LNM (+) group included 35 patients with a mean age of 12.4 years (range 6-18 years, 60% girls); and the PTC AIT (-) LNM (-) group included 11 patients with a mean age of 13.6 years (range 6-18 years, 81.8% girls) (Tables 1, 2).

The control group included 135 age- and sex-matched paediatric patients with AIT and without PTC [AIT (+) PTC (-)] (Table 2).

Patients with PTC were also divided into three age groups: prepubertal (<10 years of age), pubertal (age range 11-14 years), and late pubertal (age range 15-18 years, all female patients had regular menses) (Table 3). Puberty was assessed by researchers DJ and MW, based on the Tanner scale. Prepubertal: Thelarche/Breast I, Pubarche/Pubic hair-I, Axillarche-I, testes volume < 4 ml each.

Since 2000, we have observed an increase in patient visits due to thyroid disorders and AIT (Figure 1A). Patients with AIT represent ~1/3 of visits due to thyroid disorders (Figure 1A). This percentage has not significantly increased since the beginning of our observation because of the overall increase in the number of patients referred to our centre annually for prophylactic assessment of thyroid function (Figure 1A). However, from 2000 to 2022, we observed an increased incidence of thyroid cancer in 105 patients, including 90 patients with PTC (Figure 1B).

PTC in combination with AIT was found in 48.9% (44/90) of patients (Tables 1, 2). Patients with PTC AIT(+) were older than those with PTC AIT (-). Both groups were further subdivided according to the presence or absence of lymph node metastasis (LNM). The youngest patients were in the PTC AIT (-) LNM (+) group (Table 1). The highest percentage of female patients was found in PTC AIT (+) LNM (-) group, and the lowest was found in PTC AIT(-) LNM (+) group: 94.4 vs. 60% (Table 1). The youngest patients in PTC AIT(-) LNM(+) group presented more often with goiter or lymphadenopathy than patients from other groups (Table 1).

Out of 9 patients who developed PTC after radiotherapy of the CNS (due to acute common leukaemia, ALL) or chest (Wilm's Tumour, Hodgkin Disease, Neuroblastoma), only one patient with ALL (without bone marrow transplantation) developed AIT.

In 34/90 (37.8%), there were thyroid disorders in the first-degree relatives, including PTC in mothers of three patients and one family with Gardener syndrome.

Ultrasound variables

During the 22 years of our ultrasound observations, the length of nodules detected on US decreased significantly, as we actively surveilled patients with thyroid disorders, as described previously; however, after the COVID-19 pandemic, we observed a significant increase in the diameter of nodules and observed patients with more advanced disease (Figure 2) (24).

Among patients with PTC, hypoechogenic malignant nodules predominated over other ultrasound patterns (Figures 3, 4). In three patients with thyrotoxicosis PTC presented as lesions (Figure 5).

Ultrasound assessment revealed a single thyroid nodule in ~50% patients LNM(+) and in over 80% patients LNM (-) (Table 1). In 39 patients, lesions were unilaterally localised in the right lobe, in 21 patients in the left lobe, and in 30 patients lesions were located bilaterally. In 85% of patients with nodules, the single nodule was localised in the lower pole, between the isthmus and the lobe (Figures 3, 4). However, histopathological analyses revealed

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TABLE 1 Auxological, ultrasound, cytologic and histopathologic characterisation of patients diagnosed with PTC (n=90).

PTC (n=90) features	PTC (+) AIT (+) n=44 (48.9%)		PTC (+) AIT (-) n=46 (51.1%)		p
	LNM (+)n=26 (59.1%)	LNM (-)n=18 (40.9%)	LNM (+)n=35 (76.1%)	LNM(-)n=11 (23.9%)	
Age mean [range]	13.8 [7-18]	**15.3 [8.8-18]***	**12.4 [6-18]***	13.6 [6-18]	0.01
Gender, Female %	84.6	94.4	60	81.8	0.71
Presentation % **Goiter** **Ultrasound** **Lymphadenopathy**	 50% 50%	 16.7% 83.3%	 62.8% 31.4% 5.8%	 45.4% 54.6%	 0.42 0.44
Risk groups	1/26 - 7 yrs after Rtx (ALL)	Gardener s.	3/35 - 2,7,11 yrs after Rtx (ALL) 1/35- 9 yrs after Rtx (Wilms Tu.) 1/35- 3 yrs after Rtx (Hodgkin D.)	2/11- 9,13 yrs after Rtx (ALL) 1/11- 14 yrs after Rtx (NBL)	–
Familial PTC	2/26		1/35		–
Recurrence	1/26		4/35		–
Single nodule seen on thyroid US %	50	88.9	57.1	81.8	0.35
Lesion seen on thyroid US %	50	11.1	42.9	18.2	0.45
The largest dimension of nodule/lesion on US in mm mean [range; SD]	**21.2 [4-52; 14.3]***	**10.4 [6-16; 3.9]*,#**	**23.9 [5-60; 16.6]*,#**	13.9 [4-60; 9.0]	0.01
PTC **unilateral %** **multifocal and bilateral%**	 19.2 80.8	 61.1 38.9	 20 80	 72.7 27.3	 0.72 0.67
EU-TIRADS mean%	5 [100%]	5 [100%]	5 [100%]	5 [100%]	0.68
Pathological (round, hypo-or hyperechoic and hypervascular) lymph nodes seen on US (% of patients)	91%	–	88%	–	0.78
Largest dimension of the LNM in mm mean [SD]	9.4 [8.5]	–	6.9 [8.5]		0.71
T% **1a** **1b** **2** **3** **4**	 26.9 26.9 30.8 15.4 -	 **83.3*** 16.7 - - -	 **22.8*** 34.4 20 20 2.8	 36.4 45.4 18.2 - -	 0.01 0.32 0.42 0.41 -
N% **1a** **1b**	 **61.5*** **38.5***	 - -	 **25.7*** **74.3***	 - -	 0.01 0.01
M% **1** **0**	 19.2 80.8	 - -	 20 80	 - -	 0.51 0.42
Bethesda **mean [range]**	 3.6 [2-5]	 4.9 [2-6]	 5.1 [3-6]	 4.5 [2-6]	 0.54
LI Ki67 **mean [range]**	 10.6 [3-20]	 11.2 [10-15]	 8.9 [3-20]	 9.5 [8-20]	 0.45
PTC subtypes, n [%]: **Classic(C)** **Follicular (F)** **C,F,S** **C,S** **C,F** **S,F** **D.S.** **Columnar**	 11 [42.3] 6 [23.1] 4 [15.4] 2 [7.7] 2 [7.7] 1 [3.85]	 11 [61.1] 1 [5.56] 1 [5.56] 2 [11.1] 1 [5.56]	 17 [48.6] 3 [8.6] 4 [11.4] 4 [11.4] 1 [2.85] 1 [2.85]	 6 [54.5] 4 [36.4] 1 [9.1]	 0.43 0.45 0.51 0.54 0.53 0.64 0.42 -

(Continued)

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TABLE 1 Continued

PTC (n=90) features	PTC (+) AIT (+) n=44 (48.9%)		PTC (+) AIT (-) n=46 (51.1%)		p
	LNM (+)n=26 (59.1%)	LNM (-)n=18 (40.9%)	LNM (+)n=35 (76.1%)	LNM(-)n=11 (23.9%)	
C,F,S,T,G,C-M		1 [5.56]			-
C,F,S,C-M		1 [5.56]	1 [2.85]		-
C,F,S,O,C-M			1 [2.85]		-
F,S, D.S			1 [2.85]		-
S, anaplastic			1 [2.85]		-
Invasive encapsulated follicular variant papillary thyroid carcinoma			1 [2.85]		-

PTC, papillary thyroid carcinoma; AIT, autoimmune thyroiditis; C, classic; F, follicular; S, solid; O, oxyphylic; D.S., diffuse sclerosing; C-M, cribriform-morular; T, tall cell; G, glomerular; PTC, subtypes; LNM, lymph node metastasis (+) present, (-) absent, US-ultrasonography, Rtx-radiotherapy, NBL-neuroblastoma, D-disease, S-syndrome, ALL-acute lymphoblastic leucemia. Postoperative staging based on the tumour (T), nodes (N) and metastases (M)-TNM system proposed by the American Joint Committee on Cancer (54). Data are expressed as mean [range, SD] or %.*,#-p<0.05. Bold values represent significant differences between the data.

TABLE 2 Thyroid status in patients with papillary thyroid carcinoma (PTC, n=90) with or without coincidence with autoimmune thyroiditis [AIT(+)/(-)] and LMN(+)/LNM(-) compared with AIT (+) PTC (-) control group (n=135).

	PTC (+) GROUP n=90				AIT (+) PTC (-) CONTROL GROUP n=135		
Patients characteristics in PTC (+) group/ Ultrasound pattern in control group	PTC AIT(+) LNM (+)	PTC AIT(+) LNM (-)	PTC AIT(-) LNM (+)	PTC AIT(-) LNM (-)	Diffuse thyroiditis	Diffuse thyroiditis with irregular background	Micronodulations (pseudonodules)
n	26	18	35	11	61	52	22
TSH mean [SD] uIU/ml (n:0.4-4.0)	**4.2 a [6.7]**	**4.1 b [6.1]**	**2.4 # [1.2]**	3.01 [1.5]	**62.2 a,b,#,* [133.6]**	**5.6 * [9.2]**	16.8 [53.4]
fT3 mean [SD] pmol/l (n:3.6-6.8)	7.9 [6.9]	5.7 [3.2]	5.5 [2.7]	5.5 [1.1]	9.9 [10.3]	11.9 [8.9]	8.3 [9.1]
fT4 mean [SD] pmol/l (n: 10-25)	13.9 [13.2]	9.8 [8.8]	12.1 [5.7]	11.6 [6.2]	16.2 [17.9]	20.9 [17.1]	13.7 [10.8]
T%	11.5	–	–	–	12.7	27.8	4.8
E%	80.8	83.3	88.6	90.9	17.5	35.2	52.4
H%	7.7	16.7	11.4	9.1	69.8	37	42.8
TPOAb mean [SD] IU/ml (n<30)	**772.9 a [1838]**	**1398.9 # [2576]**	–	–	**5641.7 a,#,*,b [3500]**	**1849 * [2030]**	**1712.4 b [1760]**
TgAb mean [SD] U/ml (n<20)	**1358.2 a,c,d [1598.2]**	**637.8 a, # [1781.6]**	–	–	**1474.2 #,*,b [2642.1]**	**347.1 *,c [947.1]**	**792.3 b,d [1755.6]**
TRAb mean [SD] U/ml (n<1)	1.7 [1.3]	1.7 [1.9]	–	–	3.8 [6.05]	5.4 [7.2]	2.8 [3.0]

T, Hyperthyroid; E, Euthyroid; H, Hypothyroid. Data are expressed as mean [SD] or as %. *,#,a,b,c,d- statistically significant differences between the means in the groups (*,#,a,b,c,d-represents differences between two groups), p=0.01. Mean TSH and mean TPOAb levels were significantly higher in control group with diffuse thyroiditis than in other groups (bold). Mean TgAb was significantly higher in patients with PTC AIT (+) LNM (+) and control group with diffuse thyroiditis than in other groups (bold). Bold values represent significant differences between the data.

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TABLE 3 Auxological, ultrasound, cytologic and histopathologic characterisation of patients diagnosed with PTC (n=90) presented in age groups.

Parameter	Age groups			p
Age groups [years]	**<10**	**11-14**	**15-18**	
Mean age [years]	8.2	12.9	16.8	0.62
n	19	35	36	0.71
Females%	52.6	80	86.1	0.11
Presentation: Goiter% Ultrasound% Lymphadenopathy%	 63.1 26.3 10.6	 54.3 45.7 -	 30.5 69.5 -	 0.22 0.32
PTC mm mean [SD]	**25.4*** **[15.2]**	**20.2#** **[14.8]**	**15.6*,#** **[11.6]**	**0.01**
ETE%	**68.4***	45.7	**13.9***	**0.01**
AI%	**63.1***	**89.5#**	**27.7*,#**	**0.02**
≥2 subtypes%	**57.9***	34.3	**16.7***	**0.02**
1 subtype%	**42.1***	65.7	**83.3***	**0.02**
PTC Subtypes (n) classic follicular solid oxyphilic diffuse sclerosing cribriform-morular tall cell columnar glomerular anaplastic+solid	 14 11 10 1 2 1 - - 1 1	 28 17 5 - 1 1 1 - - -	 25 12 5 - - - - 1 - -	 **0.21** **0.22** **0.12** - - - - - - -
LI KI67 mean [SD]	11.25 [7.04]	9.5 [5.8]	9.7 [5.8]	0.45
Fibrosis%	57.9	54.3	44.4	0.55
Psammoma bodies%	57.9	54.3	33.3	0.65
LNM%	**78.9***	71.4	**58.3***	**0.04**
Recurrence%	10.5	8.6	–	0.25
AIT%	31.6	48.6	61.1	0.35
TSH mean [SD] mIU/ml	4.9 [7.8]	3.3 [4.1]	2.5 [2.4]	0.54
TPOAb mean [SD] IU/ml	149.7 [268.4]	440.3 [1557.3]	880.0 [1953.0]	0.55
TgAb mean [SD] U/ml	272.2 [426.1]	375.2 [1430]	533.0 [1519]	0.21
131 I therapy%	94.7	82.8	86.1	0.25

PTC, papillary thyroid carcinoma; AIT, autoimmune thyroiditis; C,classic; F,follicular; S,solid; O,oxyphylic; D.S.,diffuse sclerosing; C,M,cribriform,morular; T,tall cell; G,glomerular; PTC subtypes; LNM,lymph node metastasis; ETE,extrathyroidal extension, AI-angioinvasion. Data are expressed as mean [SD] or as %.*,#-p<0.05. Bold values represent significant differences between the data.

that unilateral nodules were more often found in PTC AIT (-) and LNM (-), and multifocality was found more frequently in LNM (+), independent of AIT (Table 1). The positive predictive value (PPV) that in a case of a single nodule seen on US PTC was unilateral was 53.3%, and the negative predictive value (NPV) was 46.7%. The PPV that in a case of a single nodule seen on US there are no LNM was 40% and the NPV was 60%. This observation explains why pediatric patients are subjected to total thyroidectomy with central and, if necessary, lateral LNM dissection.

The largest nodule size was seen in patients with PTC AIT (-) LNM (+) and the smallest in PTC AIT (+) LNM (-) (Table 1).

The assessment of thyroid nodules or lesions with the use of EU-TIRADS PL scale showed 100% concordance with histopathological assessment (Table 1).

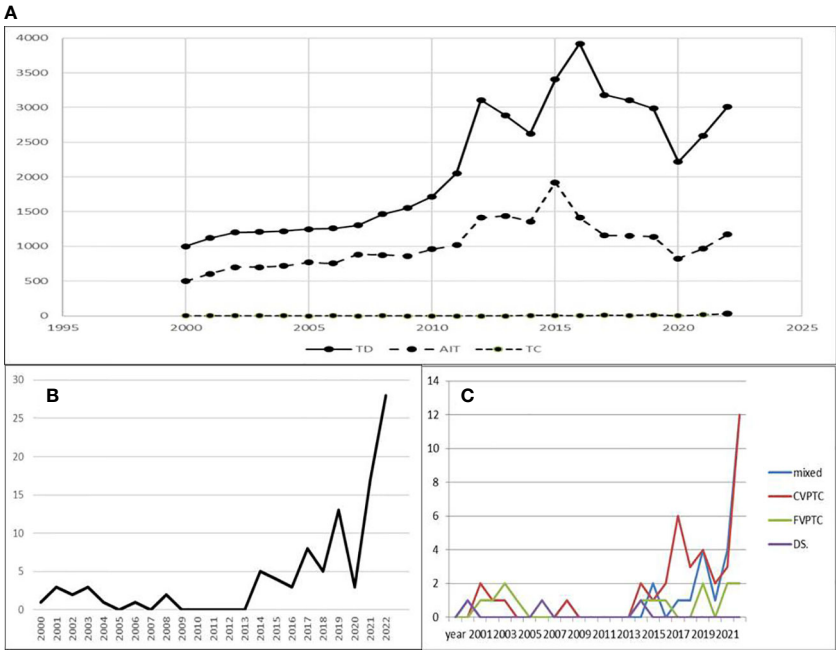

FIGURE 1
(A) The number of appointments in the Thyroid Clinic per year observed since 2000. COVID-19 pandemic temporarily decreased the number of appointments. **(B)** Increase in PTC cases per year since 2000. **(C)** Increase in classic and mixed subtypes in last three years. Legend: TD-thyroid disorders, AIT-autoimmune thyroiditis, TC-thyroid cancer, mixed-mixed subtypes of PTC, CVPTC-classic subtype of PTC, FVPTC-follicular subtype of PTC, DS-diffuse sclerosing subtype of PTC.

Pathological lymph nodes seen on ultrasound (hypo- or hyperechoic and oval or round, with nodularity inside and hypervascular) that were later confirmed to contain metastasis were observed and described in 91% of patients with AIT(+) LNM (+) and 88% AIT (-) LNM (+) (Figure 6; Table 1). The calculated PPV for ultrasound suspicion of LNM was 94.9%; the NPV, sensitivity, and specificity were 81.8%, 90.3%, and 90%, respectively.

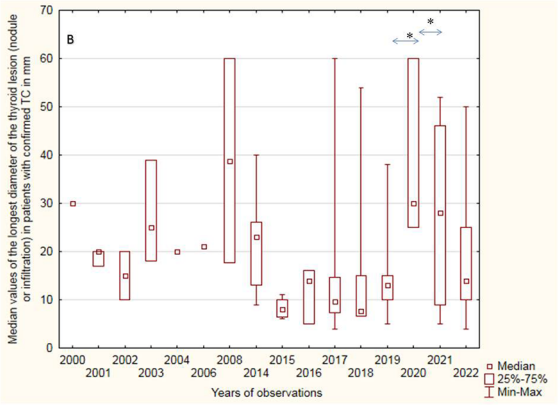

FIGURE 2
Median values of the longest diameter of the thyroid lesion (nodule or infiltration) in patients with confirmed PTC (mm). Significant increase of PTC diameter in COVID-19 pandemic compared to year before and after pandemic (*p=0.01).

Cytopathology

The Bethesda score was the highest in the AIT(-) LNM (+) subgroup (Table 1).

Histopathology

In patients from AIT (-) LNM (-) group the percentage of mixed PTC subtypes was lower than that in other groups (Table 1). No difference was found in the LI Ki67 index between groups (Table 1). Analysis of histological subtypes in the following years revealed an increase in classic and mixed subtypes (classic/follicular/solid/cribriform/morular/tall cell) (Figure 1C).

TNM evaluation

Significantly more patients with T1a stage were observed in AIT (+) LNM(-) than in AIT (-) LNM(+) group. Stage N1a was observed more often in AIT (+) LNM(+) than in AIT (-) LNM (+), in contrast to N1b stage. The percentage of M1 was similar in both groups (Table 1).

