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The clinical and histopathological characteristics of thyroid gland diseases in adolescents requiring surgical treatment: a ten-year follow-up study

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ABSTRACT

The present research aimed to determine the clinical and pathohistological characteristics of thyroid gland diseases in adolescents who were previously surgically treated at the Endocrine Surgery Center of the University Medical Center of Serbia from 01/01/2001 to 01/01/2011. The study covered 170 patients of both sexes from the population of adolescents (aged 16 to 20 years) with various malignant and benign thyroid gland diseases. The data for this study were extracted from the medical histories of patients and the electronic database of the Center for Endocrine Surgery. Detailed data analysis included diagnosis, symptomatology, surgical intervention type, and disease stage. The following thyroid status parameters were analyzed from preoperative data: thyroxine (T4), thyroxine free fraction (FT4), triiodothyronine (T3), triiodothyronine free fraction (FT3), and thyroid stimulating hormone (TSH). In addition, the pathohistological features of diagnosed thyroid diseases were also determined, with a special focus on the presence of well-differentiated cancers. Papillary carcinomas were the most common of well-differentiated cancers in adolescents over the ten-year follow-up period. Based on the assessed data, total thyroidectomy was the most commonly used type of surgical intervention in these patients. The conducted research provides essential information related to both the biological characteristics and diagnostics of these cancers and their surgical treatment in such a sensitive population. Moreover, research showed that the clinical presentation of thyroid cancer in adolescents is almost identical to that in adults.

Keywords: thyroid gland, surgical treatment, pathohistology, adolescents

INTRODUCTION

Thyroid carcinomas are a rare disease in adolescents and account for 1.5–3% of all cancers in the United States and Europe.[1] Literature data has shown that the incidence of thyroid nodules in the prepubertal period is 1–1.5%, while this prevalence can reach 13% in the postpubertal

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period.[1,2] Furthermore, in the USA, 350 people over the age of 20 are diagnosed with thyroid cancer annually, while in Brazil, the thyroid cancer incidence is 2% of all cancers in the pediatric population.[1-3] Considering the global rise in thyroid cancer incidence in adolescents, a substantial increase in the number of patients with this type of disease can be expected in the coming decades.[4] The occurrence of thyroid cancer in early childhood is very rare. However, there are isolated cases in the literature describing differentiated thyroid cancers in newborns and infants aged one year or more.[5,6]

A significant difference in the occurrence of these forms of malignancy between sexes has been reported – a much higher prevalence in women than in men. These differences relate to the postpubertal period, while the distribution between sexes in the prepubertal period is equal.[7,8]

Among the main etiological factors that lead to the occurrence of thyroid cancer in adolescents is ionizing radiation. This applies to children exposed to head and neck radiation in the past due to treatments of various benign and malignant conditions, with the risk of thyroid cancer being higher in patients treated for Hodgkin's disease.[9,10]

The most common symptoms of thyroid cancer in adolescents are a neck nodule, hoarseness, and dyspnea, requiring further diagnosis.[11] Determining the presence of thyroid nodules in adolescents is an alarm signal for the possible malignancy of the observed changes, which occurs in 10–50% of cases, ie, much more often than in adulthood.[6] The incidence of thyroid cancer is usually higher in patients younger than 20 years compared to patients aged between 20 and 50.[6] Studies have shown that cancers larger than 4 cm in diameter are present in 36% of the young population. This percentage is lower in adults and amounts to 15%, while cancers smaller than 1 cm in diameter are found in 9% of young people.[6]

Histopathological characteristics of malignant nodules show that about 95% of them are diagnosed in the form of papillary cancer, while the remaining 5% have a follicular form. Medullary, anaplastic, and poorly differentiated thyroid cancers are rarely diagnosed in the pediatric population.[6]

The golden standard in diagnosing thyroid cancer is the pathohistological tissue examination. The most common problem in postoperative diagnosis is lesions of follicular origin (follicular adenomas, follicular carcinomas, and follicular variants of papillary carcinoma), which do not differ clearly due to overlapping morphological characteristics. The only difference between follicular carcinomas and adenomas is either capsular or vascular invasion, a sign of metastatic tumor characteristics.[12,13] Surgical treatment is the foundation of the primary therapy for well-differentiated thyroid tumors since it verifies the diagnosis and removes thyroid tumor tissue.[13]

However, surgeries for malignant and benign thyroid gland diseases in adolescents are rare, and there is insufficient data on this topic in the literature. Accordingly, this study aimed to present important information on determining clinical and pathohistological characteristics of thyroid gland diseases in surgically treated adolescents during a ten-year follow-up period.

