

## THYROID DISORDERS IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS IN MUREȘ COUNTY (ROMANIA): A 25 YEARS RETROSPECTIVE STUDY

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### Abstract

**Background:** Thyroid disease in children, adolescents and young adults (TDCA) is dominated by thyroid nodules, toxic multinodular goiter, Graves' disease, autoimmune thyroiditis and malignant thyroid tumors with origin in follicular cell or parafollicular C cells of the thyroid gland. The aim of our study was to evaluate the incidence of the TDCA in the last 25 years in our institution and the pathological characteristics of papillary thyroid carcinoma (PTC), with special emphasis on the comparison of the pathologic features of tumor aggressiveness between pediatrics and adults patients with PTCs.

**Material and methods:** We performed a retrospective, cohort study on 101 cases of TDCAs (patients < 20 years old), registered in the Department of Pathology, Țirgu-Mureș Emergency County Hospital between 1990 and 2014.

**Results:** One hundred and one patients were identified, 90 girls and 11 boys, female to male ratio was 7:1 and mean age at diagnosis was  $17.57 \pm 1.0$  years. A significant increase in the incidence of malignant thyroid tumors of follicular cell origin, was observed between 2004-2014 as compared to the period between 1990-2003 (70.6 *versus* 29.4%). On the other hand, the incidence of the benign thyroid diseases was characterized by a statistically significant decrease in the last decade (66.8% *versus* 33.2%,  $p < 0.001$ ). As we expected, PTC accounted for most of the cases of malignant thyroid tumors of follicular cell origin ( $n=16/17$ , 94.1%). The most common PTC variant was conventional PTC (CPTC) (62.5%). The most common benign thyroid disease was nodular goiter (45.5%), followed by follicular adenoma (19.8%). The autoimmune thyroid diseases were present in 13 cases - Hashimoto thyroiditis 9 cases (8.9%) and Graves' disease 4 cases (4%). The comparison between the pediatric and the adult thyroid cancer patients showed that children had higher rates of larger primary tumors ( $19.38 \pm 9.729$  mm *versus*  $15.77 \pm 0.8265$  mm,  $p=0.005$ ), a higher incidence of multifocality

(43.75% *versus* 29.5%,  $p = 0.002$ ), a more significant extrathyroidal extension (37.5% *versus* 19.8%,  $p= 0.002$ ) and a more important lymph node involvement (25% *versus* 7.7%,  $p= 0.007$ ).

**Conclusion:** The incidence of TDCA has revealed significant changes in our institution over the last 25 years. The incidence of malignant thyroid tumor of follicular cell origin has increased, while the incidence of the benign thyroid disease has significantly decreased over the study period. In our institution, the pediatric thyroid cancer has a more advanced stage and shows a more extensive disease at the time of diagnosis than adulthood thyroid cancer.

**Key words:** thyroid disease, children, papillary thyroid carcinoma, extensive disease

### Introduction

Thyroid disease in children, adolescents and young adults (TDCA) is dominated by thyroid nodules, with a higher malignancy rate compared to adults, toxic multinodular goiter, Graves' disease, autoimmune thyroiditis and malignant thyroid tumors with origin in follicular cell or parafollicular C cells of the thyroid gland [1-4].

Thyroid cancer has become the fifth most common cancer in children aged 0–14 years [5] and the most common cancer in adolescents and young adults [6] with a significant increasing incidence in the last four decades, as reported by many studies around the world [7-11].

Factors attributed to the increased incidence include iodine deficiency, genetic predisposition (RET mutations) and ionizing radiations. The latter represent a proven risk factor for thyroid malignancies as confirmed by the sharp increase in the thyroid cancer after the Chernobyl disaster [12-20]. Many authors have also described the role of cytokines and genes (e.g. VEGF, TGF and EGF) during tumor development [21, 22].

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Papillary thyroid carcinoma (PTC) is the most common histological type (60–97%) observed in childhood patients with both sporadic and radiation-induced thyroid carcinoma [17, 18, 20].

Pediatric thyroid cancer tends to be more advanced at the time of diagnosis and has a higher rate of recurrence than thyroid cancers in seen in adults, nevertheless, pediatric patients have a better prognosis and a significantly lower mortality rates than adult patients [23-26].