Thyroid status

Thyroid status in patients with PTC with or without autoimmune thyroiditis [AIT(+)/(-)] compared with the most

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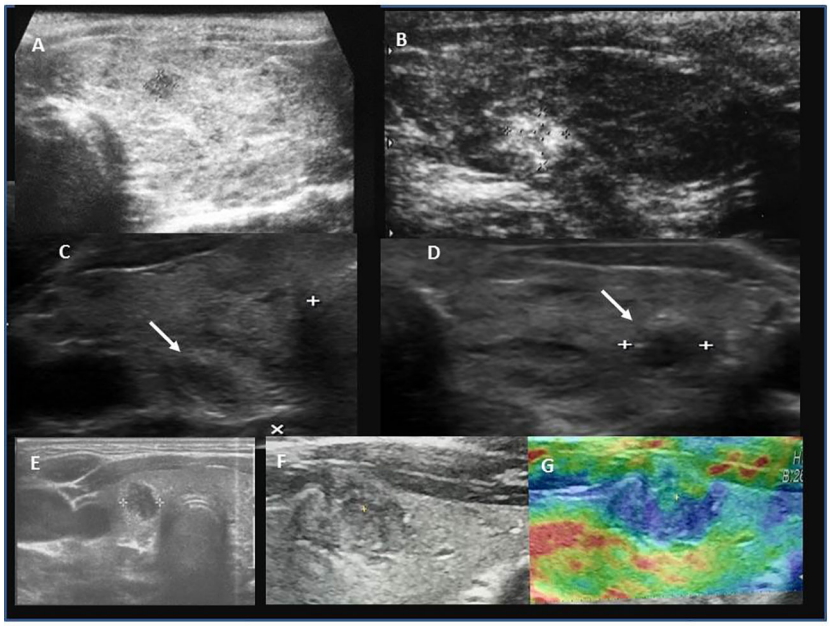

FIGURE 3
Ultrasound presentation of thyroid nodules confirmed as PTC in patients AIT (+). **(A)** female, 17.5 years, multifocal (M), bilateral (B), PTC 6.6 mm, classic, follicular; **(B)** female, 17.5 years, unilateral (U), PTC 9.8 mm, classic; **(C, D)** female, 18 years old, M,B, PTC 5 mm max lesion (white arrows), classic; **(E)** female, 13 years old, U, PTC 9 mm, classic, follicular, solid; **(F, G)** female, 15 years old, M,B, PTC 12 mm, classic, follicular, solid, G-elastography presented that malignant lesion was stiffer (blue colour) than surrounding thyroid tissue (green, yellow, red colour).

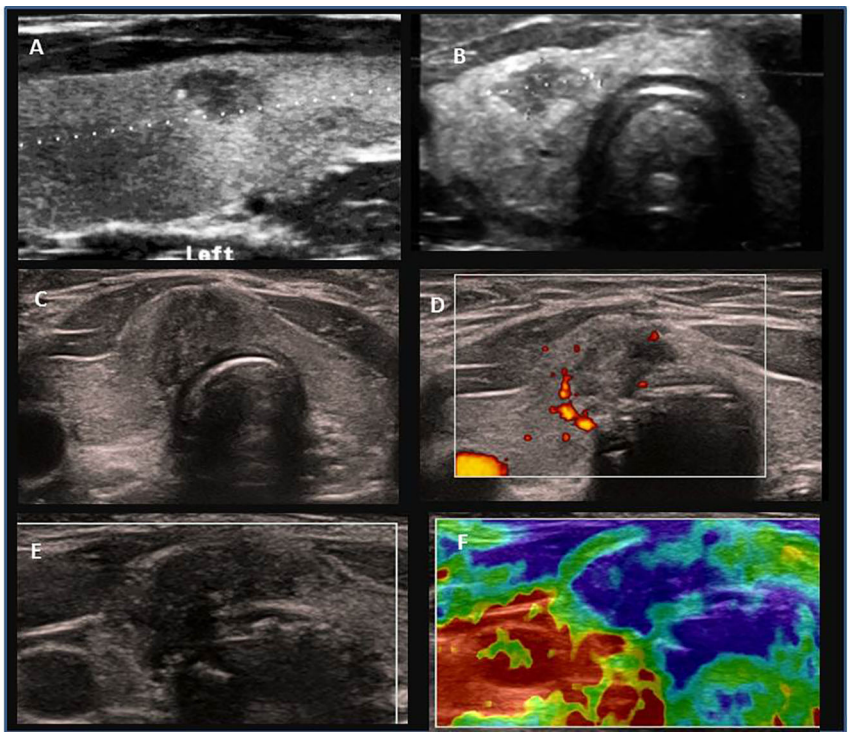

FIGURE 4
Ultrasound presentation of thyroid nodules confirmed as PTC in patients AIT (-). **(A)** female, 11.9 years old, multifocal (M), bilateral (B), PTC 7.6 mm, classic; **(B)** male, 15 years, M, B, PTC 9.5 mm, classic; **(C–F)** female, 14 years old, M,B, PTC 20 mm, classic, follicular, solid; **(D)** increased peripheral vascularization, **(F)** elastography presented that malignant lesion was stiffer (blue colour) than surrounding thyroid tissue (green, yellow, red colour).

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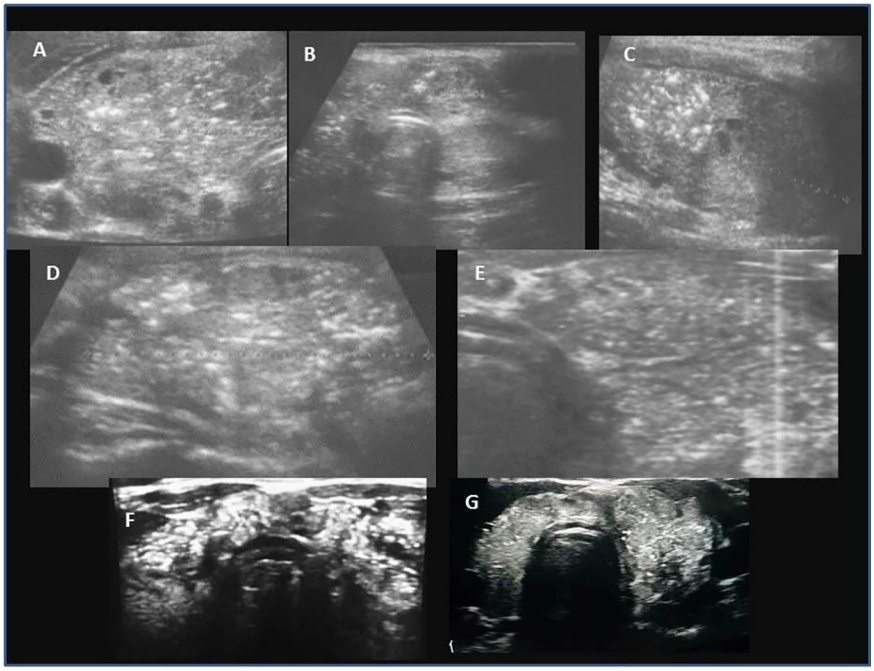

FIGURE 5
PTC in three patients presenting with thyrotoxicosis. **(A–C)** female, 12 years old, multifocal and bilateral lesion, classic PTC; **(D, E)** female, 18 years old, multifocal and bilateral lesion, classic PTC; **(F, G)**-male, 12 years old, multifocal and bilateral lesion, classic PTC.

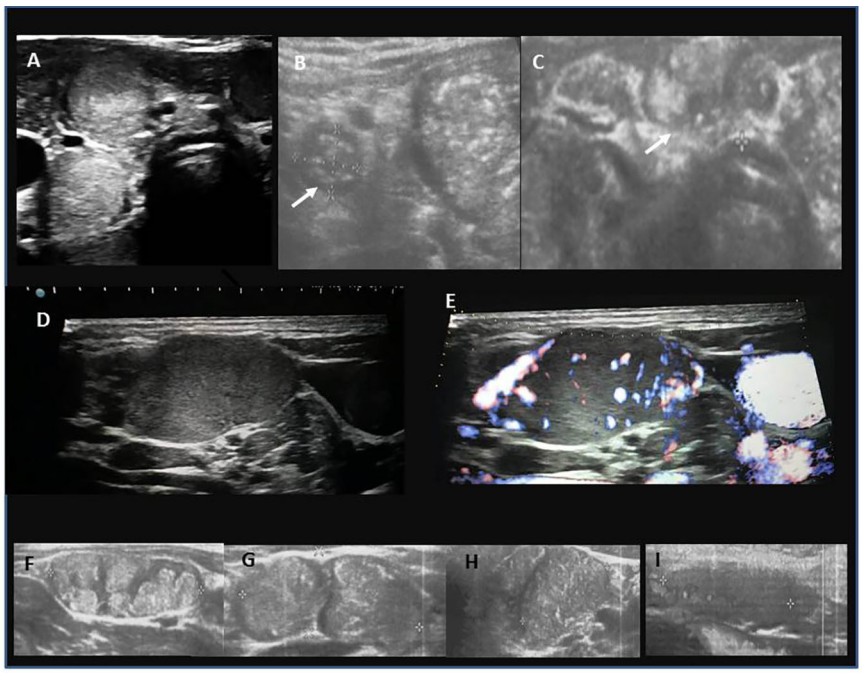

FIGURE 6
Ultrasound presentation of metastatic lymph nodes (LNM; central, C LNM; lateral, L LNM). **(A)** round C LNM with microcalcifications; **(B)** round L LNM with microcalcifications (white arrow), the echostructure of LNM is similar to the echostructure of the thyroid tissue with PTC lesion next to it; **(C)** oval C LNM with microcalcifications (white arrow); **(D)** solid, L LNM; **(E)** increased chaotic vascularization in L LNM; **(F)** nodular, irregular structure of L LNM; **(G, H)** microcalcifications in L LNM; **(I)** hypoechogenic L LMN without hilum.

common variants of AIT in control group [AIT (+) PTC(-)] is presented in Table 2. In patients with PTC LNM(+), independently on AIT, TSH was significantly lower than in patients with diffuse thyroiditis; in the former groups, 11.5% patients presented with thyrotoxicosis, over 80% were euthyroid, and 7.7% and 11.4% were hypothyroid. In the latter group, almost 70% were hypothyroid. The majority of patients with PTC AIT (-) was euthyroid. The highest TSH was observed in diffuse thyroiditis, and the lowest was observed in PTC AIT(-) LNM(+) group. The mean TPOAb level was higher in patients with diffuse thyroiditis than in the other groups. Mean TgAb level was higher in AIT with diffuse thyroiditis and in PTC AIT (+) LNM(+) groups than in AIT with irregular background or micronodulations and in PTC AIT(+) LNM(-) groups. Coincidence of PTC with thyrotoxicosis was found in three patients in AIT (+) LNM(+) group.

Age groups

Evaluation of PTC variables by age groups (Table 3) revealed that there were more boys in the youngest group of patients (< 10 years of age) than in both the older age groups. The F:M ratio was close to equal in the prepubertal group, and 4:1 in pubertal and late pubertal groups (Table 3). Patients in the youngest group more often presented with goitre, whereas a single nodule was found incidentally on ultrasound evaluation more often in the oldest patients (Table 3). The mean dimension of PTC was significantly larger, and the percentage of ETE, AI, mixed subtypes, fibrosis, psammoma bodies, and LNM was higher in the youngest patients than in the oldest age group (15-18 years of age) (Table 3). We found significant negative correlations between younger age and size of the primary tumour (r:-0.3, p=0.01), LNM (r:-0.26, p=0.02), diameter of the largest LNM (r:-0.31, p=0.01), ETE (r:-0.3, p=0.01), AI (r:-0.25, p=0.02), labeling index of a proliferation marker Ki67 (LI Ki67) (r:-0.26, p=0.03), psammoma bodies (r:-0.31, p=0.01), fibrosis (r:-0.32, p=0.02) and Bethesda score (r:-0.3, p=0.04). The percentage of recurrence was also higher in the youngest patients, but not significantly.

There were no differences in TPOAb, TgAb, and TSH levels between the age subgroups, but the percentage of AIT and the mean TPOAb level were higher in the oldest group. TgAb levels were higher than those of TPOAb in the youngest patients (Table 3). Histopathological analysis revealed that the solid subtype was observed more often in prepubertal children and diffuse sclerosing in children below 14 years of age, whereas the classic subtype dominated in late pubertal (15-18 years of age) (Table 3). Except for 1 patient with a PTC diameter of 6.7 mm, all prepubertal patients received ^{131}I therapy. In the other age groups, 6/35 and 5/37 children did not receive ^{131}I therapy (Table 3).

Associations

Univariate and multivariate analyses revealed that LNM was associated with PTC diameter and fT4 level, whereas extrathyroidal extension with age, and angioinvasion with PTC diameter and age (Tables 4, 5). The correlations between age and fibrosis, and the presence of psammoma bodies in malignant tissues were close to significant (Table 5). We did not observe an association between TSH levels and the presence of autoimmunity and PTC variables (Tables 4, 5).

Discussion

This cross-sectional retrospective study evaluated paediatric patients diagnosed with thyroid cancer at our centre since 2000. According to the WHO 2022 histologic classification of thyroid neoplasms, 96 cases of thyroid cancer included malignant follicular cell-derived neoplasms: three patients with FTC, one with IEFVPTC, 89 with PTC, one with oncocytic carcinoma of the thyroid, two with high-grade follicular-derived carcinomas (poorly differentiated TC), and nine with thyroid C-cell-derived carcinoma (MTC) (37). At present, we observed an increase only in PTC, whereas FTC and MTC rates are stably low, as observed in other centres (36).

Ultrasonographic analysis of the thyroid gland provides useful diagnostic information. Among patients with PTC, hypoechogenic malignant nodules predominated over other ultrasound patterns and single nodules that were often localised between the isthmus and the lower part of the lobe. Whereas typically in AIT or AITD ultrasound imaging reveals a hypoechogenic thyroid background due to more or less advanced lymphocytic infiltration that can be diffuse or focal, in our PTC cohort, we observed that on ultrasound imaging, the inflammatory process in the majority of patients with PTC was present, but not very advanced (18, 36, 51, 55). Our observations revealed that prepubertal children presented with more advanced disease than pubertal children and adolescents did. We found significant negative correlations between younger age and size of primary tumour, Bethesda score, lymph node metastasis (LNM), diameter of the largest LNM, ETE, AI, LI Ki67, psammoma bodies and fibrosis.

In relation to autoimmune status, the percentage of AIT was increasing with age; AIT was present only in 1/3 of prepubertal, close to 50% in pubertal, and over 60% in adolescent patients. This observation is striking because over 70% of young prepubertal children referred to medical attention presented with tumour on the neck (goitre in 63.1% or lymphadenopathy in 10.6%), in contrast to adolescents in whom PTC was detected incidentally in ~60% during active ultrasound surveillance of autoimmune thyroiditis.

Our observations are in line with two large studies on PTC in young patients. Demidchik et al. found that recurrent nodal disease and pulmonary metastasis were associated with younger age in children exposed to ionizing radiation after the Chernobyl accident in 1986 (56).

Thiesmeyer et al., in the largest study of paediatric PTC so far, also reported that prepubertal children presenting with the most extensive disease were most likely to have lymph node metastasis,

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TABLE 4 Univariate and multivariate logistic regression analysis of variables influencing LNM, ETE and AI.

	LNM-	LNM+	Univariate		Multivariate	
			OR (CI)	p	OR (CI)	p
Female sex	24 (83)	44 (71)	0.51 (0.16-1.57)	0.24	–	–
Age (years)	14.7 (6-18)	13 (6-18)	0.84 (0.73-0.98)	0.028	0.90 (0.76-1.06)	0.21
Family history	13 (45)	21 (34)	0.63 (0.25-1.57)	0.32	–	–
PTC (mm)	11 (4-32)	20 (4-60)	1.09 (1.02-1.15)	0.004	1.09 (1.03-1.16)	0.0026
AIT	18 (62)	27 (43)	0.47 (0.18-1.18)	0.11	–	–
TSH uIU/ml	2.6 (0.05-26)	2.16 (0-36)	0.98 (0.89-1.07)	0.60	–	–
fT4 pmol/l	12.9 (0.5-17.8)	14.2 (0.9-70.1)	1.07 (0.99-1.14)	0.08	1.09 (1.01-1.18)	0.032
	ETE-	ETE+	Univariate		Multivariate	
			OR (CI)	p	OR (CI)	p
Female sex	40 (74)	28 (75)	1.09 (0.40-2.90)	0.86	–	–
Age (years)	14.6 (6-18)	12 (6-18)	0.83 (0.73-0.95)	0.009	0.86 (0.75-0.99)	0.044
Family history	23 (42)	11 (30)	0.57 (0.23-1.4)	0.22	–	–
PTC (mm)	13 (4-60)	19 (4-60)	1.03 (1.0-1.07)	0.038	1.02 (0.99-1.06)	0.13
AIT	30 (55)	15 (40)	0.54 (0.23-1.29)	0.16	–	–
TSH uIU/ml	2.4 (0.02-36)	1.9 (0-26)	0.99 (0.91-1.09)	0.93	–	–
fT4 pmol/l	13.1 (0.81-31.6)	13.9 (0.5-70.1)	1.01 (0.97-1.07)	0.45	–	–
	Angioinvasion (-)	Angioinvasion (+)	Univariate		Multivariate	
			OR (CI)	p	OR (CI)	p
Female sex	36 (76)	32 (73)	0.81 (0.31-2.13)	0.67	–	–
Age (years)	15 (6-18)	13 (6-18)	0.79 (0.68-0.92	0.02	0.83 (0.71-0.96)	0.016
Family history	19 (40)	15 (34)	0.76 (0.32-1.81)	0.53	–	–
PTC (mm)	11 (4-60)	18 (4-60)	1.05 (1.01-1.09)	0.006	1.04 (1.0-1.08)	0.033
AIT	27 (57)	18 (41)	0.51 (0.22-1.19)	0.12	–	–
TSH uIU/ml	2.16 (0.02-26)	2.38 (0-36)	1.02 (0.93-1.12)	0.65	–	–
fT4 pmol/l	13.1 (0.5-31.6)	13.9 (0.9-70.1)	1.01 (0.97-1.07)	0.47	–	–

LNM, lymph node metastasis; ETE, extrathyroidal extension; AIT, autoimmunity. Only characteristics with $p<0.1$ in univariate analysis were included in the multivariate analysis, as $p<0.1$ is considered as a trend, $p<0.05$ as significant.

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TABLE 5 Univariate logistic regression analysis of variables influencing fibrosis, the appearance of psammoma bodies, unilaterality and multifocality of PTC.

	Without fibrosis	Fibrosis	Univariate	
			OR (CI)	p
Female sex	30 (71.4)	38 (77.5)	1.38 (0.53-3.61)	0.50
Age (years)	14.2 (6-18)	14 (6-18)	0.91 (0.80-1.03)	0.14
Family history	15 (36)	19 (39)	1.14 (0.48-2.70)	0.76
PTC (mm)	14 (4-60)	14 (4-60)	1.02 (0.99-1.05)	0.16
AIT	19 (45)	26 (53)	1.37 (0.59-3.16)	0.45
TSH uIU/ml	2.28 (0.02-26)	2.16 (0-36)	1.01 (0.93-1.11)	0.71
fT4 pmol/l	13.4 (0.5-31.6)	13.4 (0.81-70.1)	0.98 (0.93-1.03)	0.52
	No psammoma bodies	Psammoma bodies	Univariate	
			OR (CI)	p
Female sex	33 (71.7)	35 (77.8)	1.38 (0.52-3.61)	0.51
Age (years)	14.25 (6-18)	13 (6-17)	0.90 (0.79-1.02)	0.11
Family history	16 (35)	18 (40)	1.25 (0.53-2.96)	0.61
PTC (mm)	15 (4-60)	13 (4-60)	0.99 (0.97-1.02)	0.87
AIT	20 (43)	25 (55)	1.65 (0.70-3.76)	0.25
TSH uIU/ml	2.11 (0.02-9.66)	2.3 (0-36)	1.10 (0.95-1.29)	0.20
fT4 pmol/l	13.25 (0.97-31.6)	13.4 (0.5-70.1)	0.99 (0.95-1.04)	0.89
	Unifocal	Multifocal and bilateral	Univariate	
			OR (CI)	p
Female sex	20 (62.5)	48 (81)	2.69 (0.97-7.00)	0.55
Age (years)	14 (6-18)	14 (6-18)	0.98 (0.86-1.12)	0.79
Family history	15 (47)	19 (32)	0.53 (0.22-2.62)	0.17
PTC (mm)	12.6 (4-51)	16 (4-60)	1.04 (1.0-1.08)	0.4
AIT	17 (53)	28 (47)	0.80 (0.33-1.90)	0.61
TSH uIU/ml	2.5 (0.64-9.66)	2.1 (0-36)	1.02 (0.92-1.14)	0.67
fT4 pmol/l	13.25 (0.89-20.2)	13.4 (0.5-70.1)	1.0 (0.95-1.05)	0.95

LNM, lymph node metastasis; ETE, extrathyroidal extension; AIT, autoimmunity. As only characteristics with p<0.1 in univariate analysis could be included in the multivariate analysis, therefore multivariate analysis was not performed in these groups.

extrathyroidal extension, nodal, and distant metastases at the time of diagnosis, even in the setting of small-diameter PTC (47). Prepubertal age compared to adolescent age is an independent predictor of nodal and distant metastatic disease (47).