METHODS

Study population

This is a retrospective cohort study that was carried out between 01/01/2001 and 01/01/2011. The study covered 170 patients from the population of adolescents aged 16 to 20 years with various malignant and benign thyroid gland diseases. All patients were surgically treated at the Center for Endocrine Surgery of the Clinic of Endocrinology, Diabetes, and Metabolic Diseases of the University Clinical Center of Serbia from 01/01/2001 to 01/01/2011. The data for this study were extracted from the medical histories of included patients and the electronic database of the

Center for Endocrine Surgery. Based on the clinical examination, patients were preoperatively graded by the Tumour, node and metastasis (TNM) classification. All patients were presented to the thyroid disease counseling board to decide on the optimal mode of surgical treatment, as previously described.[14]

Ethics statement

The study was conducted following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The Ethics Committee of the University Clinical Center of Serbia has provided the necessary permissions for conducting this research (No 301/3).

Patient data are sorted and analyzed by:

1. age category: a) ages 16–18, b) ages 19 and 20
2. sex: a) male (n = 85), b) female (n = 85)

Study inclusion criteria:

1. patients of both sexes from the population of adolescents aged 16 to 20 years
2. patients with the following malignant and benign thyroid gland diseases (nodular goiter, Graves' disease, polynodular goiter, multiple endocrine neoplasia (MEN) 2a, papillary carcinoma, follicular carcinoma, medullary carcinoma, toxic adenoma, cyst)
3. absence of any other comorbidity
4. patients who were surgically treated at the Center for Endocrine Surgery of the Clinical Center of Serbia in the mentioned period.

Study exclusion criteria:

1. incomplete or otherwise irrelevant data
2. presence of any other comorbidity

The following patient data were analyzed:

1. demographic characteristics
2. diagnosis and symptoms
3. biochemical parameters of thyroidal function: triiodothyronine free fraction (FT3), thyroxine free fraction (FT4), thyroxine (T4), triiodothyronine (T3) and thyroid stimulating hormone (TSH)
4. cytological findings
5. surgical intervention type
6. disease stage
7. definite pathohistological findings

Study sample calculation

The calculation of the total sample is based on the results of a previously published retrospective study in which the pathohistological characteristics of papillary thyroid carcinomas in adolescents up to 18 years of age were determined.[15] A t-test for the bound sample was used for the calculation twice, assuming an alpha error of 0.05 and a study power of 0.8 (beta error 0.2) and using an appropriate computer program.[16] Considering the results of this study and the possibility of excluding a certain amount of data from the final analysis, it was decided that the total study sample should comprise a minimum of 150 patients.

Statistical analyses

The collected data were recorded in an Excell database, while the statistical program SPSS 20.0 for Windows (SPSS, Chicago, IL, USA) was used for the statistical processing of the results.

Shapiro Wilks or Kolmogor's Smirnov tests was used for continuous numerical variables after testing the normality of data distribution. The t-test was used to compare numerical features. Categorical variables were represented as numbers (n) and frequencies (%). The significance of differences was tested by the $\chi 2$ test, ie, parametric and nonparametric tests. The results were presented textually, tabularly, and graphically as the mean +/- standard deviation, ie, medians and interquartile ranges of volume differences. Significance was defined as $p \leq 0.05$ and a 95% confidence interval.

RESULTS

Demographic characteristics

The present study included a total of 170 patients, whose characteristics are presented in Table 1. There were 80% of females and 20% of males. The majority of the study sample (65.29%) were 19–20 years of age, while 34.71% were 16–18 years of age. The distribution of ages is presented in Figure 1.

Table 1 Demographic characteristics

Characteristic	N (%)
Gender	
Male	34 (20.00%)
Female	136 (80.00%)
Age (years)	
Average (SD)	16.84 (2.82%)
Age (categories)	
16–18 years of age	59 (34.71%)
19–20 years of age	111 (65.29%)