The aim of our study was to evaluate the incidence of the TDCA in the last 25 years in our institution and the pathological characteristics of PTC, with special emphasis on the comparison between the pathological features of tumor aggressiveness in pediatric and adult patients with PTC.

## Materials and methods

### Database and cases definition

We performed a 25 years, retrospective, cohort study on 101 cases of TDCA (patients < 20 years old) registered in the Department of Pathology, Tîrgu-Mureş Emergency County Hospital between January 1990 and December 2014.

Clinicopathological data on the study cases were retrieved from database registers and pathological reports. The following variables were included when analysing the incidence and the pathological characteristics of TDCA cases: age at diagnosis, gender, surgical procedure and type of thyroid disease. For the malignant thyroid tumors we evaluated the tumor histological type, size, multifocality (unilateral or bilateral), extrathyroidal extension and lymph node involvement.

The type of the surgical procedure was also recorded: lobectomy with or without isthmectomy, subtotal thyroidectomy, total thyroidectomy and total thyroidectomy with central or lateral neck compartment dissection.

The histopathological types of TDCA included: benign thyroid disorders (nodular goiter, follicular adenoma, Hashimoto thyroiditis and Graves's disease), tumors of uncertain malignant potential and malignant thyroid tumors of follicular cell origin.

The malignant thyroid tumors of follicular cell origin were referred as papillary thyroid carcinomas (PTCs), follicular thyroid carcinomas (FTCs), poorly differentiated thyroid carcinomas (PDTCs) and anaplastic thyroid carcinomas (ATCs). The diagnosis of PTC was exclusively based on nuclear features (Figure 1A): enlargement, overlapping, irregularity of the nuclear contours, grooves, clearing or a ground glass appearance and nuclear pseudoinclusions. Conventional PTC had a characteristic papillary architecture that was pure or admixed with a variable proportion of follicles. Tumors defined as follicular variant of PTC were composed of small to medium sized, irregularly shaped follicles, with characteristic PTC nuclear changes in most of the cells lining these follicles and virtually no papillary structures. The diagnosis of other tumors was made in accordance to the WHO criteria [25].

The 2009 TNM staging system (tumor size, extrathyroidal extension, lymph node metastasis, distant metastasis) was applied for all the cases included in the study [26].

Extrathyroidal extension was defined as tumor penetration through the thyroid capsule into the adjacent tissues, with invasion into the immediate perithyroidal soft tissues or sternothyroid muscle (TNM stage T3 tumors) (Figure 1B) [26].

Multifocality was defined as the presence of two or more isolated/non-contiguous tumor foci in the resected thyroid gland [25].

The lymph node involvement was considered positive if at least one positive lymph node was present in the lymph nodes resected during surgery.

The pathological features of tumor aggressiveness in pediatric patients were compared to a cohort of 608 adults with PTC also diagnosed in our institute in the last 25 years.

In order to analyze the incidence, clinical and pathological features of TDCA, we subdivided the total series in two main groups, according to the time of diagnosis: group one (1990-2003) and group two (after 2004). The cut-off year of 2004 has been chosen in accordance to the introduction of the new WHO classification of Endocrine Tumors [25].