He et al.in a retrospective study of 227 paediatric patients with PTC presented that 14 years is the best age cutoff to differentiate prepubertal from pubertal PTC, as it was one of the independent risk factors for progressive disease, suggesting that paediatric patients with PTC should not be considered as a single population (48). According to the ATA 2022 guidelines, a cutoff age of 18 years may be considered arbitrary, as the behaviour, natural history, and characteristics of PTC do not

suddenly change at this age (36). Patients in the age group of 16–25 years may either have PTC that behaves as 'typical' childhood PTC or may have a more 'adult'-like behaviour (36). Other studies have also implemented a cutoff for prepubertal PTC of 10 to 15 years (57–59). In our study, we accepted a cutoff of 10 years based on the physical examination of all prepubertal patients and previous reports by Liu et al. and Thiesmeyer et al. (47, 60).

The overall survival of our patients was excellent and mortality was null; however, we observed nodal recurrence in 5/90 children who were subsequently subjected to lateral lymphadenectomy. Recurrence was observed in prepubertal (<10 years) and pubertal children (<14 years of age). Studies have shown that the recurrence rate of PTC in children can reach 14–47% (60–62). In our study, the recurrence rate was 5.5%, which is lower than that in previous reports, probably related to the fact that 100% of the patients in our group underwent total thyroidectomy and 94.5% cervical neck dissection. Studies suggest that most cases recur within 5 years of diagnosis, but a few cases recur after 10 years or more, suggesting that some cases still have the possibility of future recurrence (63). Liu et al. found a greater rate of recurrence in children than in adolescents, and age was an independent variable predictive of recurrence (60). Therefore, for younger patients, the scope of surgical options should be more aggressive, and more attention should be paid to follow-up (60).

Although the advancement and recurrence rates of PTC are higher in prepubertal patients than in some adolescents, disease-specific mortality is low. The mechanism of this discrepancy is probably the differences in genetic profiles between young and prepubertal children and the greater sodium iodide symporter expression, which is related to radiosensitivity (44, 48).

The percentage of boys was higher and the F:M ratio was close to equal in prepubertal and 4:1 in older patients. Regarding sex distribution in the literature, the frequency of prepubertal PTC is higher than that of pubertal and adolescent PTC among males (48, 60, 64). Further investigations are needed to determine whether this result was caused by the small sample size of boys or whether puberty-related endocrine changes could also explain these differences (65, 66). This observation could be partially explained by the increase in thyroid autoimmunity with age, as observed in this study. Autoimmune thyroiditis is more frequent in female patients and increases with age (9). Younger patients tend to present late with more advanced disease owing to low awareness of cancer risk than actively surveilled older patients (30).

The almost 50% of coincidence of AIT and PTC in our study is concordant with two-fold increase in thyroid cancer risk in AIT paediatric patients presented in recent studies (67, 68). Similar to other studies, although AIT is associated with an increased risk of thyroid cancer, we did not find an association between AIT and the thyroid cancer stage at diagnosis (67). We believe that this could also be the effect of age and puberty on the different biological spectra of PTC in children, as suggested by He et al. and Thiesemeyer et al. (47, 48). In most cases of PTC, thyroid function tests are within normal limits (9, 18). Exceptionally rare cases of PTC have been associated with hyperthyroidism (9, 18). TSH has been proposed as a mediator of the association between AIT and thyroid cancer in adults with thyroid nodules (50, 67). However, evidence for an association between TSH and cancer among children with thyroid nodules has been conflicting (18, 19, 23, 31, 51). In this study, similar to a report by Keefe et al., TSH concentration was not associated with thyroid cancer (67). It is likely that the association of AIT with thyroid cancer in children is not mediated by elevated TSH concentrations and may be related more directly to thyroid inflammation/destruction, as we found an association between LNM and fT4 in patients not treated with levothyroxine or antithyroid thiamazole (67). These results corroborate data from Paparodis et al., who reported that the form of AITD pathology (destructive with clinically overt hypothyroiditis vs. less-destructive with clinically compensated hypothyroiditis or euthyroid) may play a role in differentiated thyroid cancer risk (55). Patients with less destructive AITD have a higher risk of differentiated thyroid cancer than those with destructive AITD (55). These observations support the hypothesis that autoimmune thyroiditis may be a secondary event.

Studies suggest that similar molecular mechanisms may influence the early stages of oncogenesis and inflammation in the thyroid gland (69). In our study, we found a significant difference in TPOAb levels between patients with AIT and those with AIT who developed PTC. In relation to preoperatively assessed TgAb levels, we found higher TgAb levels than TPOAb levels in younger patients. Additionally, we found significant differences in TgAb levels between patients with AIT(+) LNM(+) compared with patients with AIT(+) LNM(-). Thyroglobulin (Tg) and thyroperoxidase (TPO) are the main target antigens for cellular and humoral immune reactions (69–71). As presented by Ehlers et al., the tumour-protecting feature of TPOAb might be explained by (a) complement-mediated cell death, which is anti-TPO antibody-dependent because TgAb antibodies do not fix complement, and (b) TPOAb antibody-dependent cell toxicity due to the exclusive binding of anti-TPO antibodies to their effector cells *via* Fc-gamma receptor 1 (CD64), which is known to be expressed on monocytes (70). In contrast, TgAb seems to be a risk factor for PTC (70). One reason for this effect could be the fact that TgAbs from PTC patients recognise different Tg epitopes than TgAbs from patients with autoimmune thyroid diseases and from patients with PTC with associated thyroiditis (70, 71). Whether PTC develops despite autoimmunity or due to inflammation and preexisting autoimmunity, and whether AIT develops because of cross-reacting antitumour immunity, needs further research in paediatric patients (70, 71).

Although diagnostic criteria for PTC are the same regardless of patient age, differences in histotypes occur between adult and

pediatric populations (72). High-risk histologic subtypes of PTC are reported to occur in 15–37% of paediatric PTC, including 7–13% tall-cell variant, 7–16% diffuse sclerosing variant, 1–4% solid/trabecular variant, and 2–6% poorly differentiated carcinoma (72). These subtypes are more aggressive, carry an increased risk of recurrence and mortality, and are therefore classified as high-risk histologies, while classical and follicular subtypes of PTC have a more favourable prognosis and are therefore classified as low-risk histologies (72–76). Low-risk subtypes (classic and follicular subtypes of PTC) remained the most commonly encountered subtypes seen in our study in adolescents, apart from two cases of poorly differentiated PTC, whereas an increased percentage of mixed and more aggressive subtypes was observed in children ≤14 years of age. This was reflected in a more aggressive surgical approach in younger patients with concomitant ^{131}I therapy and more nodal recurrences.

In adult patients, incidental detection of small, clinically unapparent PTC, which is possible due to the increased availability of thyroid sonography, does not necessarily decrease mortality rates or improve patient health outcomes (77). Interestingly, Cancer Statistics from 2022 reveal that in adult population in The United States, after decades of increase, thyroid cancer incidence rates are now declining in both men and women at a combined rate of 2.5% per year from 2014 to 2018, partly because of recent changes in clinical practice designed to reduce over-detection (4). These changes are supported by data from autopsy studies, which indicate that the occurrence of clinically relevant thyroid tumours has remained stable since 1970 and is generally similar in men and women, despite a 3-fold higher overall incidence rate in women (4). However, in the most recent analysis published in 2023, the incidence of thyroid cancer increased in most countries among individuals irrespective of age (78). Moreover, the incidence increased in populations aged <40 years in several countries including Poland (78).

Therefore, we think that in cases of paediatric populations characterised by more advanced disease, children at risk, with AIT, with positive family history of thyroid problems (37.8% in our study), after radiotherapy, with lymphadenopathy, benefit from earlier detection, prior to lymph node metastasis, as it enables less aggressive surgical approach and might exclude from ^{131}I therapy. ATA 2022 recommends that future studies be conducted to evaluate the impact of limited surgery for paediatric PTC with respect to recurrence and remission rates, considering the potential side effects of aggressive therapies (36). It was suggested that, in paediatric patients with incidentally found very small thyroid carcinoma and non-aggressive histological features, hemithyroidectomy may be considered a therapeutic option (36). Based on the results of the present study, such an attitude could be considered in some adolescents with early detected PTC.

The limitation of our study was the retrospective and institutional nature of the study, but the main advantage was that all researchers in this study were involved in therapy and monitoring of described patients, and it comprehensively presents patient evaluation from preoperative to concomitant ^{131}I therapy, and includes histopathological evaluation.

Additionally, the limitations of our study relate not only to the limited sample size but also to the lack of tumour genetic profile information. We were unable to correlate the molecular differences between prepubertal and pubertal PTC. Recently, a few studies have shown that younger patients have a higher prevalence of fusion oncogenes than the *BRAFV600E* point mutation, which is regarded as the main molecular pathogenetic cause of adult PTC (45, 46). This finding suggests that diverse genomic alterations may exist in children, adolescents, and young adults with PTC.

The strength of our study was that we presented the associations between PTC variables not only in relation to puberty, dividing patients based on their examination of prepubertal (<10 years of age), pubertal (11-14 years), and adolescent/late pubertal, but also in relation to autoimmunity, assessed prior to thyroid surgery, and confirmed histopathologically.

Conclusions

1. The youngest patients (<10 years old) present more often with goitre and lymphadenopathy and less often with AIT than adolescents (15-18 years of age).
2. In paediatric patients with AIT, the natural course of PTC may be less aggressive than that in patients with PTC AIT (-), partially because of active ultrasound surveillance and detection of smaller nodules prior to extensive lymph node metastasis.
3. We suggest that pre-operative evaluation of paediatric patients with thyroid nodules could include the assessment of TSH, fT3, and fT4, as well as the evaluation of TPOAb, TgAb, and TRAb together with comprehensive neck ultrasonography (thyroid and whole neck with lymph nodes).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Bioethics Committee of the Jagiellonian University opinion number: 1072.6120.288.2021. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

Study design: DJ. Study conduct: DJ, AT, AK-W, MK, MW, WG. Data collection: DJ, MK, AT, AK-W, MW. Data analysis: DJ, MW, MC, MK. Data interpretation: DJ, MW, MK, MC, AT, AK-W. Drafting manuscript: DJ, MW. Revising manuscript content: DJ, MW, WG, JS. Approving final version of manuscript: DJ, MW, JS, WG. DJ takes responsibility for the integrity of the data analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Case Report - Multinodular goiter in a patient with Congenital Hypothyroidism and Bannayan-Riley-Ruvalcaba syndrome: the possible synergic role of TPO and PTEN mutation

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We report the case of a paediatric female patient affected by Bannayan-Riley-Ruvalcaba syndrome (BRRS) and congenital hypothyroidism (CH) with homozygous mutation of the TPO gene. She underwent total thyroidectomy at the age of seven years because of the development of a multinodular goiter. BRRS patients present an increased risk of benign and malignant thyroid disease since childhood because of inactivating mutation of PTEN, an onco-suppressor gene. Instead, homozygous mutations in the TPO gene can be associated with severe forms of hypothyroidism with goiter; previous studies have described cases of follicular and papillary thyroid cancer in CH patients with TPO mutation despite a perfectly controlled thyroid function with Levothyroxine therapy. To our knowledge, this is the first case that describes the possible synergic role of coexisting mutation of both TPO and PTEN in the development of multinodular goiter underlining the importance of a tailored surveillance program in these patients, especially during childhood.

KEYWORDS

case report, PTEN hamartoma tumor syndrome, congenital hypothyroidism, TPO, goiter

1 Introduction

Bannayan-Riley-Ruvalcaba syndrome (BRRS) is caused by germline inactivating mutations of phosphatase and tensin homolog (PTEN) gene inherited with an autosomal dominant mechanism. The PTEN gene, located on chromosome 10q23, is a tumor suppressor gene with a fundamental role in cell growth, migration, and apoptosis via the PI3K/AKT/mTOR pathway (1). An excessive activation of this pathway leads to overgrowth and an increased risk for tumor development as described in PTEN hamartoma tumor syndrome (PHTS), which encompass not only BRRS but a spectrum of syndromes including Cowden syndrome, Lhermitte-Duclos syndrome, Proteus-like syndrome and autism spectrum diseases with macrocephaly (2). BRRS is considered the PHTS form of childhood (3). Macrocephaly (head circumference > 97° ple) is the hallmark of this syndrome (4), variably associated with developmental delay, lipomas, hemangiomas, intestinal hamartomatous polyps, penile freckling and other highly variable phenotypic features as downward slanting palpebral fissures, frontal bossing, macrosomia, café au lait spots, hypotonia, joint hyperextensibility, hypoglycemia and seizures (3, 5). All patients are at high risk of tumor development especially affecting endometrium, kidneys, skin and thyroid, therefore cancer surveillance programs are recommended and needed also for paediatric population (6, 7). Thyroid diseases are common in these children: two thirds of all BRRS patients present with autoimmune thyroiditis, nodular goiter and benign or malignant thyroid tumors, either follicular or papillary thyroid carcinoma (1). In this paper, we describe the case of a girl affected by BRRS presenting with multiple thyroid nodules, previously diagnosed with severe congenital hypothyroidism (CH) due to TPO gene mutation: as far as we know this is the first description of BRRS associated with congenital hypothyroidism.

2 Case presentation

Our patient was born at 31 + 4 gestational weeks because of premature rupture of membranes. At birth her auxological parameters were adequate for gestational age (weight 0,4 SDS, length 1,5 SDS and head circumference 0,6 SDS). In the first days of life she suffered from respiratory distress, neonatal jaundice and patent ductus arteriosus pharmacologically closed. Due to prematurity, cerebral ultrasound was performed, resulting within limits. At neonatal screening, she was detected with a high blood TSH value (152 microU/mL). A severe form of congenital hypothyroidism was subsequently diagnosed (TSH 1016 µIU/mL, fT4 <0,4 ng/dL) and at ten days of life Levothyroxine (LT4) was started at a dosage of 10 mcg/kg/day. The thyroid ultrasound revealed the presence of a hyperplastic gland with inhomogeneous echotexture in the absence of thyroid antibodies. Genetic analysis was performed, revealing the presence of a homozygous mutation in the TPO gene (ins.GGCC395, exon 8) inherited from both parents. The father presented with normal thyroid function; the mother suffered from non-autoimmune hypothyroidism with right lobe hypoplasia diagnosed at the age of sixteen. At six months of age, an increasing head circumference (>97° percentile) and facial abnormalities such as triangular face, frontal bossing and hyperthelorism were observed. Karyotype was normal (46 XX) while the array-CGH showed the presence of a non-pathological variation in the copy number without chromosomal imbalance (arr(1-22,X)x2). At seven months, a brain MRI was performed showing a minimal amplification of the subarachnoid space and a slight para physiological reduction of the myelinisation signal. During the follow-up, a mild delay in neuromotor development (first steps at 18 months, first words at 24 months) was observed. Since the second year of life, multiple lipomas were diagnosed and subsequently surgically removed. At the age of six, she appeared in good clinical conditions, with regular growth both in height (25° ple) and weight (25° ple) but with a persisting important macrocrania. She also presented with an important thyromegaly, despite well controlled thyroid function values since the very first months of age. Therefore, a neck ultrasound was performed showing the presence of an enlarged thyroid (antero-posterior and transversal diameters: 16,5*15,6 mm right, 14,5*14,4 mm left, Figure 1A) with non-homogeneous echotexture and multiple nodules with intrinsic and peripheral vascularisation: five in the right lobe (diameter: 7-16 mm, Figure 1B) and four in the left lobe (diameter: 6-15mm). Six months later the nodules were increasing both in number and size: six-seven in the right lobe (diameter: 4-19 mm) and six in the left lobe (diameter: 4-17 mm). Moreover, brain MRI was repeated revealing the presence of a bone alteration in the orbital roof (1,8-2 cm) suspicious for haemangioma. Because of all the clinical peculiarities presented (macrocrania, neuromotor delay, facial abnormalities, lipomas, thyroid nodules, doubt of hemangioma), after genetic counselling, the sequencing analysis of PTEN gene was performed showing the presence of a heterozygous mutation (c.635-1G>C) coding for a truncated protein causing Bannayan-Riley-Ruvalcaba syndrome (BRRS). In consideration of the increased risk of developing thyroid cancer, the patient underwent total thyroidectomy at the age of seven; the histological exam showed 21 adenomatous nodules (0.1 to 1.7 centimetres) with microfollicular and trabecular architecture and poor in colloid. In 8/8 nodules analysed, the immunohistochemical analysis revealed a loss of nuclear expression of PTEN. Later in the follow-up, she developed an arteriovenous malformation at her right ankle that was surgically removed and genetically analysed confirming the presence of the PTEN gene alteration. Finally, at the latest follow-up (12 years), a breast nodule was observed and confirmed at the ultrasound, as well as duodenal and colic polyps at the endoscopic exam performed because of the presence of faecal occult blood.

3 Discussion

PTEN hamartoma tumor syndrome (PHTS) patients present an increased risk of developing benign and malignant thyroid disease. Nodules, goiter and autoimmune thyroiditis have been described in up to 75% of all patients affected by PHTS, including children with BRRS (1, 2). Previous studies have demonstrated that patients with PTEN gene mutations present a cumulative lifetime risk of developing thyroid carcinoma ranging from 21 to 38%, in particular the risk of paediatric differentiated thyroid carcinoma

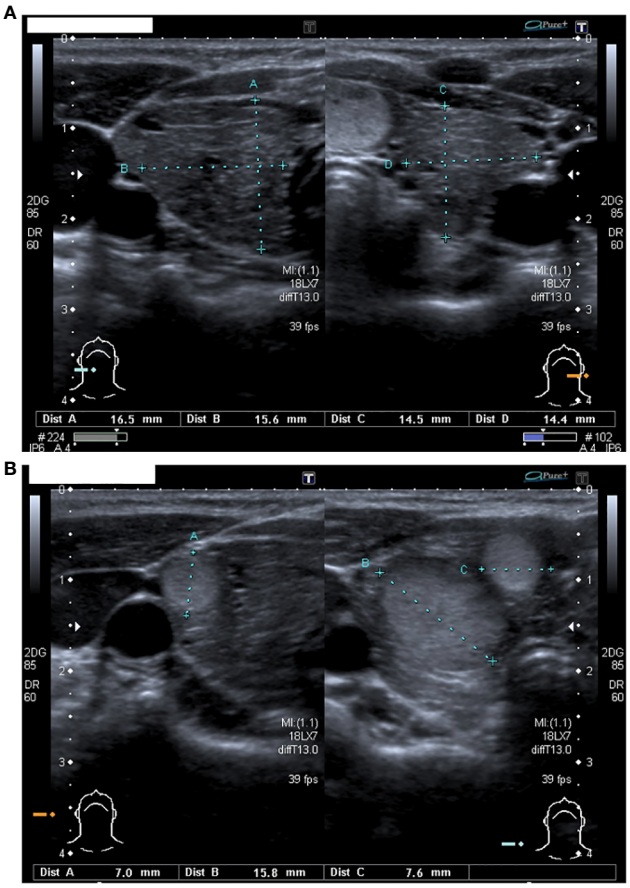

FIGURE 1
(A) The thyroid ultrasound performed at 6 years of age: an enlarged and non-homogeneous echotexture gland with increased antero-posterior and transversal diameters (16,5*15,6 mm for right lobe and 14,5*14,4 mm for left lobe). **(B)** Nodules in the right lobe.