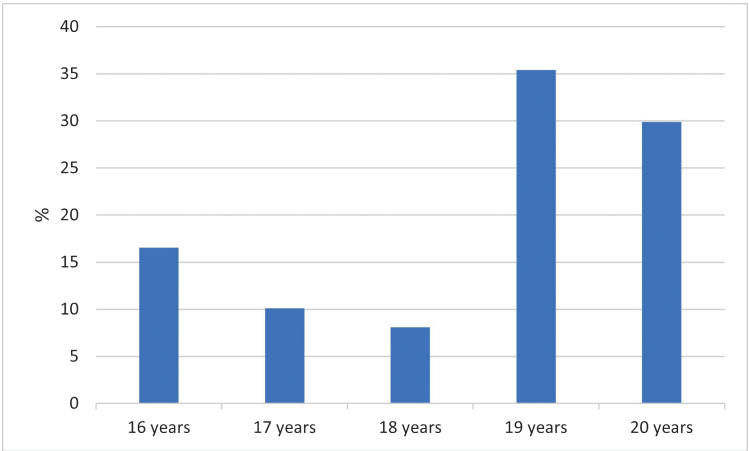

Fig. 1 Age distribution of patients

Diagnosis

Diagnoses of the examined patients at the moment of admission are presented in Table 2. The most common diagnosis was nodular goiter, found in 62 patients (37.2%). It is followed by diagnoses of Graves' disease and struma polynodosa. There was no data about the diagnosis for 12 patients (7.2%).

Table 2 Patients diagnosis at admission

Diagnosis	**N (%)**
Struma nodosa	62 (37.20%)
Grave's disease	40 (23.50%)
Struma polynodosa	21 (12.40%)
Multiple endocrine neoplasia (MEN) 2A	6 (3.60%)
Toxic adenoma	5 (3.00%)
Cysts	3 (1.80%)
Hyperthyroidism	3 (1.80%)
Ca papillare	3 (1.80%)
Lymphadenopathy	2 (1.20%)
Lymph nodes metastasis	2 (1.20%)
Malignant neoplasm	1 (0.60%)
Dermoid cysts	1 (0.60%)
No data	12 (7.20%)

Ca papillare: carcinoma papillare

Symptoms

The most common symptoms of the investigated patients are presented in Table 3. The majority of patients were asymptomatic (80%). Patients who expressed symptoms reported thyrotoxic disturbances (5.3%) and difficulty breathing and swallowing (2.9%). Mechanical disorders were noticed in 4 patients (2.4%), lymphadenopathy and fatigue in 2 patients (1.18%), while all other symptoms were reported in one patient.

Table 3 Symptoms

Symptoms	**N (%)**
Asymptomatic	136 (80.00%)
Thyrotoxic disturbances	9 (5.28%)
Difficulty breathing and swallowing	5 (2.93%)
Mechanical disorders	4 (2.35%)
Fatigue	2 (1.18%)
Lymphadenopathy	2 (1.18%)
Palpitations	1 (0.59%)
Palpitations, anxiety, stifling	1 (0.59%)

Content leakage	1 (0.59%)
Stifling, sweating, tremor, anxiety	1 (0.59%)
Feeling of tightness in the neck	1 (0.59%)
Feeling of a foreign body when swallowing	1 (0.59%)
Pain and difficulty swelling	1 (0.59%)
Palpitations, fatigue	1 (0.59%)
Difficulty swallowing	1 (0.59%)
Weakness, insomnia, tachycardia, anxiety	1 (0.59%)
No data	2 (1.18%)

Biochemical parameters of thyroidal function

Biochemical parameters of the thyroidal function are presented in Table 4. The mean value of T4 was 98.21 ± 41.81, while FT4 was 15.38 ± 7.65. Oppositely, the ratio of T3 and FT3 was more favorable (5.00 ± 11.45 vs. 4.0 ± 2.32), while the mean value of TSH was 1.33 ± 1.80.

Table 4 Biochemical parameters of thyroidal function

Parameter (ref value)	Mean	SD
T4 (66–181 nmol/L)	98.21	41.81
FT4 (12–22 pmol/L)	15.38	7.65
T3 (1.3–3.1 nmol/L)	5.00	11.45
FT3 (3.1–6.8 pmol/L)	4.01	2.32
TSH (0.27–4.2 μIU/mL)	1.33	1.80

FT3: triiodothyronine free fraction
FT4: thyroxine free fraction
T4: thyroxine
T3: triiodothyronine
TSH: thyroid stimulating hormone

Cytological findings

Figure 2 shows specific cytological findings of the examined patients. The most common cytological finding was a follicular lesion observed in 28 patients (16.5%) and a benign cytological finding in 26 patients (15.3%). Other cytological changes were sporadic in 1–3 patients. However, all patients had specific cytological changes, while only one had a normal finding.