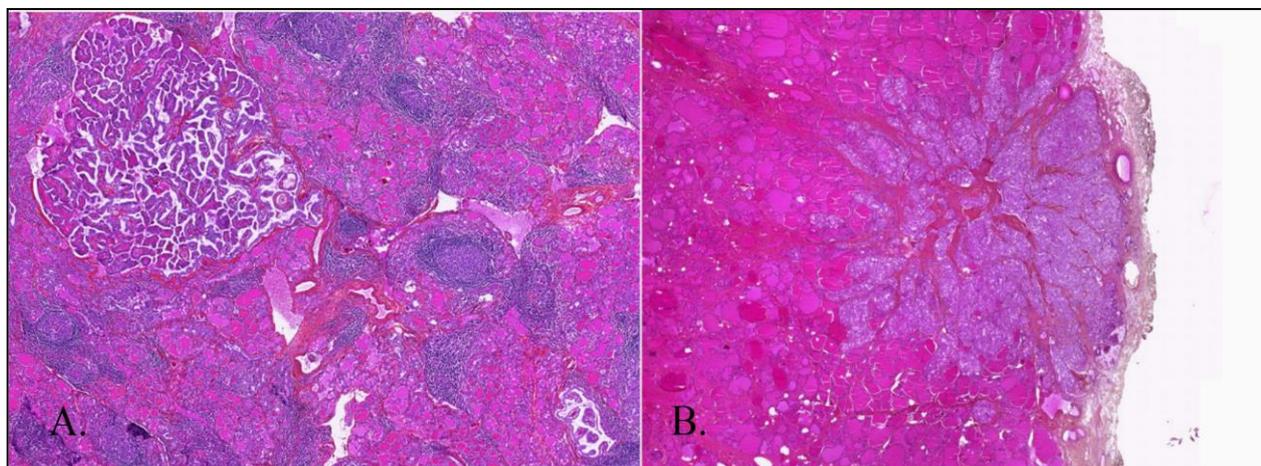


Figure 1: Intrathyroidal versus extrathyroidal papillary thyroid carcinoma: a multifocal, intrathyroidal conventional, papillary thyroid carcinoma case (A); extrathyroidal extension, defined as tumor penetration into the adjacent adipose or muscular tissues (B).

Data analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 20, Chicago, IL, USA). Data were labelled as nominal or quantitative variables. Nominal variables were characterized by means of frequencies. Quantitative variables were tested for normality of distribution using Kolmogorov-Smirnov test and were described by mean ± standard deviation or median and percentiles (25%; 75%), whenever appropriate. The frequencies of nominal variables were compared with a chi-square test. Differences in the mean or median between groups were analyzed using the *t* test and ANOVA test. The level of statistical significance was set at  $p < 0.05$ .

**Results**

From a total of 4890 tumoral and non-tumoral thyroid lesions registered in our department over the last 25 years, 101 (2.1%) were TDCA.

Regarding the surgical procedure, total thyroidectomy, subtotal thyroidectomy, lobectomy and total thyroidectomy with central or lateral neck compartment dissection were

performed in 45 (44.5%), 20 (19.8%), 34 (33.8%) and 2 (1.9%) cases, respectively.

The majority of TDCA cases occurred in females (87.2%), with the female to male ratio of 7:1. The mean age at diagnosis was  $17.57 \pm 1.0$  years-old, ranging from 5 to 19 years-old with no statistically significant difference by gender group.

The incidence of various TDCA is shown in Table 1. A significant increase in the incidence of malignant thyroid tumors of follicular cell origin was observed between 2004-2014 as compared to the period between 1990-2003 (70.6 *versus* 29.4%) On the other hand, the incidence of the benign thyroid diseases was characterized by a statistically significant decrease in the last decade (66.8% *versus* 33.2%,  $p < 0.001$ ) (Table I).

The most common benign thyroid disease was nodular goiter (45.5%), followed by follicular adenoma (19.8%). The autoimmune thyroid diseases were present in 13 cases - Hashimoto thyroiditis 9 cases (8.9%) and Graves' disease 4 cases (4%) (Table I).

Table I. Incidence and histopathological characteristics of 101 TDCAs

Histopathological types of TDCAs	No. of cases Total (%)	No. of cases 1990-2003 (%)	No. of cases 2004-2014 (%)	p
Benign thyroid diseases	79	53 (66.8)	26 (33.2)	<0.001
Nodular Goiter	46 (45.5)			
Follicular adenoma	20 (19.8)			
Hashimoto Thyroiditis	9 (8.9)			
Graves' Disease	4 (4)			
Malignant thyroid tumors with follicular cells origin	17 (16.8)	5 (29.4)	12 (70.6)	<0.001
Papillary thyroid carcinoma	16			
Poorly differentiated thyroid carcinoma	1			
Thyroid tumors of uncertain malignant potential	5 (5)	1(20)	4 (80)	<0.001
<b>Total TDCA</b>	<b>101</b>	<b>59 (31.7)</b>	<b>42 (68.3)</b>	