(DTC) is estimated between 4 and 12% with an incidence of 5% from the age of ten (8–11). Therefore, considering the early involvement of the thyroid gland and the possible development of thyroid cancer, clinical and ultrasound surveillance should be performed early in childhood. However, a clear consensus regarding both the time of initiation and the timepoints of thyroid cancer surveillance in paediatric patients has not been established yet. Although the youngest patient described in literature with PHTS and thyroid carcinoma is a four years old boy (10), most authors have suggested that thyroid disease surveillance should begin at age of seven or ten (10, 11). As described by Smith et al. in their retrospective study on 64 children with PHTS, 44% of patients undergoing thyroid ultrasound present with a clinically significant thyroid nodule at the mean age of 13.3 years with a later presentation in males than females according to gender pubertal period. In this cohort, nodules were rare before the age of seven years (11). On the contrary, in a recent study conducted on a small group of 12 children with PTHS, 41.7% of subjects with nodular thyroid disease were less than seven years old (3). Nonetheless, confirming the prevalence of benign nodular disease in children with PHTS, no patient developed DCT during an average follow-up period of five years, thus not suggesting the need for anticipating the starting age of thyroid cancer surveillance (3). According to the recent comprehensive review of the German paediatric guidelines by Plamper et al., patients with PHTS should undergo a comprehensive physical examination and thyroid ultrasound right after the diagnosis; the following thyroid ultrasound should then be repeated annually or more frequently in case of any suspicious result. Furthermore, children under the age of seven without proof of thyroid nodules are allowed to repeat an ultrasound after 2-3 years (1, 12). Another recent prospective study investigated the development and progression of thyroid nodules and DTC in patients with PHTS both in the presence and absence of thyroid disease at initial ultrasound, with the aim of providing stronger evidence to refine current surveillance recommendations and stratify surveillance intervals based on the initial ultrasound result (13). According to these authors, in contrast with current recommendations, patients without thyroid nodules at the first ultrasound should repeat the exam after 3-5 years; patients with nodules should instead repeat the ultrasound depending on the presence of any suspicious pattern (13). Despite the optimal thyroid function values with LT4 therapy, our patient presented with an important thyromegaly and from the age of six multiple thyroid nodules were described. Homozygous mutations in TPO gene, inherited with an autosomal recessive pattern, are associated with severe forms of hypothyroidism with goiter (14). The combination of CH and DTC is a rare condition with no

established causal relationship. As recently suggested by Penna et al., the long exposure to elevated serum TSH levels, a congenital goiter as well as the presence of stimulating factors or the absence of tumor suppressor genes, the type of mutation and the iodine intake could all be factors involved in the development of DTC in patients with CH due to dyshormonogenesis (15, 16). Previous studies have described cases of follicular and papillary thyroid carcinoma in CH patients with TPO mutation and a perfectly controlled thyroid function (17, 18) suggesting that genetic and environmental factors other than TSH level might be involved in the development of thyroid cancer in dyshormonogenic multinodular goiter (MNG) and perhaps play a synergic role in the development of DTC. Tobias et al. analysing the long-term outcome of 33 CH patients with TPO mutations showed that 61% of them developed MNG over time at an average age of 8,6 years (19) without an association with higher TSH levels. In this case series, thyroidectomy was performed in eight patients (24%) leading to the diagnosis of a minimally invasive follicular carcinoma and seven cases of follicular hyperplasia or adenoma (19). Thus, the high rate of MNG development and the risk for thyroid carcinoma indicates the need for regular ultrasound and a long-term follow up in these patients (19). Although most patients affected by PTHS develop benign nodular goiter (3, 20, 21), our patient underwent total thyroidectomy at the age of seven without previously performing a cytological investigation by fine-needle aspiration. According to recent studies, the direct surgical approach could be justified because fine needle biopsy may not be sufficient to exclude malignancy in patients with more than one suspicious lesion (1). Nevertheless, paediatric patients, even more PTHS children with neuromotor delay, are often uncooperative (22) and most cases need general anaesthesia for FNA (1). Furthermore, the cytological analysis does not allow to distinguish a benign follicular adenoma from follicular carcinoma (23). Therefore, prophylactic thyroidectomy should be considered in selected patients with multiple nodules (24). However in the decision-making process, the consequences of total thyroidectomy should be always carefully analysed, such as the need of a lifelong daily replacement therapy and the risk of a surgical procedure in patients with other comorbidities. When indicated, thyroidectomy should be performed by an expert surgeon to minimize the risk of complications.

In conclusion, this is an original case where TPO and PTEN mutation could have played a synergic role in the development of multinodular goiter. Both TPO and PTEN patients need a strict ultrasound follow-up because of the risk of benign and malignant thyroid carcinoma. Further studies are needed to better understand the natural history of thyroid involvement in patients with TPO and/or PTEN mutations in order to provide stronger evidence to refine paediatric surveillance recommendations and develop a tailored diagnostic and therapeutic approach for these patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ultrasonographic, clinical, and pathological features of papillary thyroid carcinoma in children and adolescents with or without Hashimoto's thyroiditis

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Objective: To compare the ultrasonographic, clinical, and pathological features of children and adolescents with papillary thyroid carcinoma (PTC) with and without Hashimoto's thyroiditis (HT)

Materials and methods: A total of 52 children and adolescent patients surgically diagnosed with PTC between 2017 and 2022 were included; 14 children and adolescent patients with PTC were diagnosed with HT *via* pathological examination. The preoperative ultrasonographic, postoperative histological, and molecular and clinical characteristics were retrospectively analyzed.

Results: The prevalence rate of PTC in patients with HT was 27%. Papillary thyroid microcarcinomas were found in 11 of 38 patients without HT, but none in patients with HT ($p = 0.023$). Extrathyroidal extension, capsular invasion, and lymph node metastases were more frequent in patients with PTC and HT than in patients with PTC alone ($p < 0.05$ for both). The ultrasonographic features of nodule composition, echogenicity, shape, margin, Thyroid Imaging Reporting and Data System categories, and total points were similar. The patterns of echogenic foci were more prominent in the nodules of patients with HT than in those of patients without HT ($p = 0.016$).

Conclusion: The frequency of papillary thyroid microcarcinomas in patients with PTC and HT was less, whereas that of extrathyroidal extension, capsular invasion, and lymph node metastasis was significantly higher in patients with PTC and HT than in those with PTC alone. The patterns of echogenic foci on ultrasonography may represent a risk for PTC.

KEYWORDS

Hashimoto's thyroiditis, papillary thyroid carcinoma, ultrasonographic features, histopathological features, children and adolescents

1 Introduction

Thyroid cancer is rare in children and adolescents; however, the incidence appears to be increasing in recent years (1, 2). According to the Surveillance, Epidemiology, and End Results database, the incidence of thyroid cancer in children and adolescents aged ≤18 years increased by an average of 4.43% per year during 1998–2013 in the United States (3, 4). Papillary thyroid carcinoma (PTC)is the most common one, accounting for more than 90% of all children and adolescent cases; the incidence of PTC peaks between the ages of 15 and 18 years (5).

Hashimoto's thyroiditis (HT) is an organ-specific autoimmune disease and the most common cause of hypothyroidism in iodine-sufficient areas; it is characterized by diffuse lymphocytic infiltration and affects 1.3%–9.6% of children and adolescents (6–8).

Whether HT is a risk factor for PTC remains unclear (9). Many studies have shown a higher risk of PTC in patients with HT (10–12), whereas others did not demonstrate the increased risk (13, 14). PTC intertwined with HT in children and adolescents is extremely rare; few studies have assessed the association between PTC and HT in children and adolescents.

In the present study, we aimed to compare the preoperative ultrasonographic, clinical, and pathological features of children and adolescents with PTC with and without HT.

2 Patients and methods

2.1 Study design and patients

Approval for this retrospective study was obtained from the Institutional Research Ethics Board of Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; the requirement for informed patient consent was waived.

The medical records of our institution were searched between January 2017 and 2022; 52 patients (mean age: 14 years, range: 4–18 years) who underwent thyroid cancer surgery and lateral cervical lymph node (LN) dissection were included.

The medical records of all subjects were retrospectively reviewed, and patient demographics (age and sex), ultrasonographic features [composition, echogenicity, shape, margin, echogenic foci, total points, and TI-RADS level based on the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) classification (15), LN metastasis (LNM)], pathological findings (primary tumor size, HT, multifocal tumor, extrathyroidal extensions, capsular invasion, LNM, $BRAF^{V600E}$ mutation status), and TNM stage were analyzed. PTC was confirmed by pathological findings and staged according to the 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer TNM staging system for differentiated and anaplastic thyroid carcinoma (16).

2.2 Ultrasound examination of thyroid nodules

Real-time ultrasonography and Doppler examinations were performed using Resona 7 (Mindray medical system, Shenzhen, China) equipped with L14-5 WU linear array transducer (5–14 MHz); ACUSON Sequoia (Siemens Healthcare, Erlangen, Germany) equipped with 18L6 linear array transducer (6–18 MHz); ALOKA Arietta 850 premium (FUJIFILM Corporation, Tokyo, Japan) equipped with SML2-22 linear array probe (2–22 MHz) by three radiologists with more than 5 years of experience in thyroid ultrasonography.

According to the 2017 ACR TI-RADS, the five categories for ultrasound appearance of all thyroid nodules were analyzed: (1) composition: cystic, mixed, or solid or almost completely solid; (2) echogenicity: hypoechoic, isoechoic, or hyperechoic; (3) shape: wider-than-tall or taller-than-wide; (4) margin: smooth, ill-defined, lobulated, or irregular or extra-thyroidal extension; (5) echogenic foci: none or large comet-tail artifacts, macrocalcifications, punctate echogenic foci (PEF). Moreover, the five categories from the ACR-TIRADS 2017 point were registered. The total point of each nodule was added to determine the TI-RADS level. Furthermore, the LNs were considered metastatic if their shortest diameter exceeded 7 mm in levels I and II or 6 mm in levels III, IV, and V, and the ratio of their shortest to longest diameters exceeded 0.5 mm concurrently. In case of any discrepancy, the final ACR TI-RADS point scores and specific ACR TI-RADS classification were taken as the average with an agreement after discussion.

2.3 Pathology examination

The patients underwent thyroidectomy (lobectomy, near total thyroidectomy, total thyroidectomy) with regional lymphadenectomy (central neck dissection, lateral neck dissection, superior mediastinal dissection, or a combination of the above). The selection of all surgical methods is based on the American Thyroid Association guidelines for pediatric thyroid nodules (5) and Chinese expert consensus on thyroid nodules and differentiated thyroid cancer for Chinese children (5). The thyroid gland and LN histological sections were stained with hematoxylin and eosin staining, and the histological slides were independently evaluated by two senior pathologists using a double-blind method. The patients were diagnosed with HT based on the presence of diffuse lymphocytic and plasma cell infiltration, oxyphilic cells, and lymphoid follicles with reactive germinal centers.

The baseline information, including age, sex, primary tumor size, diagnosis of HT, number of lesions, pathological type, LNM, extrathyroidal extensions, capsular invasion, $BRAF^{V600E}$ mutation status, and TNM stage, was collected. All patients were staged using the thyroid cancer staging system released by the American Joint Committee on Cancer (8th ed., 2017).

2.4 Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive analyses were expressed as mean ± standard deviation (X ± SD) for normally distributed variables, median (range) or median (interquartile range) for non-

normally distributed variables, and the interquartile range for categorized variables. The student's t-test, Mann–Whitney U-test, or χ^2 test were used to assess the heterogeneity of demographic characteristics between groups with or without HT. $P < 0.05$ was considered statistically significant.

3 Results

3.1 Clinical features and pathological findings

A total of 52 children and adolescent patients were included. They were divided into the HT group (n = 14, mean age = 15.07 ± 2.62 years; 1 male and 13 female) and the non-HT group (n = 38, mean age = 14.34 ± 3.32 years; 9 male and 29 female). The comparison of demographics and pathological findings of PTC between the two groups is summarized in Table 1. All patients underwent thyroidectomy with regional lymphadenectomy. In the HT group, 7 patients underwent lobectomy, 2 patients underwent near thyroidectomy, 5 patients underwent total thyroidectomy. In the non-HT group, 18 patients underwent lobectomy, 6 patients underwent near thyroidectomy, 14 patients underwent total thyroidectomy; the final pathology was PTC in all cases.

There were 11 papillary thyroid microcarcinomas (≤1 cm diameter) in the non-HT group (11/38, 28.9%) and none in the HT group (28.9% vs. 0.0%, p = 0.023). Compared with the non-HT group, the HT group was significantly associated with higher incidences of extrathyroidal extension (47.4% vs. 85.7%, p = 0.013) Figures 1A–D) and capsular invasion (71.1% vs. 100.0%, p = 0.023). On the other hand, there were no significant differences in age, sex, multifocal, TNM staging, T staging, N staging, and $BRAF^{V600E}$ mutation status (all $p < 0.05$).

3.2 Ultrasonographic features

The ultrasonographic features of patients with and without HT are shown in Table 2. In both groups, most of the patients presented with typical PTC characteristics such as solid or almost completely solid nodules, marked hypo-echogenicity, irregular shape, irregular margins, PEF, and lateral neck lymph node metastasis (LLNM). Among patients with PTC and HT, 92.9% (13/14) had LNM (Figures 2C, D), 50.0% (7/14) had central lymph nodes metastasis (CLNM) only, and 42.9% (6/14) had both CLNM and LLNM; among patients without HT, 63.2% (24/38) had LNM (Figures 2A, B), 26.3% (10/38) had CLNM only, and 36.8% (14/38) had both CLNM and LLNM, with a statistically significant difference (p = 0.036). There were no differences between the groups regarding composition, echogenicity, shape, margin, TI-RADS categories, and total points. The frequency of PEF in patients with PTC and HT (Figures 3C, D) was significantly higher than that in patients with PTC and HT alone (p = 0.016) (Figures 3A, B).

4 Discussion

Lindsay et al. (17) first reported the association between HT and PTC in 1952; however, to date, the relationship between these two disorders remains complex and not completely understood (18, 19). Patients with HT are at an increased risk of PTC compared with the general population (20), some studies showed HT increased the risk of PTC (21, 22). There are few reports on the ultrasonographic features of PTC in children and adolescent patients with HT; moreover, the association between PTC and HT has been poorly defined in China. Therefore, we herein retrospectively analyzed the ultrasonographic, clinical, and histopathologic features of children and adolescent patients with PTC with and without HT.

A total of 52 children and adolescent patients with PTC who underwent thyroidectomy were included; 14 patients were diagnosed with HT confirmed by pathology. The prevalence rate of PTC in children and adolescent patients with HT was 27% in the thyroidectomy specimens obtained from our patients, which was similar to the findings from a previous systematic meta-analysis that reported a PTC prevalence rate of 33% among patients with HT (20). These incidences are comparable to the worldwide prevalence of PTC of approximately 23% (10%–58%) in adult patients with HT (23).

The relationship between HT and thyroid cancer may be related to chronic inflammation and autoimmune dysfunction. Chronic inflammation will lead to the release of reactive oxygen species and inflammatory cytokines, inducing cell proliferation, cell repair, and the formation of a chronic inflammatory environment (24). Reactive oxygen species produced in an inflammatory environment can cause DNA damage in organs, which is a common mechanism of cancer development (25). Autoimmune dysfunction may lead to the immune escape of tumor cells, making it further difficult for the tumor cells to be detected and cleared by the immune system, thus promoting the development of tumor (26). However, Radetti et al. (27)concluded that HT may impact the development of thyroid nodules but not cancer in pediatric patients. This is different from our study's conclusion. The probable reason is that Radetti et al. studied the development of HT patients who had no nodules from the beginning and we studied the cancer biology behavior of diagnosed PTC. Up to now, whether pre-existing HT should be considered a high-risk factor for PTC development in pediatric patients remains unclear. More studies on the association between HT and the risk of PTC are needed (28).

Most of the studies on the potential association between PTC and HT development have been conducted in adults; reports on this association in children and adolescents are rare. Therefore, we compared the ultrasonographic, clinical, and pathological features of children and adolescents with PTC with and without HT.

The results of the present study showed that the percentage of papillary thyroid microcarcinomas was higher in the non-HT group than in the HT group and that the rate of extrathyroidal extension and capsular invasion was higher in patients with HT than in those with PTC alone, which were consistent with the findings of our previous study (12, 29). Patients with thyroid cancer who have an

TABLE 1 Characteristics between children and adolescents' patients with or without Hashimoto's thyroiditis (HT).

Characteristics	PTC with TH	PTC without TH	P value
Number of patients	14(26.92%)	38(73.08%)	
Years			
Mean ± SD	15.07 ± 2.62	14.34 ± 3.32	
Range	8-18	4-18	0.356
Gender			
Female	13(25.00%)	29(55.77%)	
Male	1(1.92%)	9(17.31%)	0.179
Primary tumor size (cm)			
< 1	0	11(21.15%)	
≥ 1	14(26.92%)	27(51.92%)	0.023
Mean ± SD	22.00 ± 8.89	23.76 ± 17.73	
Range	13-45	3-80	0.725
Multifocal tumor			
Yes	3(57.69%)	9(17.31%)	
No	11(21.15%)	29(55.77%)	0.864
Extrathyroidal extension			
Yes	12(23.08%)	18(34.62%)	
No	2(3.85%)	20(38.46%)	0.013
Capsular invasion			
Yes	14(26.92%)	27(51.92%)	
No	0	11(21.15%)	0.023
T staging			
T1	8(15.38%)	13(25.00%)	
T2	5(9.62%)	20(38.46%)	
T3	1(1.92%)	5(9.62%)	0.323
N staging			
N0	1(1.92%)	11(21.15%)	
N1a	7(13.46%)	13(25.00%)	
N1b	6(11.54%)	14(26.92%)	0.239
$BRAF^{V600E}$ mutation			
Positive	4(7.69%)	13(25.00%)	
Negative	8(15.38%)	17(32.69%)	
Not detected	2(3.85%)	8(15.38%)	0.715

extrathyroidal extension and capsular invasion are considered to have more advanced tumors. Our present results showed that the presence of HT is associated with a bigger tumor size and stronger invasion ability and that the rate of LNM was more frequent in patients with HT and PTC than in patients with PTC alone, which was similar to our previous findings that extrathyroidal extension is strongly associated with LNM (30).

HT is the most common form of thyroiditis, a condition characterized by diffuse lymphocytic infiltration, gradual destruction of the gland, and fibrosis (31). Histologically confirmed HT is considered an independent risk factor and presents a higher incidence of PTC in children and adolescents (32, 33). The results of the present study showed that the positive rate of LNM is significantly higher in patients with PTC and HT

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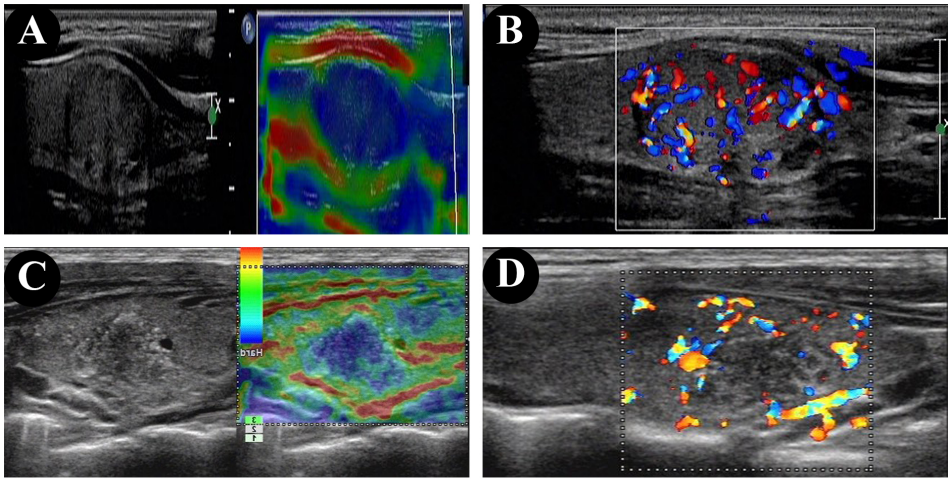

FIGURE 1
Ultrasonographic and elastography findings of PTC showed the tumor is closely attached to the capsule in the patient without HT **(A, B)**, and extrathyroidal extension in the patient with HT **(C, D)**.