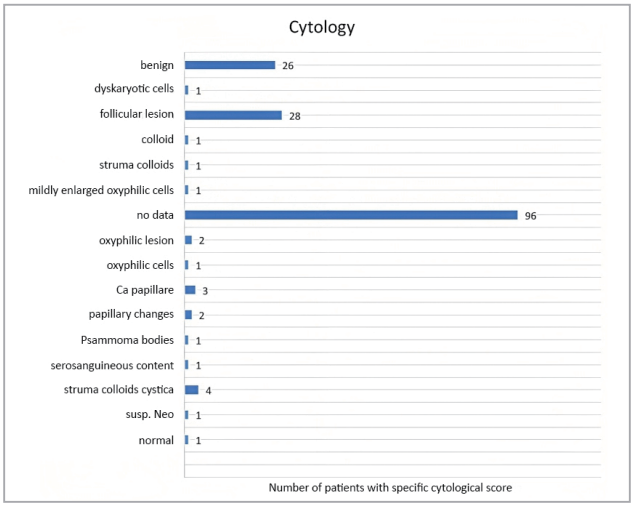

Fig. 2 Prevalence of certain cytological changes among the examined patients
Ca papillare: carcinoma papillare
susp. Neo: suspected neoplasia

Surgical Intervention Type

Table 5 presents the different modes of surgical treatment of the examined patients. The majority of patients, 70 (41.17%), underwent total thyroidectomy or thyroidectomy combined with another procedure or hemithyroidectomy. The second most common approach was lobectomy of various types, while a central dissection was performed in fewer patients.

Table 5 Applied surgical interventions on investigated patients

Surgical intervention	N (%)
Thyroidectomy	91 (53.67%)
Hemithyroidectomy	23 (13.50%)
Dissection	2 (1.20%)
Extirpation	6 (3.60%)
Lobectomy	46 (27.30%)

Stage of the disease

Table 6 shows the classification of diseases by stages and the representation of patients in a particular disease stage. The most frequent stage was T2NxMx, found in 13 patients (7.64%), followed by T2N0M0, found in 8 patients (4.71%) and T1NxMx, found in 6 patients (3.52%).

Table 6 The percentage of a certain stage of the disease

Stage of the disease	N (%)
T1N0M0	3 (1.76%)
T1N0Mx	3 (1.76%)
T1N1aM0	1 (0.59%)

T1N1aMx	1 (0.59%)
T1N1Mx	1 (0.59%)
T1NxMx	6 (3.52%)
T2N0M0	8 (4.71%)
T2N0Mx	3 (1.76%)
T2N1aMx	3 (1.76%)
T2N1bMx	3 (1.76%)
T2NxM0	1 (0.59%)
T2NxMx	13 (7.64%)
T3N1aMx	1 (0.59%)
T3NxMx	2 (1.18%)
T4N1bM0	1 (0.59%)
T4N1bMx	4 (2.35%)
TxN1aMx	1 (0.59%)
TxN1bMx	1 (0.59%)

Definitive pathohistological findings

Table 7 presents the definitive pathohistological findings of the patients. The most common pathohistological finding was strumae diagnosed in 59 patients (34.80%), followed by carcinoma papillare in 51 patients (29.6%) and adenoma in 48 patients (28.28%).

Table 7 Definite pathohistological findings

PH	**N (%)**
Adenoma	48 (28.28%)
Ca medullare	6 (3.60%)
Ca papillare	51 (29.60%)
Cysts	4 (2.40%)
Strumae	59 (34.80%)
Hashimoto thyroiditis	2 (1.20%)

PH: pathohistological findings
Ca medullare: carcinoma medullare
Ca papillare: carcinoma papillare

DISCUSSION

Considering that surgical treatment of thyroid gland diseases in adolescents is not common, the present research aimed to provide important information on determining clinical and pathohistological characteristics of these diseases in such a sensitive population.

Due to their nature and significance, thyroid cancers should be given special attention. Unlike for the adult population, whose characteristics of thyroid cancers are well-documented, literature

sources related to the young population are still limited.[17,18] So far, it has been known that papillary carcinomas are the most frequent in the younger population, with predominance in females in which they are found as a solid or cystic formation.[19]

This retrospective study showed that, among all well-differentiated cancers, only papillary carcinoma was found in adolescents during the follow-up period. These findings pointed out that, same as in adults, papillary carcinoma is convincingly the most represented tumor in adolescents.[18] This knowledge might be of great importance in diagnostic and predictive terms. Our research results are in line with the literature and empirical data obtained from previously conducted studies, showing a significantly higher incidence of this carcinoma in female adolescents (approximately 80% of the study sample).[20-22]

Recent research has shown an increased incidence of well-differentiated thyroid cancers in most countries, raising concern about this disease's clinical and epidemiological severity.[21] Nevertheless, there are still no relevant analyzes of the incidence of thyroid cancer or metastasis to this gland in the countries of Southeastern Europe. A retrospective study conducted at the Center for Endocrine Surgery of the Clinical Center of Serbia from 1995 to 2015 showed that 3.344 patients subjected to thyroidectomy had thyroid malignancy.[22] Although the ten-year survival of these cancers is more than 90%, the outcome is lethal in 5 to 10% of cases.[23] Metastases occur in about half of the patients, with lymph node metastases indicating a good prognosis in adolescents compared to adults.[24]