As we expected, PTC accounted for most of the cases of malignant thyroid tumors of follicular cell origin ( $n=16/17$ , 94.1%). The most common PTC variant was conventional PTC (CPTC) (62.5%), followed by follicular variant of PTC (FVPTC) (37.5%). The incidence and clinicopathologic characteristics of different histological variants of PTC cases are summarized in Table II. Despite the smaller mean tumor size of CPTC versus FVPTC cases ( $15.77 \pm 0.8265$  mm versus  $19.02 \pm 0.8622$  mm,  $p=0.02$ ), the other pathological features of tumor aggressiveness were more prevalent among CPTC: extrathyroidal extension (100% versus 0%,  $p < 0.001$ ), lymph node involvement (100%

versus 0%,  $p < 0.001$ ) and multifocality (85.7% versus 14.3,  $p < 0.001$ ).

The comparison between the pediatric and the adult thyroid cancer patients showed that children had higher rates of large primary tumors ( $19.38 \pm 9.729$  *versus*  $15.77 \pm 0.8265$ ,  $p=0.005$ ), a higher incidence of multifocality (43.75% *versus* 29.5%,  $p = 0.002$ ), a more significant extrathyroidal extension (37.5% *versus* 19.8%,  $p = 0.002$ ) and a more important lymph node involvement (25% versus 7.7%,  $p = 0.007$ ) as compared to adults (Table III).

Table II. Clinicopathologic characteristics of classical/conventional papillary thyroid carcinoma cases and follicular variant.

Factors	CPTC (%)	FVPTC (%)	p
Total	10 (62.5)	6 (37.5)	
Mean age (years-old)	17.8 ± 1.8	17.2 ± 2.2	0.477
Female	8 (80)	4 (66.6)	0.402
Tumor size (mean, mm)	15.77± 0.8265	19.02±0.8622	0.02
≤ 10	1 (10)	1 (16.7)	0.028
11-20	5(50)	3 (50)	
21-40	3 (30)	2 (33.3)	
>40	1 (10)	0 (0)	
pT stage <sup>a</sup>			<0.001
pT1a	1 (10)	1 (16.7)	
pT1b	2 (20)	4 (66.6)	
pT2	1 (10)	1 (16.7)	
pT3	6 (60)	0 (0)	
Lymph node involvement	4 (100)	0 (0)	<0.001
Multifocality	6 (85.7)	1 (14.3)	0.001
Extrathyroid extension	6 (100)	0 (0)	<0.001

Legend: papillary thyroid carcinoma- PTC, conventional PTC-CPTC, follicular variant of PTC – FVPTC

<sup>a</sup> - TNM Classification of malignant tumors. 7th Edition ed. Springer (2009).

Table III. Pathological characteristics in pediatric and adult patients with PTC.

Factors	PTC in pediatric patients (%)	PTC in adult patients (%)
Total	16	608
Tumor size (mean, mm)	19.38± 9.729	15.77± 0.8265
p		0.005
Lymph node involvement	4 (25)	46 (7.7)
p		0.007
Multifocality	7 (43.75)	179 (29.5)
p		0.002
Extrathyroid extension	6 (37.5)	120 (19.8)
p		0.002

Legend: papillary thyroid carcinoma- PTC

## Discussions

Our study revealed important changes in the incidence of various TDCA in our institution over the last 25 years (1990-2014). The incidence of malignant thyroid tumors of follicular cell origin was characterized by a statistically significant increasing trend after the year 2004 as compared to the previous period in our institution. Similar results have been reported in many countries around the world, and especially in countries from Europe and North America [7-10].

Many factors can be attributed to the increasing incidence of malignant thyroid tumors. Some well-known risk factors for follicular-derived thyroid carcinomas, like the ionizing radiations (radiotherapy, fallouts, diagnostic X-rays), lifestyle habits (overweight, low iodine intake), some environmental pollutants (dioxins, polychlorinated biphenyls etc.) are also present in our region.

The thyroid gland in children is most sensitive to ionizing radiations [12], which explains the increasing proportion of thyroid cancer diagnosed in older children who underwent radiation therapy for their first primary tumor [13-15,29,30].