TABLE 2 Ultrasonographic features between children and adolescent patients with papillary thyroid carcinoma with or without Hashimoto's thyroiditis (HT).

Ultrasonographic	PTC with HT	PTC without TH	p
Number of patients	14	38	
Composition			
Cystic and mixed	0	1	0.534
Solid or almost completely solid	14	37	
Echogenicity			
Hyperechoic or isoechoic	0	7	0.843
Hypoechoic	14	31	
Shape			
Wider-than-tall	14	37	0.534
Taller-than-wide	0	1	
Margin			
Smooth	0	2	0.167
Ill-defined	1	11	
Lobulated or irregular	9	13	
Extra-thyroidal extension	4	12	
Echogenic foci			
None or large comet-tail artifacts	0	11	0.016
Macrocalcifications	0	1	
Punctate echogenic foci	14	26	
Lymph node metastasis			
No LN metastasis	1	14	0.036
LN metastasis (central/lateral)	13(7/6)	24(10/14)	

(Continued)

TABLE 2 Continued

Ultrasonographic	PTC with HT	PTC without TH	p
TI-RADS categories			
TR 3	0	5	0.219
TR 4	1	6	
TR 5	13	27	
Total points			
Mean ± SD	9.21 ± 1.63	7.79 ± 2.65	0.066
Range	4-11	3-12	

than in patients with PTC alone, consistent with the findings of a previous study (29). However, there is disagreement with the point of view that HT in children and adolescents with PTC does not affect LNM (34). For instance, a cross-sectional study evaluated the differences between 106 children and adolescents with PTC and 23 patients with PTC and HT and reported that 16 (69.6%) and 10 (43.5%) patients were separately positive for CLNM and LLNM with PTC and HT compared with 67 (63.2%) and 50 (47.2%) patients with PTC alone. There were no differences between the two groups in terms of LNM (32). In the present study, among patients with PTC and HT, 92.9% (13/14) had LNM, 50.0% (7/14) had central lymph nodes metastasis (CLNM) only, and 42.9% (6/14) had both CLNM and LLNM; among patients without HT, 63.2% (24/38) had LNM, 26.3% (10/38) had CLNM only, and 36.8% (14/38) had both CLNM and LLNM, with a statistically significant difference (p = 0.036). This finding suggests that the coexistence of HT and PTC should be considered a higher risk for LNM in children and adolescents.

PEF are useful in diagnosing PTC and predicting the aggressiveness of PTC (35); our study showed a higher detection rate (100%) of PEF in the HT group than in the non-HT group (68.4%). In the 2017 ACR TI-RADS, PEF is assigned 3 points, associated with a high suspicion of malignancy (15). Middleton et al. (36) reported that the risk of malignancy was 29.8%–40.5% in solid nodules and 5.9%–15.1% in nodules mixed with PEF. PEF in thyroid nodules is considered as predictor of malignant thyroid cancer in children and adolescents (35, 37, 38). The cause of PEF is related to the rapid growth of cancer cells and insufficient blood supply to tissues, followed by degeneration, necrosis, and calcium deposition (39–41). It is commonly held that small echogenic foci without sound shadow on ultrasonographic features, often termed microcalcifications or psammoma bodies in thyroid tumors (38). However, in a few cases, the rear sound shadow can be generated due to the aggregation of multiple PEF (42).

Due to the high invasiveness of HT and PTC, surgical techniques, including lobectomy, total or near-total thyroidectomy, whether they

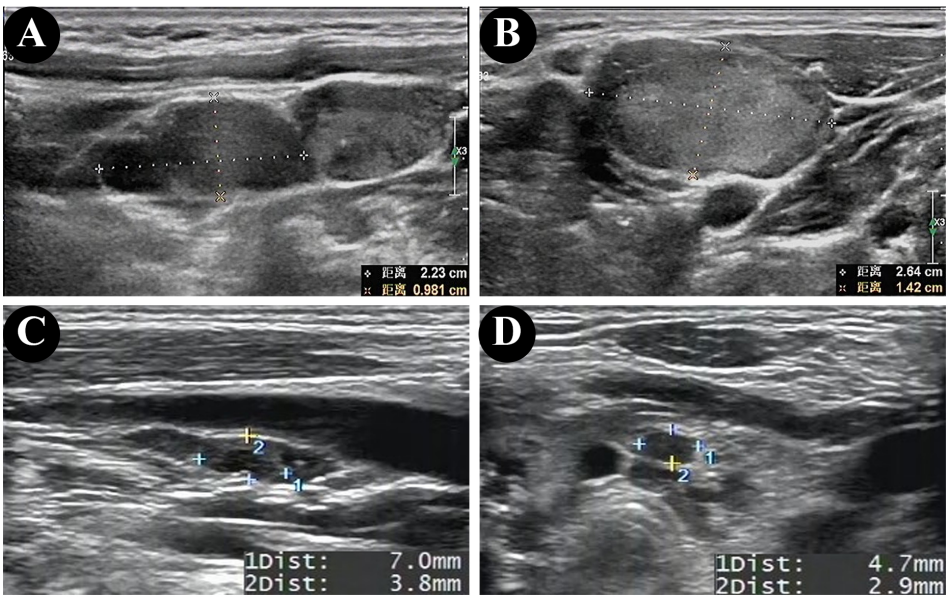

FIGURE 2
Ultrasonographic findings of lateral lymph node metastasis in patients without HT **(A, B)** and central lymph node metastasis in patients with HT **(C, D)**.

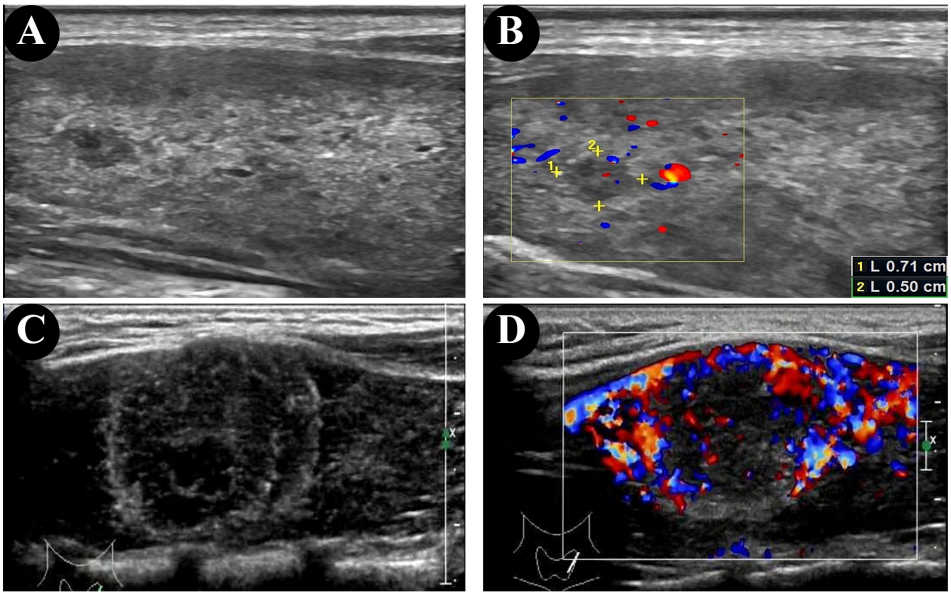

FIGURE 3
Ultrasonographic findings of papillary thyroid microcarcinomas (PTMC) in the patient without HT **(A, B)** and punctate echogenic foci in the patient with HT **(C, D)**.

have peripheral lymph node dissection, need to be comprehensively evaluated. The collaborative diagnosis and treatment of multidisciplinary teams are crucial. It could guarantee the precise treatment of thyroid cancer, thus improving the prognosis.

Nevertheless, there are some potential limitations to our study, including the retrospective study design and the potential for bias in diagnostic coding. Moreover, the number of cases encountered in a single institution was very small; therefore, these factors must be carefully considered when interpreting the findings of our study. Moreover, the lateral neck region was selectively dissected; therefore, a few LNMs might have been missed *via* LN staining. However, the $BRAF^{V600E}$ mutation status was detected in 42 out of 52 PTC cases, and not all patients, further increasing the bias of the associations of HT with the gene of $BRAF^{V600E}$ in this study.

The serum thyroid antibodies of all patients in the HT group were listed in Supplementary Table 1. The serum antibodies result of patient 3 and patient 4 do not increase. Radetti et al. reported that 10–15% of patients with HT will be negative for thyroid antibodies, normal serum thyroid level does not exclude the diagnosis as in many cases of thyroiditis the function may be perfectly normal (43). And some studies implied that the presence of lymphocytes in contact with thyroid cells is considered the most important element to make a differential diagnosis between HT and thyroid tumors (6, 43). T lymphocytes are the major subgroup of tumor-infiltrating immune cells, among which CD8+ T cells and CD4+ T cells comprise the primary immune cells responsible for anti-tumor immunity. Wang et al. showed that CD4+ and CD8+ TILs infiltration in PTC with HT tissues were significantly higher than in PTC tissues (44). Pan et al. showed that the immune cells in tumors exhibited distinct transcriptional states, and the presence of tumor-infiltrating B lymphocytes was predominantly linked to concurrent HT origin. Trajectory analysis of B cells and plasma cells suggested their migration potential from HT adjacent tissues to tumor tissues (45). And HT presents diffuse lymphocytic infiltration while tumor presents partly lymphocytic infiltration. The pathology results showed that these 14 patients had diffuse lymphocytic infiltration. We have insulted pathologists in our institute and made an agreement that HT can be diagnosed by pathology. Here in our study, post-surgery pathology has proved whether patient suffered HT.

In addition, a control group such as patients with benign disease with and or Hashimoto's thyroiditis is needed in the prospective study of the association of PTC and HT, which can decrease the bias and collect enough data to analyze, which makes the results more persuasive.

Finally, we just compared the ultrasonographic, clinical, and histopathological features of children and adolescent patients with PTC and HT with those of patients without HT. Future studies might also need to include other aspects, such as thyroid autoimmune antibodies (TGAb and TPOAb), PTC types, and the genes related to thyroid carcinoma, control group to construct large sample research.

In conclusion, our results suggest that HT may be an independent risk factor in children and adolescents with PTC, which showed more aggressive features, including larger tumor size, higher rate of extrathyroidal extensions, capsular invasion, PEF, and LNM compared with PTCs in patients without HT.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Approval for this retrospective study was obtained from the Institutional Research Ethics Board of Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; the requirement for informed patient consent was waived.

Author contributions

RL and JR designed the study. YJ and ML reviewed the literature, analyzed data, and drafted the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1198468/full#supplementary-material

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Risk of thyroid neoplasms in patients with 22q11.2 deletion and DiGeorge-like syndromes: an insight for follow-up

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Introduction: The chromosome 22q11.2 deletion syndrome comprises phenotypically similar diseases characterized by abnormal development of the third and fourth branchial arches, resulting in variable combinations of congenital heart defects, dysmorphisms, hypocalcemia, palatal dysfunction, developmental or neuropsychiatric disorders, and impairment of the immune system due to thymic dysfunction. Other genetic syndromes, often called DiGeorge-like, share clinical and immunological features with 22q11.2 deletion syndrome. This syndrome has been rarely associated with malignancies, mainly hematological but also hepatic, renal, and cerebral. Rarely, malignancies in the head and neck region have been described, although no aggregate of data on the development of thyroid neoplasms in patients with this clinical phenotype has been conducted so far.

Materials and methods: To characterize this possible association, a multicenter survey was made. Thus, we present a case series of five pediatric patients with 22q11.2 deletion syndrome or DiGeorge-like syndrome who were occasionally found with confirmed or highly suspected neoplasms of the thyroid gland during their follow-up. In three cases, malignancies were histologically confirmed, but their outcome was good due to an early recognition of suspicious nodules and precocious surgery.

Conclusions: This study underlines for clinicians the higher risk of neoplasms in the head and neck district for patients affected by these syndromes. It also emphasizes the importance of a prolonged clinical and ultrasound follow-up for patients with this clinical and immunological phenotype.

KEYWORDS

thyroid cancer, thyroid nodules, 22q11 deletion syndrome, DiGeorge, genetic syndrome

Introduction

The chromosome 22q11.2 deletion syndrome (22q11.2DS) is caused by a hemizygous deletion that is *de novo* in more than 90% of cases (1). In addition, 22q11.2DS encompasses several phenotypically similar diseases that share abnormal development of the third and fourth branchial arches, resulting in variable combinations of congenital heart defects, dysmorphisms, hypocalcemia, palatal dysfunction, developmental delay, neuropsychiatric disorders, and impaired immune function due to thymic hypoplasia or aplasia (2).

The most famous of these diseases is DiGeorge syndrome (DGS) that is usually caused by the loss of the *TBX1* gene (MIM_188400), located in the 22q11 region, which is an important transcription factor necessary for the development of the thyroid, parathyroids, palate, teeth, thymus, and heart (2). Sometimes, DGS is not caused by 22q11.2 deletion but *TBX1* pathogenic mutations (3). Nevertheless, there are many other genetic syndromes, often called DiGeorge-like, with clinical features like DGS but other chromosomal deletions, such as 10p13 (MIM_266500), 17p13.1 (MIM_613776), 16p11.2 (MIM_611913), and 4q34.1q35.2 (4–7), or others within the context of CHARGE (MIM_214800) or Opitz G/BBB syndrome (MIM_300000) (8, 9). However, in 6%–17% of patients, a genetic cause remains unknown (10).

Thyroid anomalies are frequently discovered in 22q11.2DS. Approximately half of the patients have structural anomalies such as thyroid hypoplasia, absent isthmus, and abnormal extension probably due to *TBX1* haploinsufficiency (11–13). Thyroid dysfunction can also be caused by autoimmunity. It is estimated that over 8% of patients with 22q11.2DS will develop autoimmunity with age (14). Recently, we described 73 children with 22q11.2DS, followed up for 9.51 ± 5.72 years. Totally, 21.9% developed autoimmune thyroid disease (ATD) before the age of 18, including 20.5% Hashimoto's thyroiditis (HT) and 1.4% Graves' disease (GD) (15). Among 22q11.2DS patients who developed ATD, one case of thyroid cancer in one adolescent developing GD was described, strongly recommending periodic screening with ultrasound scan in these patients (15).

It is known that many congenitally inherited syndromes are associated with a higher risk of malignancy (16, 17) with the development of malignancies, mainly hematological but also hepatic, renal, and cerebral (8, 18). Malignant tumors in the head and neck region, as well as in other districts, have rarely been described (19–21). The risk of malignancy in 22q11.2DS is moderately increased when compared to the healthy general pediatric population with a reported frequency of 1% in the 22q11.2DS population (20). A recent Finnish nationwide register-based cohort study by Wahrmann et al. (22) described a 2.1% rate of malignancy in 98 patients with 22q11.2DS.

Very few cases of patients with 22q11.2DS and thyroid neoplasms, benign or malign, have been described so far (8, 14, 19). On the other hand, to the best of our knowledge, no cases of thyroid neoplasms have been reported in patients with DiGeorge-like syndromes.

To characterize this possible association, a multicenter survey was made. Thus, we present a case series of five pediatric patients with 22q11.2DS or DGS-like who were occasionally found with confirmed or highly suspected neoplasms of the thyroid gland during their follow-up.

Materials and methods

We performed a retrospective multicenter study of patients with 22q11.2DS or DGS-like who presented with thyroid or parathyroid neoplasms before the age of 18 between 4 January 1985 and 6 July 2022. The study recruited patients with a confirmed genetic diagnosis of 22q11.2DS or with a DGS-like, based on a highly evocative clinical and laboratory phenotype, from the Paediatric Immunology Division and Auxo-endocrinology Division of Meyer Children's Hospital in Florence (University of Florence), Santa Chiara's Hospital in Pisa (University of Pisa), and Bambino Gesù Children Hospital in Rome (University of Roma Tor Vergata), Italy. The Tobias and the European Society of Immunodeficiencies (ESID) criteria were initially used to evaluate patients' susceptibility to genetic analysis for 22q11.2DS (23, 24). All patients were monitored annually or biannually up to the age of 18 through clinical assessments and thyroid ultrasounds and blood tests to measure thyroid function and autoantibodies. A total of three patients with 22q11.2DS and confirmed thyroid cancers were extensively described below.

The study was conducted according to the Declaration of Helsinki II. Written informed consent from the patients' parents or legal guardians was acquired before data collection. Patient data were retrospectively retrieved from the clinical records and anonymously collected in an Excel® spreadsheet. A specific approval by the local ethical committee was not required because all analyses included in this study were performed as part of routine clinical activity according to Good Clinical Practice.

Clinical, ultrasound, and histological data were collected from the clinical records of all patients during the follow-up. Ultrasound scans were performed with a linear multifrequency transducer. An extended immunologic phenotype was performed. All values were evaluated by standard methods and compared with age-matched normal values.

Results

Between 4 January 1985 and 6 July 2022, a total of 275 patients with 22q11.2DS (260 patients) and DGS-like (15 patients) were consecutively observed in the three centers for multidisciplinal follow-up and periodic thyroid ultrasound scans. During follow-up, thyroid malignancies were found by ultrasound scans in three patients with 22q11.2DS (two boys and one girl) with a median age of 10.30 years ± 1.48 years at cancer diagnosis. None of them was previously exposed to radiation (Figure 1). None of them had a family history of thyroid or parathyroid carcinoma or adenoma. Two patients had autoimmune hypothyroidism and hyperthyroidism, respectively, at the time the nodules were discovered. The mean maximum diameter of confirmed malignant nodules was 23.16 ± 15.18 mm. According to

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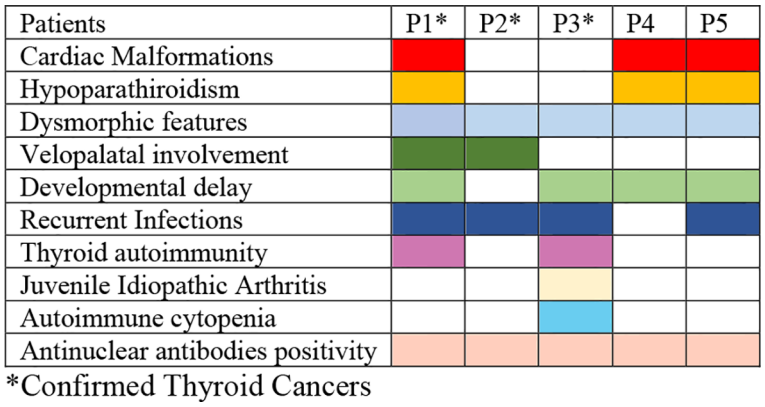

FIGURE 1
Graphical representation of the main clinical features of the patients. *Confirmed thyroid cancers.

the classification of the American Thyroid Association (ATA), all three nodules showed ultrasound characteristics of a high risk of malignancy (25). The clinical, ultrasound, and immunophenotypic characteristics of the patients are described in Figure 2 and Tables 1, 2.

Case 1

P1 is a 12-year-old boy with 22q11.2DS diagnosed through comparative genomic hybridization array (CGH-array) and fluorescence *in situ* hybridization (FISH) at age 9 for a history of speech delay, palatal insufficiency, and submucosal cleft palate. Initial cardiologic evaluation identified pervious foramen ovale (PFO) and aortic root ectasia. During follow-up, his growth was good, and he did not complain of relevant infections. At age 11, routine blood tests for thyroid function and autoimmunity showed decreased thyroid-stimulating hormone (TSH) levels and significantly elevated TSH receptor (TSHR) antibodies. Ultrasound scans revealed diffuse thyroid gland overflow, leading to a diagnosis of Graves' disease (GD). Treatment with Tapazole was initiated, resulting in good disease control without side effects. However, subsequent ultrasound scans performed after 6 and 9 months revealed diffuse inhomogeneity and a hypoechogenic nodule in the right lower lobe (14 × 19 × 6 mm), indicative of a potential thyroid abnormality. Fine-needle aspirate biopsy (FNAB) was conducted, identifying TIR3b cytology, and total thyroidectomy was performed. Histologic examination confirmed the presence of follicular carcinoma, which was classified as T1N0M0 according to TNM staging. Due to the early diagnosis, the patient did not require adjuvant radiometabolic therapy and is currently disease-free with substitutive therapy.