Well-differentiated thyroid carcinomas are most often found in the form of slow-growing, solid, and irregular nodules. Although the disease usually appears subclinical, regional lymphadenopathy may occur. Clinical signs such as hoarseness, dyspnea, and dysphagia indicate more severe forms of cancer. While a significant number of patients have no functional disorders, some cases of thyrotoxicosis are documented.[25]

The current study's findings indicate that the most common diagnosis of our study population was nodular goiter, indicating the importance of the timely performance of further diagnostic tests in these patients. In addition, most patients did not have symptoms (approximately 80%), but some experienced dyspnea and dysphagia, which is in line with the abovementioned literature data.[25] These data are also significant and suggest that the absence of symptoms in a large percentage of cases may be associated with the presence of thyroid disease.

Although ultrasound and scintigraphy are the key diagnostic tools, a physical examination is still an irreplaceable diagnostic procedure that reveals the presence of a thyroid nodule or enlarged lymph nodes.[26] As for the physical examination of our patients, it seems that the obtained data are entirely in line with the data from other papers and textbooks since the clinical inspection revealed a solitary nodule or diffuse goiter in most cases.[19,26]

These findings are valuable, considering that all previously conducted studies included the adult population.[19,26] Moreover, to the best of our knowledge, here we showed for the first time that the clinical presentation of cancer in adolescents is almost identical to that found in adults.

On the other hand, after analyzing the hormone status of our patients, it was observed that the average value of all examined hormones was within limits, except for T3, which was slightly elevated. These data correlate with previous results and again emphasize the importance of further diagnostic tests if the biochemical indicators of thyroid function are unchanged. In addition, the fact that the most significant percentage of these patients were asymptomatic is equally dangerous and important, as this strongly aggravates treatment and increases the risk of complications. This result is significant because it shows that severe thyroid gland diseases in adolescents can have an asymptomatic character, in contrast to adults.

We also noticed that according to the TNM classification, the study sample is highly dispersed. All disease stages were evenly distributed with below 2%, except for the T2NxMx stage, which

was represented by 7.64%.

Consensus on the scope of surgery in patients with thyroid cancer has not been reached over the past three decades.[27,28] This primarily refers to cases when the tumor tissue is less than 100 mm in size, the thyroid capsule is not affected, and there is no cervical lymph node disease. In these terms, hemithyroidectomy, total thyroidectomy, or total thyroidectomy with prophylactic central lymph node dissection are most often used as operative solutions.[29]

The Center for Endocrine Surgery of the Clinical Center of Serbia data show that preoperatively verified or suspected thyroid cancer treatment requires an individual approach, including local findings, age, presence of local lymph node disease, and distant metastases. Therefore, most specialists consider total thyroidectomy as an intervention of choice for treating these cancers. On the other hand, treatment with L-thyroxine and total thyroidectomy after three months is recommended when surgeries smaller than total thyroidectomy are required and in the cases of an unexpected ex tempore histological finding appearance.[22,29] Total thyroidectomy of thyroid cancers is the procedure of choice due to the low risk of specific postoperative complications such as hypoparathyroidism and paralysis of the lower laryngeal nerve. Additionally, this surgery provides much more efficient monitoring of patients using radioactive iodine 131 scintigraphy and thyroglobulin measurement to detect cancer recurrence.[29,30]

Our study indicates that total thyroidectomy was the most used type of surgical intervention in adolescents in the ten-year follow-up period. This result entirely correlates with all literature data and empirical suggestions of the abovementioned Center. Based on these findings, it can be noted that the surgical method is the golden standard for all thyroid diseases presented in our research.[31]

This study's primary limitation is its retrospective design, which made it impossible to obtain accurate information about thyroid cancer incidence. However, this is one of the most extensive studies investigating this topic, and the results obtained from our Center can be of great clinical significance.

CONCLUSIONS

The most important results of this ten-year follow-up retrospective study showed that papillary carcinoma is the only type of well-differentiated tumor presented in adolescents. In addition, the novelty of this research is that, for the first time in this area, we have shown that the clinical presentation of cancer in adolescents is almost identical to that in adults. Finally, in the follow-up period, total thyroidectomy was the most frequently used type of surgical intervention in adolescents. Knowledge of all these data can be of great importance in diagnostic and predictive terms. Conducting a large multicenter study is necessary to verify and make the data of this research more uniform.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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