Taylor A.J *et al.* showed that in a cohort of 17,980 patients, followed for an average of 17.4 years, eighty-eight percent of thyroid carcinomas were found in patients undergoing radiotherapy for primary pathologies in the cervical region. The risk of thyroid carcinoma was higher in patients treated for Hodgkin's disease (RR 3.3—IC: 1.1–10.1) and non-Hodgkin lymphoma (RR 3.4—IC: 1.1–10.7) [16].

Our region was affected in April 1986 by the Chernobyl nuclear power plant disaster, but further research is still needed to prove the involvement of the radioactive particles in the initiation and progression of TDCA in our country.

Exposure to ionizing radiation during and after the Chernobyl accident increased the risk for the development of well-differentiated thyroid cancer in those exposed in childhood and adolescence, as demonstrated in many studies [16-19].

In 2006, Cardis *et al.* indicated that the number of thyroid cancer cases in children aged between 0 to 14 years, started to increase 4–5 years after the Chernobyl disaster and reached a peak at about 10 years, while for those aged 15 to 18 years, the peak was reached 15 years after exposure [18].

The incidence of the benign thyroid diseases (surgically treated) has significantly decreased in the last decade in our institution. We found that the most common benign thyroid disease was nodular goiter, followed by follicular adenoma. A possible explanation for this result is the fact that besides the mandatory use of iodized salt in our country since 2002, our region is still mildly iodine-deficient and multinodular goiter is still relatively frequent. A re-evaluation of the national program for the prevention and control of iodine deficiency in our country is mandatory.

In our study, the incidence of malignant thyroid carcinoma was 16.8% and the PTC was diagnosed in 94.1% cases, similar to the incidence from other reports [1-3]. CPTC was the most common variant of PTC in our study

(46.9%), followed by FVPTC (45.6%), in accordance with other published studies [31].

Regarding the histological variant, many studies have shown that follicular variant of PTC is associated with a more favourable prognosis compared to the conventional PTC [32, 33].

In accordance to previous results, in our study, the conventional PTC revealed a higher rate of lymph node involvement, extrathyroidal extension, multifocality and more prevalent TNM T3 tumor stage, compared to the follicular variant.

Based on the data reported in scientific literature, regarding that pediatric thyroid cancer tends to be more advanced at the time of diagnosis and has a higher rate of recurrence than adulthood thyroid cancer [23-26], we have analysed the prevalence of the pathologic features of tumor aggressiveness between these two groups of patients.

In our study, children with PTC presented with more extensive disease as compared to adults with PTC. Lymph node involvement at diagnosis was observed in 25% of children compared to 7.7% of adults. Similar studies have shown that the lymph node involvement at diagnosis is seen in 40% to 90% of children compared to 10% to 50% of adults [23-25].

The prevalence of extrathyroidal extension in pediatric patients with PTC was 37.5%, significantly higher than that in adult PTC patients where it was only 19.8%. Extrathyroid extension is an independent factor predicting a poor prognosis, an important risk factor used in TNM based staging system [4, 28].

Multifocal disease was more common in children than adults and is seen in about 43.75% of childhood PTC cases. In a recent retrospective review of 150 pediatric patients, Lee YA *et al.* demonstrated that the recurrence was higher in pediatric patients with multifocal papillary thyroid cancer than adult patients [26]. Other studies have shown that multifocality was an independent risk factor for PTC recurrence, metastasis or disease-specific mortality [23, 33, 34].

An important limitation to our study is the lack of data regarding the mortality and/or disease-specific survival rates in pediatric patients with PTC. However, we succeeded to determine the incidence and the pathological characteristics in our population over a period of 25 years.

## Conclusions

In summary, the incidence of TDCA has revealed significant changes in our institution over the last 25 years. The incidence of malignant thyroid tumors of follicular cell origin has increased, while the incidence of the benign thyroid disease has significantly decreased over the period of the study. In our study, the follicular variant of PTC is associated with more favourable pathological characteristics as compared to conventional PTCs. In our institution, the pediatric thyroid cancer has a more advanced stage and shows a more extensive disease at the time of diagnosis than adulthood thyroid cancer.

### Conflicts in interest

The authors declare that they have no conflicts of interest.

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