Case 2

P2, a 24-year-old man, underwent surgery for intestinal occlusion due to malrotation at 6 days of age. The diagnosis of 22q11.2DS was prompted by dysmorphic features and an interventricular defect and confirmed at 1 month of age through FISH. During the follow-up, multiple thyroid ultrasound scans were performed, all yielding negative results. At the age of 9, a routine ultrasound scan revealed a solid nodular formation completely occupying the right thyroid lobe (40 × 30 × 20 mm). The nodule exhibited hyperechogenic spots in the peripheral zone and inhomogeneous hypoechogenicity in the central zone. Additionally, a right cervical lymphadenopathy was identified, with hyperechogenic spots. FNAB identified a TIR4 phenotype; thus, total thyroidectomy with cervical right lymphadenectomy was performed. Histologic examination revealed papillary thyroid carcinoma infiltrating the peri-thyroid lax tissues, which was classified as T3N1bMx due to metastatic involvement of four right recurrent lymph nodes (NR1, NR3, NR4) and three right lateral cervical lymph nodes (N1, N2). After 5 months, recurrence of disease was observed at the right lateral cervical site (right mandibular angle), necessitating additional surgery and radiometabolic therapy. P2 is currently disease-free and continues to receive care from an adult immunology center.

Case 3

P3 is an 18-year-old woman with 22q11.2DS diagnosed through FISH at the age of 12 months for dysmorphic features and neurodevelopmental delay. Recurrent respiratory infections were observed since early childhood. At age 3, she was diagnosed with ATD based on increased TSH levels and positive autoantibodies. Substitution therapy with levothyroxine was initiated. Of note, familiar history was positive for autoimmune diseases (aunt with ATD and grandmother with Sjögren's syndrome). During the follow-up, multiple thyroid ultrasound scans were performed. At the age of 10, a routine ultrasound scan revealed an inhomogeneous nodule (12 × 10.5 × 9.5 mm), with hypoechogenic areas, peripheral vascular overflow, and a suspected lymph node (long axis 10.5 mm). The first FNAB identified a TIR1 cytology, but 5 months later, the second FNAB identified a TIR3B phenotype. Consequently, hemithyroidectomy was performed. Histologic examination identified a papillary thyroid carcinoma Warthin-like variant (pTIb). Histology also showed lymphocyte infiltration as for

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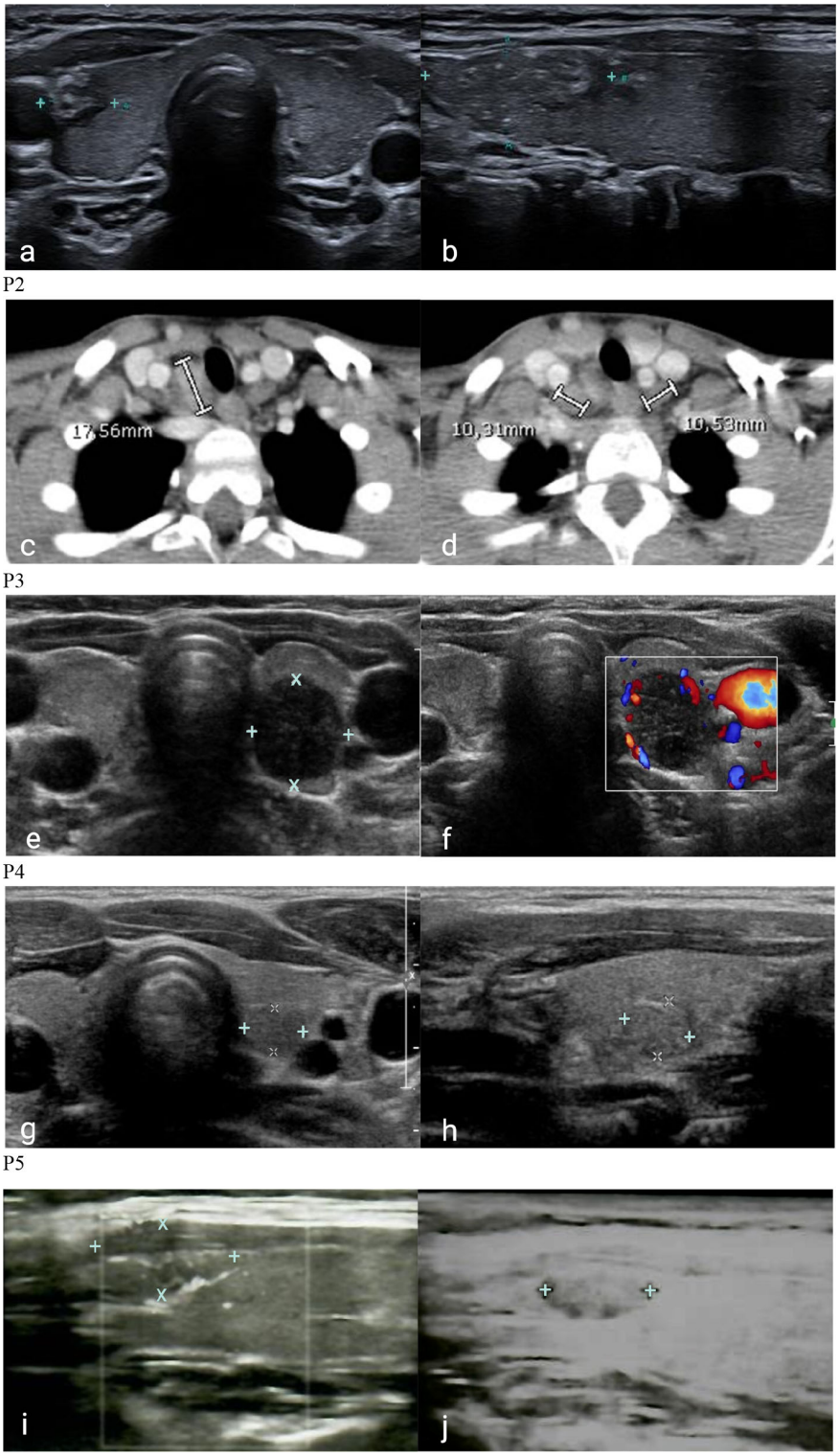

FIGURE 2
Cervical ultrasonography and computerized tomography of patients with 22q11DS and DiGeorge-like syndrome. P1. Inhomogeneous hypoechoic nodule in the right lower lobe in coronal **(A)** and sagittal **(B)** ultrasound projections. P2. Metastatic involvement of right lateral cervical lymph nodes **(C)** and normal lymph nodes **(D)** in coronal CT. P3. Inhomogeneous nodule with hypoechogenic areas **(E)** and peripheral vascular overflow **(F)** in the left lobe in coronal ultrasound projections. P4. Roundish hypoechoic nodule in the posterior region of the left lobe in close proximity to the carotid artery in coronal **(G)** and sagittal **(H)** ultrasound projections. P5. Iso-hypoechoic nodule in the upper third of the right lobe with blurred margins, and intra- and perilesional vascularity in sagittal ultrasound projections in sagittal ultrasound projection: first identification **(I)** and 1-year follow-up **(J)**.

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TABLE 1 Lymphocyte subsets of the patients.

Patient	P1*	P2*	P3*	P4	P5
Lymphocyte (10^3/μL)	2.268 2.500 (1.662 – 3.448)	**1.324** 2.285 (1.340 – 3.173)	**1.040** 2.500 (1.662 – 3.448)	2.773 2.500 (1.662 – 3.448)	**1.411** 3.800 (2.340 – 5.028)
CD3 (10^3/μL)	**1.176** 1.793 (1.239 – 2.611)	**0.281** 1.629 (0.954 – 2.332)	**0.623** 1.793 (1.239 – 2.611)	1.011 1.629 (0.954 – 2.332)	**0.558** 1.793 (1.239 – 2.611)
CD3CD4 (10^3/μL)	**0.335** 1.030 (0.646 – 1.515)	**0.149** 0.887 (0.610 – 1.446)	**0.351** 1.030 (0.646 – 1.515)	0.705 0.887 (0.610 – 1.446)	**0.339** 1.030 (0.646 – 1.515)
CD3CD8 (10^3/μL)	0.465 0.595 (0.365 – 0.945)	**0.114** 0.518 (0.282 – 0.749)	**0.205** 0.595 (0.365 – 0.945)	**0.262** 0.518 (0.282 – 0.749)	**0.187** 0.595 (0.365 – 0.945)
CD19 (10^3/μL)	0.593 0.403 (0.276 – 0.640)	0.367 0.321 (0.173 – 0.685)	**0.215** 0.403 (0.276 – 0.640)	0.468 0.403 (0.276 – 0.640)	**0.256** 0.403 (0.276 – 0.640)
CD3CD16CD56 (10^3/μL)	0.335 0.262 (0.120 – 0.483)	0.296 0.230 (0.087 – 0.504)	0.236 0.262 (0.120 – 0.483)	0.311 0.230 (0.087 – 0.504)	**0.126** 0.403 (0.276 – 0.640)
CD4CD45CD31 (%)	**24%** 55% (43% – 67%)	**5%** 49% (37% – 62%)	**12,5%** 49% (37% – 62%)	**35%** 55% (43% – 67%)	50% 55% (43% – 67%)
CD4CD45RA+ (%)	**27%** 65.0% (53.3%–74.0%)	**12%** 54.3% (40.9%–65.7%)	15% 54.3% (40.9%–65.7%)	76% 65.0% (53.3%–74.0%)	45% 65.0% (53.3%–74.0%)
CD4CD45RO+ (%)	**73%** 29.0% (22.1%–36.6%)	**88%** 35.7% (25.1%–52.1%)	**85%** 35.7% (25.1%–52.1%)	24% 29.0% (22.1%–36.6%)	**55%** 29.0% (22.1%–36.6%)
CD19CD27+ (%)	**3.74%** 16.5% (12.7% - 24.5%)	**1.5%** 12.7% (7.9% - 19.8%)	**3.2%** 16.5% (12.7% - 24.5%)	**3.06%** 16.5% (12.7% - 24.5%)	**2.88%** 16.5% (12.7% - 24.5%)
CD27+IgD+ (%)	**2.32%** 10% (7.5% – 12.4%)	**0.25%** 7.3% (4.6% - 10.2%)	**0,76%** 10% (7.5% – 12.4%)	**1.13%** 10% (7.5% – 12.4%)	**1.96%** 10% (7.5% – 12.4%)
CD27+IgD- (%)	**1.42%** 6.5% (5.2% - 12.1%)	**1.25%** 5.4% (3.3% - 9.6%)	**0.99%** 6.5% (5.2% - 12.1%)	**1.93%** 6.5% (5.2% - 12.1%)	**0.92%** 6.5% (5.2% - 12.1%)

The absolute and/or relative numbers of cell subsets are indicated for each patient (upper line). Lower lines indicate normal absolute or relative values for age (26–28).
*Confirmed thyroid cancers.
Bold values are those that deviate from normal values.

TABLE 2 Ultrasound features and laboratory details of patients with 22q11.2DS and DiGeorge-like syndrome and thyroid neoplasms.

	P1*	P2*	P3*	P4	P5
Thyroid dimension (mL)	6.79 (2.05 - 9.17)	15.08 (1.20 - 7.09)	5.55 (1.20 - 7.09)	3.41 (2.05-9.17)	10.21 (4.04-13.19)
Nodule Dimension (mm)	14*19*6	40*30*20	12*10.5*9.5	7*5*7.5	9.8*6.7*5
Overflow	–	–	+	+	+
Calcifications	–	+	–	–	–
Inhomogeneity	+	+	+	+	–
Hypoechogenicity	+	+	+	+	–
Lymph Nodes	–	+	+	+	–
TSH (mcU/mL)	0.005 (1.12 – 5)	1.85 (0.8 – 3.5)	150 (1.12 – 5)	2.11 (0.8 – 4)	2.85 (0.8 – 4)
fT4 (ng/mL)	2.38 (1.01 -1.63)	1.53 (1 – 1.9)	0.18 (1.01 -1.63)	1.05 (0.7 – 1.8)	1.09 (0.8 – 1.8)
TG-Ab	–	–	29.9	–	–
TPO-Ab	–	–	2738	41.3	–
TSHR-Ab	9.47	–	–	–	–

The thyroid volume was calculated with Pi/6 × length × width × depth for each lobe and then by adding the two values. Lower line indicates normal values (min–max) for age (29).
Worst laboratory values (lowest or highest) are represented.
*Confirmed thyroid cancers.

Hashimoto thyroiditis, while no signs of metastases were found in lymph nodes. She subsequently underwent total thyroidectomy and then radiometabolic therapy with 131-I for ablation of residual thyroid tissue. Later, she remained stably disease-free with substitutive therapy.

Of note, it is worth mentioning that two additional patients with suspected thyroid malignant nodular lesions were identified during their follow-up. The first patient is a boy with 22q11.2DS who is under close surveillance with serial ultrasounds due to the presence of a slightly growing suspicious thyroid nodule that cannot be biopsied due to its proximity to the carotid artery (P4) while awaiting a more radical intervention in case of worsening ultrasound findings. The other patient is a girl with DGS-like who underwent FNAB and right lobectomy for a suspected malignant nodular lesion, which was subsequently identified as Hurtle cell adenoma (P5). Their clinical, ultrasound, and immunophenotypic characteristics are described for comparison and completeness alongside those of patients P1, P2, and P3 in Figure 2 and Tables 1, 2.

Discussion

Our results seem to suggest that patients with 22q11.2DS and probably DGS-like can develop a broad range of thyroid neoplasms with a higher degree of malignancy. It is known to date that the prevalence of pediatric thyroid diseases of surgical interest, particularly thyroid cancer, is a rare entity and significantly lower than that of adults (30). Epidemiological surveillance data described 1.2 cases per 100,000 patients under the age of 20 but 0.4 cases per 100,000 in patients aged under 15 (31). However, the incidence of pediatric thyroid nodules and cancer appears to be steadily increasing and associated with a worse prognosis (32), far higher than the expected value in the adult population (5%) (33). In clinical practice, the management of pediatric thyroid nodules largely follows the adult thyroid guidelines (25), with some peculiarities related to pediatric age.

Although limited, our data appear to indicate that 22q11.2DS patients have a significantly higher prevalence of thyroid cancers, confirming the suggestions of the literature (34, 35) and strongly recommending periodic screening also with thyroid ultrasound scan in these patients. In fact, considering only malignant thyroid neoplasms confirmed by histological investigation through a long follow-up and periodic routine thyroid ultrasound scans, a total of three cases of malignant thyroid nodules (P1, P2, and P3) were identified out of a total of 260 patients with 22q11.2DS (1.15%).

Although not specifically intended for drawing conclusion on the thyroid cancer rate, we chose to mention in this case series two patients with 22q11.2DS and DGS-like phenotype who exhibited suspicious thyroid nodules during their follow-up to raise awareness among physicians about the potential risk associated with these conditions.

Indeed, the incidence of thyroid malignancy in patients with 22q11.2DS may be underestimated. This is exemplified by the case of P4, who presents a thyroid nodule with suspicious features of malignancy but cannot be biopsied. Patients with DGS-like phenotype may also have an increased risk of developing thyroid neoplasms, but due to the lack of specific literature on neoplasms in DGS-like patients, this association may have been overlooked. It is important to note that many DGS-like patients remain undiagnosed and thus do not receive comprehensive immunologic and endocrinologic follow-up. However, given their shared clinical and immunophenotypic features with 22q11.2DS patients, some centers adopt a similar follow-up approach for both groups. Our findings highlight the importance of regular ultrasound monitoring in DGS-like patients, as exemplified by the detection of a suspicious nodule in P5, although not confirmed as malignant.

To date, less is known about why patients with clinical phenotypes including 22q11.2DS, and probably DGS-like too, may have an increased risk of malignancies. One of the reasons could lay on the T-cell defects that are common in 22q11.2DS and in DGS-like too (10, 36, 37). As widely described for HIV infection, T lymphopenia or reduced natural killer cells, as well as their dysfunction, may predispose to poor surveillance against neoplastic cells. T-cell dysfunction can also lead to B-cell hyperproliferation and overactivation resulting in a higher risk of developing lymphomas (38, 39). In fact, cases of B lymphoma in patients with 22q11.2DS and severe T-cell impairment have been reported in the literature in the past (40, 41). It is unclear whether the few thyroid cancers described to date in patients with 22q11.2DS were associated with T lymphopenia (34, 42). Generally, there is limited understanding regarding the relationship between the development of thyroid adenomas or carcinomas and lymphopenia. A recent work by Rabold et al. (43) found that T-cell lymphopenia in patients with thyroid cancer indicates an aggressive tumor behavior and might badly influence the outcome of the disease. Lymphopenia could play a role also for persistent infections by oncogenic viruses. As proof for this, there is increasing evidence in the literature on the association between viral infections and thyroid cancer development. Recent work by Moghoofei et al. (44) described the detection of Epstein Barr virus (EBV) DNA in 71.9% of 57 thyroid tumor specimens and thus demonstrated that persistent EBV infection could be associated with an increased risk of thyroid cancer. This evidence was confirmed by a systematic literature review conducted in 2020 by Mostafaei et al. (45) who demonstrated the potential pathogenetic association with several viral infections, not only EBV.

All patients (P1, P2, and P3) with 22q11.2DS who developed thyroid cancer had T lymphopenia, especially in the $CD3CD4^+$ and $CD3CD8^+$ compartments at immunophenotype analysis. Variable degrees of T lymphopenia were also found in P4 and P5 as described in Table 1.

Probably, this may have played a role in cancer development, but we cannot assume that T lymphopenia alone was their only risk factor because there are numerous inborn errors of immunity with profound T-cell deficiency in which an increased risk of thyroid neoplasms is not reported in the literature.

Thus, likely in addition to lymphopenia, there could be other reasons related to the syndrome that we do not fully understand to date but that could contribute to the risk of developing thyroid cancers.

Since allelic losses of chromosome 22q arm were described by molecular analysis of well-differentiated thyroid cancer specimens (46), authors have tried to emphasize the role of this chromosomal region loss in thyroid cancer predisposition. For instance, atypical deletions could involve the tumor suppressor gene *SMARCB1* (MIM_609322), which is associated with rhabdoid tumors, or *DGCR8* gene (MIM_609030), which has been found to result in aberrant levels of miRNA leading to an increased susceptibility to malignancies (47, 48). However, if the reason was related only to this, many more cases of thyroid tumors among patients with 22q11.2DS would have been described so far.

Moreover, this pathogenesis cannot explain why patients with DGS-like, who do not have 22q deletion, may eventually share an increased risk.

Since, in 22q11.2DS, the development of the third and fourth branchial arches from which the thyroid gland derives is impaired (2), an embryological role in predisposition to thyroid cancer cannot be ruled out. Recently indeed, a model of fetal carcinogenesis of thyroid tumors has been proposed (49). According to this model, within a differentiated thyroid gland, there would exist three different types of fetal thyroid cells that could give rise to thyroid cancer cells. Finally, it is necessary to consider thyroid autoimmunity. It is well known that patients with 22q11.2DS have an increased risk of autoimmunity, both thyroid and non-thyroid (2). According to Shugar et al. (50), there is a higher rate of hypothyroidism and hyperthyroidism in children with 22q11.2DS than in the general population. However, as demonstrated in our previous work, through a long ultrasound and endocrinological follow-up, thyroid autoimmunity could be detected in up to 21.9% of patients with 22q11.2DS (15). Moreover, sometimes also ultrasound changes could precede the rise of thyroid autoantibodies or hormone impairment.

A recent study by Montin et al. (51) in patients with 22q11.2DS showed that certain immunologic features, including reduced numbers of recent thymic emigrants (RTEs), reduced naive T cells, and reduced B memory switched, are associated with the development of hematologic autoimmunity. This was also demonstrated in a study by Ricci et al. (52). Much evidence suggests that inflammation induced by thyroid autoimmunity may promote tumor development, although the precise mechanism has not been identified. Nevertheless, the presence of a proinflammatory environment, variable expression of transcriptional regulators, and increased TSH values together could promote tumor development or growth (53).

Two patients (P1 and P3) developed thyroid autoimmunity before tumor, although with different temporal latencies. Both had predisposing conditions for autoimmunity as explained above. In fact, both had reduced numbers of circulating naive T cells, RTEs, and switched B memory. However, these alterations were also present in P2 who never presented thyroid autoimmunity.

Although, in the case of P3, the temporal latency from the onset of autoimmunity suggests that autoimmunity may have contributed to cancer development, we cannot assume the same for P1. In fact, in this case, it is not possible to determine with certainty, given the short temporal latency, whether it was the autoimmunity that induced the tumor or the tumor at an early stage that fostered the autoimmunity.

Beyond the various hypotheses presented and depicted in the summary in Figure 3, with this work, we draw attention to the fact that prolonged follow-up protocols that include annual or biannual thyroid ultrasound scans not only allow recognition of autoimmune thyroid pathologies before autoantibodies or clinical symptoms become positive but also allow an earlier identification of thyroid nodules, particularly in adolescents with 22q11DS. In fact, all of our cases, both confirmed malignant and suspected, occurred in the age

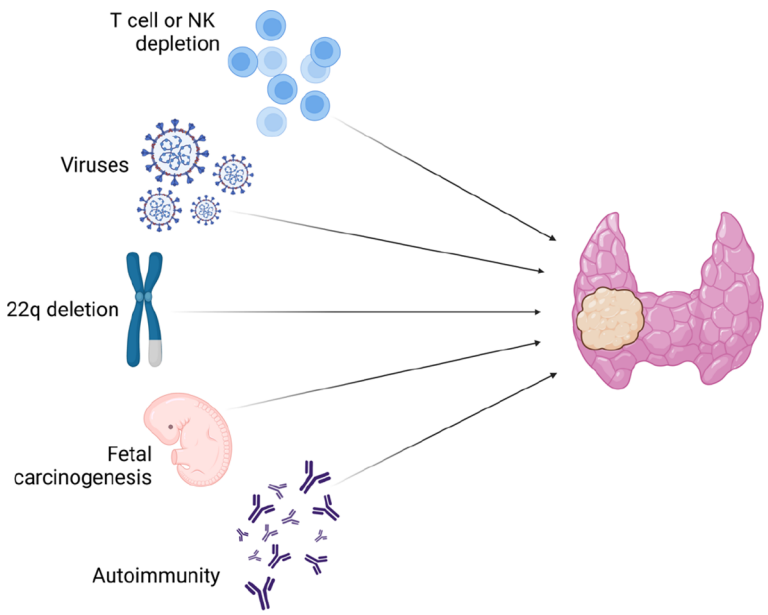

FIGURE 3
Etiologic hypotheses for increased risk of thyroid neoplasms in 22q11.2DS and DiGeorge-like syndrome patients.

range of 9–15 years. We therefore suggest increasing clinicians' attention and thyroid ultrasound follow-up in patients within this age group. Early ultrasonographic detection of a thyroid nodule is indeed important because it provides early identification of suspicious features of malignancy, early referral of patients to FNAB, and eventually surgery. Moreover, in case of malignant lesions, it offers the possibility of lowering the risk of metastasis, the need for radiometabolic therapy, and unfavorable outcomes. In addition, it also enables a detailed tracking of any morphological changes in suspicious nodules that cannot undergo early surgery because of a difficult location, as demonstrated for P4. Among the described patients, three patients developed malignant thyroid nodules, and only one of them had a recurrence of disease that required new surgery for lymphadenectomy. In any case, none of these patients presented distant metastases. All of them, reflecting the importance of an early diagnosis, had an excellent prognosis and all of them are steadily disease-free.

Conclusion

To the best of our knowledge, this work represents the first aggregate of data on the development of thyroid neoplasms in patients with this clinical phenotype. Our data suggest a significantly increased prevalence of neoplasms among patients with 22q11.2DS and highlight how the thyroid may be one of the preferred sites for the development of neoplasms in these patients. Our data also demonstrate that the risk of developing thyroid neoplasms could also be shared by patients with DiGeorge-like syndromes. Thus, in patients with this clinical and immunological phenotype, ultrasound scans of thyroid and parathyroid glands should be performed at the time of diagnosis and then periodically, mostly in adolescence, to ensure early detection and more proper and precocious treatment of neoplasms. A long clinical and ultrasound follow-up for these patients, especially in the presence of more pronounced immunologic changes, is recommended since the risk of neoplasms could persist lifelong.

Anyway, our data are limited to obtain significant conclusions regarding the effective increase of the thyroid cancer risk for 22q11.2DS and DGS-like patients, and more extensive studies will be necessary to be conclusive. A large registry of studies enrolling individuals with 22q11.2DS, regardless of reason or age at diagnosis, would be useful to define the exact risk, especially given the variability in reported cancer types, and begin to understand the precise mechanisms behind.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

All authors participated in the drafting of the article unanimously. All authors read and approved the final article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Global incidence and prevalence of differentiated thyroid cancer in childhood: systematic review and meta-analysis

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Objective: Differentiated thyroid cancer (DTC) is rare in childhood and adolescence although it represents the most frequent endocrine malignancy in this population. DTC includes both papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Most pediatric DTCs are PTCs, while FTCs are rare. To date, no systematic reviews on the global epidemiology of pediatric and adolescent DTC have been published. This systematic review and meta-analysis aims to estimate the overall incidence and prevalence of DTCs in patients aged 0–19 years.

Methods: The systematic research was conducted from January 2000 to December 2021 through MEDLINE via PubMed, Cochrane Library, and Embase databases. Two separate meta-analyses were performed for PTC and FTC.

Results: After the selection phase, a total of 15 studies (3,332 screened) met the inclusion criteria and are reported in the present systematic review. Five studies were conducted in Europe, five in North America, two in South America, one in Asia, one reported data for 49 countries and territories across the five continents, and one from both the USA and Africa. Most of the studies (n = 14) reported data obtained from national registries, and only one provided information collected from hospital medical records. Beyond the actual trend over time, our study reported a pooled global incidence rate (IR) of PTC and FTC in the pediatric age of 0.46 (95% CI: 0.33–0.59) and 0.07 (95% CI: 0.02–0.12) per 100,000 person-years, respectively. The highest IRs were recorded among Caucasian girls, and the lowest in black or other races/ethnicities.

Conclusion: Our data confirm that DTC in the pediatric population is a rare condition. The pooled IRs of the studies included in this meta-analysis are ~0.5 for PTC, which is the most common histological type when both genders and all

age groups are considered. The implementation of a prospective international registry on pediatric DTC, as part of the wider European Registries for Rare Endocrine Conditions, has been recently proposed. In addition to providing relevant information on the clinical behavior of this rare disease, standardization of data collection will be pivotal to fill current gaps and allow an accurate estimation of the real incidence and risk factors of DTC.

KEYWORDS

differentiated thyroid cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, children, meta-analysis, incidence, prevalence

1 Introduction

Differentiated thyroid cancer (DTC) is rare in childhood and adolescence although it represents the most frequent endocrine malignancy in this population (1). DTC includes both papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), while poorly differentiated thyroid carcinoma (PDTC), anaplastic thyroid carcinoma (ATC), and medullary thyroid carcinoma (MTC) are subsets of thyroid cancer not included in this definition.

The Surveillance, Epidemiology, and End Results (SEER) database revealed that overall thyroid cancer accounts for 1.9% of all cancers in a population aged less than 20 years (2). The annual incidence of thyroid cancer in Americans aged 0–19 years has been estimated at 6.9 cases per million in the period 1975–2018 (2). However, the incidence rates (IRs) increase with age, and most cases are found in adolescents, with a predominance of female cases (3, 4). Specifically, the IRs increase from 0.43 in children aged 5–9 years to 3.5 in adolescents aged 10–14 years and up to 15.6 per million in those aged 15–19 years (5–7). While the rates are equally distributed between the male and female gender in prepubertal children, a clear female predominance in adolescence becomes evident, with the female-to-male ratio increasing up to 1:6 and making thyroid cancer the second most common malignancy in adolescent girls (6–8).

The increasing incidence over time is largely attributed to increased detection, though this does not account entirely for the rise in cases, and a true incidence increase cannot be definitely excluded (5). Jensen et al. recently reported an increase in the incidence of DTC presenting in young adults but not in children or adolescents in the Danish population (9).

Thyroid nodules are rarer in children than in adults but require prompt investigation, as the rate of malignancy is reported to be between 10% and 50%, significantly higher than in adults, in whom the reported rates range between 5% and 15% (10–12). Most cases of DTC in children and adolescents are PTC, while FTC is uncommon in this age group. Furthermore, DTC in children seems to differ in its behavior from that observed in adults, as children with DTC tend to present with more advanced disease (13–15), often with lymph node involvement at diagnosis (15, 16). Distant metastases, most commonly pulmonary, are also more frequent in children than in their adult counterpart (13, 14).

To date, no systematic reviews on the global epidemiology of pediatric and adolescent DTC have been published. Therefore, this systematic review and meta-analysis aimed to estimate DTC global incidence and prevalence in people aged 0–19 years, to evaluate the quality of study reporting, and to analyze the factors possibly contributing to trend modifications over time.

2 Material and methods

2.1 Literature search strategy and selection criteria

This systematic review and meta-analysis was conducted in accordance with The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (17) (Supplementary Table 1). A literature search on the epidemiology of pediatric DTC was carried out using the bibliographic databases MEDLINE and Embase from January 2000 to December 2021. Both databases were searched for terms related to DTC, prevalence, incidence, and epidemiology. Citations, titles, and abstracts were exported into Endnote X9. The complete search strategy for each database is provided in Supplementary Table 2.

Only original observational research articles written in English and reporting numerical and well-defined data on the epidemiology of pediatric DTC, including the number of cases, the underlying population, and the observation period, were considered. Narrative or systematic reviews and meta-analyses, as well as book chapters, editorials, and conference abstracts, were excluded; however, the references included in the narrative or systematic reviews and meta-analyses were screened to identify other potential studies to be included. Studies were also excluded if they used pharmacoeconomics or segregation analysis methods since, in the latter, epidemiological evaluations are based on mathematical models that make projections of the number of expected cases in a given population, thus concerning predicted and not actually observed incidence or prevalence (18). No geographic exclusion criteria were imposed.

After removing duplicates from the two different databases, six medically trained experts in pediatric endocrinology and pharmacoepidemiology (FC, LC, DC, MDM, GPe, GPa) screened

individually the title and abstract of all records identified to remove articles that were clearly not relevant; the full texts of the articles were then independently reviewed by three experts (TA, MM, MW) to define whether they met the inclusion criteria or not. Any disagreements were resolved through discussion or, if consensus was not reached, through the intervention of a 10th expert (GT).

2.2 Data extraction and quality of study reporting assessment

Data from each included study were individually extracted by two authors (SCr, FC). The collected information included author (s) and year of publication, study catchment area, data source, prevalence/incidence type, study population, study period, study design, DTC definition, and the epidemiological estimate. For each included study, the incidence of the disease was defined as the number of new DTC cases per 100,000 person-years. The quality of study reporting was independently evaluated by two experts (SCr, FC) through a checklist specifically adapted for observational studies on the epidemiology of rare diseases from Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (19). An overall low, medium, and high score (see Supplementary Document 1 for the complete quality assessment) was assigned to each included study, based on the following five fields: description of the study design and setting, eligibility criteria, study population, outcomes, and study participants. Disagreements in scoring were resolved through the intervention of a third expert (GT).

2.3 Statistical analyses

The meta-analysis of IRs was performed assuming that each study-specific rate was normally distributed and that the corresponding standard error (SE) was either provided by the authors or derived on the basis of the reported 95% confidence interval (CI) or *p*-value. A linear mixed effects model with random intercept was fitted to provide a pooled estimate of the IRs. The classical Cochran's *Q* test and its derived inconsistency measure (I^2) were computed to assess the between-study heterogeneity, and it was claimed to be present when Cochran's *Q* test *p*-value was <0.10 or I^2 >40% (19). Both study-specific and pooled epidemiological estimates were represented graphically, along with their 95% CI, on a forest plot. Two separate meta-analyses were performed for papillary and follicular thyroid carcinomas. Test for publication bias and metaregression were not performed due to the limited number of included studies (i.e., less than 10 studies) (20). Statistical analyses were performed using the R Foundation for Statistical Computing (version 4.2, package: *metafor*).

3 Results

3.1 Study selection and characteristics

The PRISMA flowchart describing the process of study selection is reported in Figure 1. A total of 4,080 studies were identified through the literature search. After the removal of duplicates (n = 748, 18.3%), 3,332 titles and abstracts were screened. Records excluded by title and abstract were 3,295, and only 37 (0.9%) full-text articles were retained for further evaluation. Among these, 15 (0.37%) studies met the inclusion criteria and were finally included in the systematic review (9, 21–34).

The characteristics of the included studies are shown in Table 1. Overall, five (35.7%) studies were conducted in Europe (9, 23, 27, 31, 32), five (35.7%) in North America (21, 22, 25, 26, 29), two (14.4%) in South America (24, 30), one (7.1%) in Asia (28), one (7.1%) reported data for 49 countries and territories across the five continents (33), and one from both the USA and Africa (34).

Most of the studies (n = 14, 93.3%) reported data obtained from national registries (9, 21, 22, 24–34) and only one (23) provided information collected from hospital medical records.

Overall, incidence data were obtained over a median period of 25 years (range 4–40 years, IQR 14–35 years), and all the included studies stratified data by gender and, with few exceptions only (9, 24, 30, 32), according to two (21, 34) or ≥3 age groups (22, 23, 25–29, 31, 33).

Thyroid cancer definition was based on the International Classification of Diseases for Oncology (ICD-O) third edition (ICD-O-3) in just over half of the included studies (53.3%) [21, 22, 25, 26, 29, 30, 9, 34), on both the ICD-O-2 and ICD-O-3 in one study (24), on the ICD-O-1 and ICD-O-2 in one study (32), and according to the International Classification of Diseases (ICD) ninth (ICD-9) and 10th (ICD-10) edition in one (31) and two (27, 28) studies, respectively. The ICD edition used to define thyroid cancer was not specified in two studies (23, 34).

Six studies (42.8%) reported both tumor stage and size at diagnosis (22, 23, 25, 26, 29, 31), although in two of these studies (22, 29), information on the above characteristics was available only for a part of the study period. One additional study reported data on tumor stage only (32).

Of the 15 studies included in the systematic review, nine (60%) (9, 23, 26, 28–30, 32–34) were not included in the meta-analysis because no distinction between histological subtypes was applied in the calculation of the incidence rate or because neither the 95% CI nor the denominator used to calculate the prevalence and/or the incidence was reported in the full-text articles. Overall, the quality of study reporting was evaluated for 15 studies (Supplementary Table 3). In total, it was estimated as medium for 10 (66.7%) studies, as high for 3 (20.0%) studies, and as low for 2 (13.3%) studies.

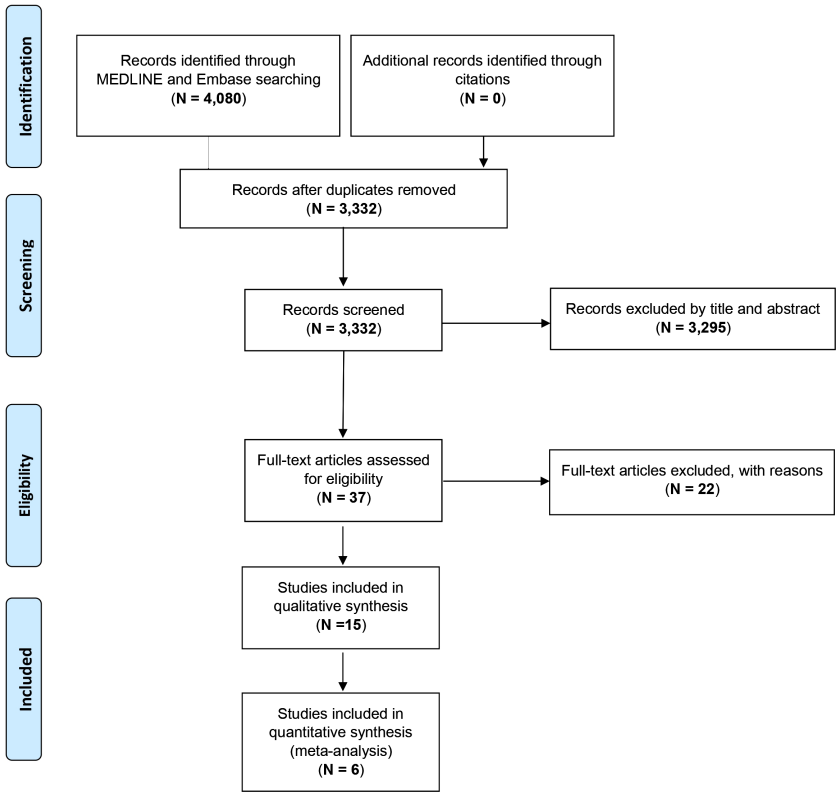

FIGURE 1
PRISMA flowchart showing the process of literature search and study selection.

3.2 Epidemiology of pediatric differentiated thyroid cancer

Fourteen studies (93.3%) reported the incidence of pediatric thyroid cancer, as either period/annual (9, 21, 23–27, 29–32) or age-standardized (22, 28) IRs, and only one study (34) estimated the period prevalence of pediatric thyroid cancer.

IRs for race/ethnicity were computed only in four of the included studies (4/15, 26.7%), all of which had been conducted in the USA and reported data from the SEER program (25, 26, 29) and the North American Association of Central Cancer Registries (NAACCR) (22). In all the above studies, the highest IRs were recorded among Caucasian girls, and the lowest in black or other races/ethnicities.

Concerning DTC histotypes, 12 studies (80%) (9, 21–24, 27, 29–34) evaluated the IRs of both PTC and FTC separately, whereas one study focused on PTC only (25), one on FTC only (26), and one did not distinguish DTC subtypes (28). Among the studies included in the systematic review, IRs ranged from 0.13 (95% CI: 0.10–0.16) (24) to 0.61 (95% CI: 0.59–0.62) (22) cases per 100,000 persons for PTC and from 0.01 (95% CI: 0.00–0.02) (24) to 0.16 (95% CI: 0.06–0.27) (27) cases per 100,000 persons for FTC. The pooled IRs of the studies included in the meta-analysis were 0.46 [95% CI: 0.33–0.59] for PTC and 0.07 [95% CI: 0.02–0.12] for FTC when both sexes and all age groups were considered (Figure 2). Considerable heterogeneity was detected among the studies exploring both PTC (Q = 1,022.80, df = 5, $p < 0.001$; I^2 = 99.5%) and FTC (Q = 148.15, df = 3, $p < 0.001$; I^2 = 98%) IRs. Due to the limited number of included studies (<10), both metaregression and test for publication bias could not be performed.

4 Discussion

The prevalence of thyroid nodules in childhood and adolescence has been estimated to range between 0.5% and 2%, according to the method used for their screening (i.e., ultrasonography or palpation), the considered nodular size (i.e., only those having dimensions of more than 10 mm or even smaller nodules), and the background nutritional iodine status (35–39). While most of the thyroid nodules detected in this age group are benign, the risk of a nodule >10 mm being malignant is approximately two- to threefold higher in children than in adults (20%–25% vs. 5%–10%) (10, 11). Also, epidemiological data indicate that the worldwide incidence of DTC in pediatric patients is rising, this trend substantially mirroring the one reported in the adult population (21–25, 28, 29, 32, 33, 40, 41). In this regard, a recent large population-based registry study focused on the global patterns and trends in the incidence of thyroid cancer in children and adolescents analyzing data from 49 countries and territories worldwide (33). Despite the considerable variability in adjusted standardized ratios (ASRs) observed between countries, a clear temporal increase in incidence rates across geographically and ethnically divergent populations was evident, particularly among

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TABLE 1 Characteristics of the included studies investigating the epidemiology of differentiated thyroid cancer in childhood.

Ref.	First author (year)	Catchment area	Data source	Study period	Study population considered in the systematic review	Thyroid cancer definition	Epidemiological parameter	Included in the meta-analysis: yes or no (reason)
(21)	Aschebrook-Kilfoy (2013)	USA	National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program	1980–2009	PTC children aged 0–9 years and 10–19 years FTC children aged 0–9 years and 10–19 years	ICD-O-3 codes 8050, 8260, 8340-44, 8350, 8450, 8452, 8460 (PTC); ICD-O-3 codes 8290, 8330-32, 8335 (FTC)	Period incidence rates per 100,000 person-years	Yes
(22)	Bernier (2019)	USA	North American Association of Central Cancer Registries (NAACCR)	1998–2013	PTC children aged 0–9 years, 10–14 years, and 15–19 years FTC children aged 0–9 years, 10–14 years, and 15–19 years	ICD-O-3 codes 8050, 8052, 8130, 8260, 8340-44, 8450, 8452, 8460 (PTC); codes 8290, 8330-32, 8335 (FTC)	Age-standardized incidence rates per 1,000,000 person-years	Yes
(23)	Berontiene (2017)	Lithuania	Medical records from three hospitals in Lithuania (Hospital of the Lithuanian University of Health Sciences Kauno klinikos, Vilnius University Hospital Santariskiu Klinikos, Klaipedos University Hospital)	1980–2014	PTC children aged 7–9 years, 10–12 years, 13–15 years, and 16–18 years FTC children aged 7–9 years, 10–12 years, 13–15 years, and 16–18 years	Postoperative pathology examined at three main university hospitals in Lithuania	ASR per 1,000,000 person-years	No (epidemiological estimates of histological subtypes are not provided)
(24)	De Souza Reis (2020)	Brazil	Eleven population-based cancer registries encompassing five geographic regions of Brazil	2000–2013	PTC children aged 0–14 years FTC children aged 0–14 years	ICD-O-2 and ICD-O-3 codes 8050, 8052, 8130, 8260, 8340-44, 8450, 8452 (PTC); 8290, 8330-32, 8335 (FTC)	Period incidence per 1,000000	Yes
(25)	Golpanian (2015a)	USA	National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program	1973–2011	PTC children aged 0–4 years, 5–9 years, 10–14 years, and 15–19 years	ICD-O-3 all variants of PTC (codes not specified)	Period incidence per 100,000	Yes
(26)	Golpanian (2015b)	USA	National Cancer Institute's	1973–2011	FTC children aged 0–4 years, 5–9 years, 10–14 years, and 15–19 years	ICD-O-3 non-papillary types	Period incidence per 100,000	No (in this series, FTCs were 54% of all

(Continued)

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TABLE 1 Continued

Ref.	First author (year)	Catchment area	Data source	Study period	Study population considered in the systematic review	Thyroid cancer definition	Epidemiological parameter	Included in the meta-analysis: yes or no (reason)
			Surveillance, Epidemiology, and End Results (SEER) program			including follicular thyroid carcinoma, medullary thyroid carcinoma, and Hurtle cell carcinomas (codes not specified)		non-papillary cancers and results only for FTC could not be excerpted)
(27)	Grønhøj (2018)	Denmark	Danish Cancer Registry	1978–2014	PTC children aged 0–4 years, 5–9 years, and 10–14 years FTC children aged 0–4 years, 5–9 years, and 10–14 years	ICD-10 papillary and follicular thyroid carcinoma, based on MORPHO-3 registration	Period incidence per 100,000	Yes
(28)	Lee (2021)	South Korea	National Health Information Database of the National Health Insurance Service	2004–2016	DTC children aged 0–9 years, 10–14 years, 15–17 years, and 18–19 years	ICD-10 code C73	ASR per 100,000 person-years	No (epidemiological estimates of histological subtypes are not provided)
(29)	Qian (2019)	USA	National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program	1973–2013	PTC children aged 0-9 years, 10–14 years, and 15–19 years FTC children aged 0–9 years, 10–14 years, and 15–19 years	ICD-O-3, C73, codes 8050, 8260, 8340-44, 8350, 8450-60 (PTC); 8290, 8330-35 (FTC)	Period incidence per 100,000	No (study period and data sources overlap with those used by Golpanian et al.)
(30)	Ramirez-Vick (2011)	Puerto Rico	Central Cancer Registry of Puerto Rico database	1985–2004	PTC children aged 0–19 years FTC children aged 0–19 years	ICD-O-3, codes 8050, 8052, 8130, 8260, 8340-44, 8450, 8452 (PTC); 8290, 8330-32, 8335 (FTC)	Incidence rate per 100,000 in 2004	No (epidemiological estimates of histological subtypes are not provided)
(31)	Russo (2017)	Italy	Sicilian Regional Register for Thyroid Cancer	2002–2009	PTC children aged <5 years, 5–9 years, 10–14 years, and 15–19 years	ICD 9, PTC (all variants) and FTC (all variants) (codes not specified)	Period incidence per 100,000	Yes
(9)	Schmidt Jensen (2018)	Denmark	Danish Cancer Registry; Danish Pathology data Bank; central population register	1980–2014	PTC children aged 0–17 years FTC children aged 0–17 years	ICD-O-3, MORPHO-3 codes 80503, 82603, 82903, 83303 (PTC); 83303, 83313, 83403 (FTC)	Annual Incidence per 100,000 in 2014	No (epidemiological estimates of histological subtypes are not provided)

(Continued)

TABLE 1 Continued

Ref.	First author (year)	Catchment area	Data source	Study period	Study population considered in the systematic review	Thyroid cancer definition	Epidemiological parameter	Included in the meta-analysis: yes or no (reason)
(32)	Smailyte (2006)	Lithuania	Lithuanian Cancer Registry	1978–2003	PTC children aged 0–19 years FTC children aged 0–19 years	ICD-0-1 site codes 1930–1939 for the period 1978–1997 and ICD-O-2 site codes C730-739 for the period 1998–2003	Annual incidence per 100,000 in 2003	No (epidemiological estimates of histological subtypes are not provided)
(33)	Vaccarella (2021)	47 countries across five continents	159 registries from 47 countries and territories across the five continents	2008–2012	PTC children aged 0–9 years, 10–14 years, and 15–19 years FTC children aged 0–9 years, 10–14 years, and 15–19 years	ICD-O-3 codes for all variants of PTC and FTC (codes not specified)	ASR per 1,000,000 person-years	No (the 95% confidence intervals of the epidemiological estimates are not reported)
(34)	Woodruff (2010)	Nigeria–USA (Texas)	West African Center's Cancer Registry Database Surgery database University of Texas Southwestern Medical Center at Dallas	1980–2004	PTC children aged 0–10 years and 11–20 years FTC children aged 0–10 years and 11–20 years	Diagnosis of DTC subtypes at both institutions based on WHO criteria (not otherwise specified)	Period prevalence in 1980–2004 in West Africa Period prevalence in 1997–2008 in UT Southwestern Medical Center	No (epidemiological estimates of histological subtypes are not provided)

girls in the 10–19-year age group (33). Whether this trend (similar to what is assumed for the adult population) may be accounted for by overdetection of subclinical lesions is plausible, it is currently unproven. As a matter of fact, a US study reported a significant increase between 1998 and 2013 in the rates of either small (<1 cm) or large (>2 cm) tumors, as well as in diseases at early (DTC confined to the thyroid gland) or late (DTC with distant metastases) stages, with the above trends over the time period being significant for the age group 10–19 years and across racial and ethnic groups (22). Noteworthy, the temporal distribution of the recorded cases was skewed toward the last years, with approximately half of the newly diagnosed cases being detected in the last 6 years of the 16-year study period. In our view, rather than driven by significant changes in environmental/behavioral factors potentially affecting thyroid cancer incidence, this trend may argue in favor of increased medical surveillance, likely related to the overall growing concern toward DTC. Emblematic in this regard are the findings of a thyroid ultrasonography mass screening program implemented in Fukushima following the 2011 Nuclear Power Plant Accident and aimed at establishing the baseline prevalence of thyroid cancer among children and adolescents living in areas with different degrees of radiation exposure (42). An overall, and unexpected, prevalence of 37.3 per 100,000 childhood thyroid cancer was recorded in this study, but no significant differences were found between areas with the highest radioactive contamination and those with minimal radiation exposure. According to the authors, since recruitment in this study was carried out within the putative latent period for radiation-related cancers, the larger-than-expected number of cancers detected among children and adolescents is likely consistent with an overdiagnosis due to mass screening rather than an actual increase in DTC occurrence (42).

More recently, an observational study compared data collected by the International Agency for Research on Cancer (IARC) through the "Cancer Incidence in 5 continents plus" (CI5 plus) project with those of the latest report from the Global Cancer Observatory (GLOBOCAN 2020 project). An overall increasing prevalence of thyroid cancer was found in the age groups 10–19, with female late adolescents presenting a much higher incidence with respect to girls aged 10–14 years old (43).

Beyond the actual trend over time, our study reported a pooled global IR of PTC and FTC in the pediatric age of 0.46 (95% CI: 0.33–0.59] and 0.07 (95% CI: 0.02–0.12) per 100,000 person-years. When IRs for PTC and FTC were computed separately, the IR for PTC was almost 7 times higher than for FTC [0.46 (95% CI: 0.33–

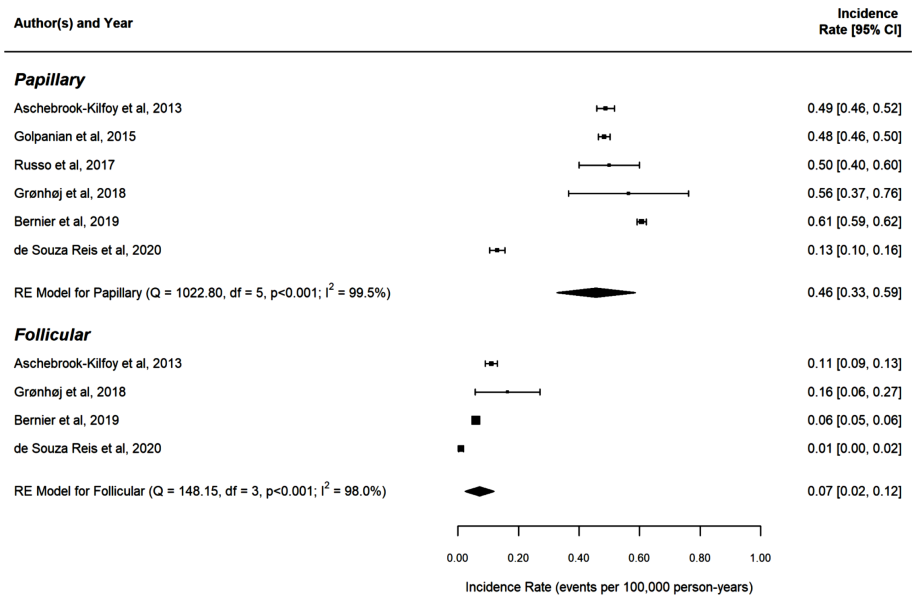

FIGURE 2
Forest plot of the thyroid carcinoma incidence rates, reported in each study (during its "study period") per 100,000 person-years along with their 95% confidence intervals, stratified by thyroid carcinoma types (subgroups). Each square corresponds to the study-specific incidence rate (IR) estimate and its size is proportional to the inverse of the IR variance (ie the narrower the confidence interval, the targer the size of the square). The pooled estimate (centre line of diamond) and its confidence interval (lateral tips of diamond) are shown at the end of each subgroup. RE: Random-effects model (ie the pooled estimate was computed from a linear mixed-effects with a random intercept), Q: the value of Cochran's Q test, which follows a Chi-Square distribution with degrees of freedom (df) equal to the number of studies minus one p: p-value associated to the Q-test I2: the percentage of vanation across studies that is due to heterogeneity rather than chance and it is computed as follows: I2= P 100% x (Q-d)/Q.

0.59) vs. 0.07 (95% CI: 0.02–0.12)], thus confirming the papillary histotype to be the more prevalent also in the pediatric population. It is worth noting that these estimates do not include DTC occurring in children who had been (potentially) exposed to radioactive fallout from nuclear accidents (i.e., Chernobyl or Fukushima power plant accidents), since radiation exposure represents a known risk factor for thyroid cancer and, thus, a clear confounding factor.

Unfortunately, we were not able to obtain more detailed estimates of thyroid cancer incidence according to gender and age groups due to several reasons. First, most of the studies included in the meta-analysis did not report detailed rates by sex for a precise estimate to be made. Second, the age groups examined were highly heterogeneous, thus precluding the possibility of exploring differences within the category of children/adolescents, between younger and older subjects, or between prepubertal children and adolescents. The above issues deserve special attention because of the potential influence of pubertal changes on thyroid cancer incidence in both boys and girls. In this regard, Zhao et al. (41) retrospectively examined cases of thyroid cancer from 2004 to 2017 in patients aged <10 (prepubertal), 10–15 (pubertal) and >15 (postpubertal) years and found that the annual proportion of total cases increased from 3% to 8% for <10-year-old children, from 31% to 40% for 10–15-year-old children, and from 52% to 66% for >15-year-old children (41). It could be argued that age groups as a proxy measure for defining puberty may not reliably reflect the pubertal status of all subjects, especially because of ethnic and environmental disparities in pubertal development (44). Nonetheless, the risk of DTC dramatically increases among postpubertal female and male subjects, and therefore, considering as a *unicum* an age group including either children or subjects with fully completed pubertal development may result in incorrect estimates.

Possible explanations for the observed increased risk of DTC in postpubertal female subjects compared with their male counterparts include mechanisms involving female sex hormones, with estrogen and estrogen receptors (ERs) being the most investigated target of current research. Several *in-vitro and* animal studies have evaluated the influence of sex steroids on the proliferation of thyroid cells, although considerable discrepancies with respect to ER expression patterns in thyroid cancer tissues actually exist (43, 45, 46).

Another potential limitation to a comprehensive data analysis comes from the lack of information on the nutritional iodine status of the populations under examination, with only one study comparing the patterns of DTC with respect to changes in iodine supply at the population level (34). This study showed a clear shift at any age toward a preponderance of PTC over FTC occurring in parallel with iodine nutrition improvement, although the rates of FTC still exceeded those reported in countries with well-established iodine sufficiency (34). These data confirm previous findings in adults showing a higher percentage of the more aggressive FTC in iodine-deficient areas (47) and the clear temporal relationship in many countries between the implementation of iodine prophylaxis programs and a relative increase in the incidence of PTC (48). Even more importantly, iodine deficiency increases the thyroid uptake of radioactive iodine and the proliferation rate of thyroid cells (49). Both the above effects facilitate the occurrence of thyroid cancer after radiation exposure, especially in children because of the

highest sensitivity to radiation in this age category (50, 51). Paradigmatic in this regard is the marked increase in the incidence of thyroid cancer as early as 5 years following the accident at the nuclear power plant at Chernobyl in Ukraine—an iodine-deficient region—in children who were aged 0–5 years at the time of the accident and for whom no timely iodine prophylaxis measures were adopted (49).

The high sensitivity of the thyroid gland to the carcinogenic effects of ionizing radiation during childhood and adolescence is also evidenced by the radiation-related excess risk of second primary thyroid cancer after radiotherapy to the cervical region for a childhood cancer (52–54). Presently available evidence indicates that after a mean dose to the thyroid as low as 0.05 Gy to 0.1 Gy during childhood, a significant thyroid cancer risk is evident within 5 to 10 years of childhood exposure to radiation and remains elevated for potentially many decades (53). Also, the risk of developing a second primary DTC has been reported to be remarkably increased in children receiving alkylating agents in combination with radiation doses up to 20 Gy (53), as well as among survivors of pediatric hematopoietic stem cell transplantation conditioned with chemotherapy alone (55). Of the studies included in our systematic review, only three (9, 21, 22) specifically excluded second primary thyroid tumors from analysis, the remaining either not reporting this information (24–27, 29–32, 34) or admittedly including second primary thyroid tumors (23, 28). A recently published Italian registry-based study showed that thyroid cancer as a second primary tumor was diagnosed more frequently than in the general population, the overall standardized IR being 1.49 (95% CI: 1.42–1.55) but as high as 6.1 (95% CI: 2.9–11.2) or 4.4 (95% CI: 2.2–7.8) after acute lymphoid leukemia and bone cancers, respectively (56). Unfortunately, no data specifically addressing the pediatric population are reported in this large study, which would have been helpful to understand the actual impact of previous cancers (and related therapy) on thyroid cancer occurrence/diagnosis in this age group.

The high between-study heterogeneity should also be acknowledged. This could be partly explained by the characteristics of the total reference population in each included study or data collection methods (e.g., claims databases, electronic medical records, or disease registries).

In conclusion, our data indicate that DTC in the pediatric population is a rare condition, the pooled IRs of the studies included in this meta-analysis being as low as ~0.5 for PTC, which is by far the most common histotype when both sexes and all age groups are considered. The implementation of a prospective international registry on pediatric DTC, as part of the wider European Registries for Rare Endocrine Conditions, has been very recently proposed (57). In addition to providing relevant information on the clinical behavior of this rare disease, which can be helpful in offering patients evermore tailored therapeutic strategies (58), standardization of data collection will be pivotal to fill current gaps and allow an accurate estimation of the real incidence and risk factors of DTC.

Author contributions

MM: Conceptualization, Data curation, Investigation, Validation, Writing – original draft, Writing – review & editing. TA: Data curation, Investigation, Writing – original draft, Writing – review & editing, Validation. SCr: Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. GT: Conceptualization, Supervision, Validation, Writing – review & editing. DC: Data curation, Investigation, Validation, Writing – review & editing. GPe: Data curation, Investigation, Validation, Writing – review & editing. LC: Data curation, Investigation, Validation, Writing – review & editing. MDM: Data curation, Investigation, Validation, Writing – review & editing. GPa: Data curation, Investigation, Validation, Writing – review & editing. AF: Methodology, Validation, Writing – review & editing. FC: Data curation, Investigation, Methodology, Validation, Writing – review & editing. SCa: Conceptualization, Supervision, Validation, Writing – review & editing. MW: Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review & editing, Validation.

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Conflict of interest

The authors declare that no that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1270518/full#supplementary-material

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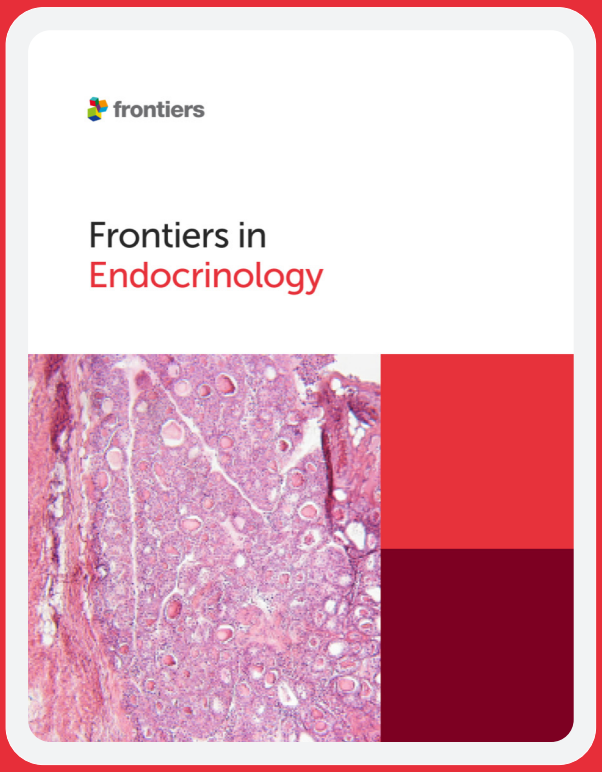

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