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COURSE OF PAPILLARY THYROID CARCINOMA DIAGNOSED IN CHILDHOOD AND ADOLESCENCE AND FOLLOWED THROUGH ADULTHOOD: EXPERIENCE FROM A TERTIARY REFERRAL CENTER*

ÇOCUKLUK VE ADÖLESAN DÖNEMDE TANI KONULAN ERİŞKİNLİK DÖNEMİ BOYUNCA TAKİP EDİLEN PAPİLLER TİROİD KARSİNOMUNUN SEYRİ: BİR ÜÇÜNCÜ BASAMAK MERKEZ DENEYİMİ*

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ABSTRACT

Objective: Differentiated thyroid cancer accounts for 1.5% of all pediatric malignancies. Papillary thyroid cancer (PTC) is the most common subtype and is associated with more advanced disease at diagnosis compared to adults. This study aimed to identify long-term outcomes of pediatric PTC.

Material and Method: Records of 30 patients with PTC diagnosed in childhood and adolescence and followed up at the Istanbul Faculty of Medicine were reviewed retrospectively.

Result: The mean age of 30 patients (21 females, 9 males) at diagnosis was 14.7±2.3 years. The mean duration of follow-up was 10.6±3.8 years. The patients underwent total thyroidectomy

ÖZET

Amaç: Diferansiye tiroid kanseri, tüm pediatrik malignitelerin %1,5'ini oluşturur. Papiller tiroid kanseri (PTK) en sık görülen alt tiptir ve tanı anında hastalık evresi erişkinlere kıyasla daha ileridir. Bu çalışmanın amacı, pediatrik PTK'nin uzun vadeli sonuçlarını değerlendirmekti.

Gereç ve Yöntem: İstanbul Tıp Fakültesi'nde takip edilen çocukluk ve adölesan döneminde PTK tanısı konulan 30 hastanın retrospektif olarak verileri incelendi.

Bulgular: Otuz hastanın (21 kadın, 9 erkek) tanı anındaki ortalama yaşı 14,7±2,3 idi. Ortalama takip süresi 10,6±3,8 yıldı. Dokuz hastaya total tiroidektomi, dokuz hastaya santral lenf nodu di-

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(n=9), total thyroidectomy with central lymph node dissection (n=9), or total thyroidectomy with central and lateral lymph node dissection (n=12). The mean tumor diameter was 1.6±1.5 cm and was microcarcinoma in 12 of the patients. There were five patients with T2 and two patients with T3 disease. At diagnosis, half of the patients had lymph node metastasis to the neck or upper mediastinum (N1a=5, N1b=10), and two also had lung metastasis. Post-operative radioactive iodine (RAI) treatment was administered to 22 patients, the median cumulative dose was 150 mCi (range 50 to 1100)]. Sixteen patients had excellent responses following single (n=13) or multiple (2 for persistent and 1 for recurring disease after 8.3 years) RAI administrations. The remaining three patients had structural incomplete and three had indeterminate responses.

Conclusion: Although PTC presented at a more advanced stage in childhood and adolescence, the response to treatment was fairly good with appropriate management.

Keywords: Papillary thyroid cancer, thyroid, pediatric, radioactive iodine

seksiyonu ile total tiroidektomi, 12 hastaya ise santral ve lateral lenf nodu diseksiyonu ile total tiroidektomi uygulandı. Ortalama tümör çapı 1,6±1,5 cm idi ve 12 hastada mikrokarsinom saptandı. T2 hastalığı olan beş hasta ve T3 hastalığı olan iki hasta vardı. Tanı sırasında hastaların yarısında boyun veya üst mediastende lenf nodu metastazı (N1a=5, N1b=10), iki hastada da ayrıca akciğer metastazı vardı. Ameliyat sonrası 22 hastaya radyoaktif iyot (RAI) tedavisi uygulandı, ortanca kümülatif doz 150 mCi (aralık 50-1100) idi. Hastaların 13'ü tekli doz, 3'ü (2 hasta persistan hastalık, 1 hasta 8,3 yıl sonra gelişen nüks hastalık nedeniyle) çoklu doz RAI uygulamasının ardından mükemmel yanıt verdi. Kalan üç hastada yapısal inkomplet ve üç hastada indetermine yanıt alındı.

Sonuç: PTK çocukluk ve ergenlik döneminde daha ileri evrede ortaya çıksa da uygun hastalık yönetimiyle tedaviye yanıt oldukça iyiydi.

Anahtar Kelimeler: Papiller tiroid kanseri, tiroid, pediatrik, radyoaktif iyot

INTRODUCTION

Thyroid cancer is an uncommon malignancy in childhood and adolescence; however, it is the most common endocrine cancer in this age group (1). Between 1973 and 2013, the annual incidence rate of pediatric thyroid cancer was reported as 0.6/100 000, but it is increasing worldwide (2,3). The most common type of thyroid cancer is papillary thyroid cancer (PTC) which accounts for approximately 86.0% of pediatric thyroid malignancy. Follicular thyroid cancer and medullary thyroid cancer constitute 8-9.0% and 4.0% of the remaining cases, respectively (2). Exposure to radiation increases thyroid cancer risk. Although the majority of thyroid cancer in children is sporadic, having a family history is one of the most important risk factors for the development of thyroid cancer. Syndromes such as familial adenomatous polyposis, PTEN (phosphatase and tensin homolog) hamartoma tumor syndrome, Carney complex type 1, McCune-Albright, multiple endocrine neoplasia type 2 A, Peutz-Jeghers, DICER1, and Werner syndrome are associated with non-medullary thyroid cancer (4,5).

At the time of diagnosis, children with PTC tend to present with more advanced disease and have larger tumors compared to adults. Regional lymph nodes and distant metastases are more common. The lung is the most common distant metastasis site of PTC (6,7). Therefore, all patients with PTC should be evaluated by a comprehensive neck USG preoperatively, and a fine-needle aspiration biopsy should be performed if there is a suspicious lateral cervical lymph node to optimize the surgical procedure. Total thyroidectomy is the procedure of choice for the majority of patients. Additionally, if there is evidence of metastasis, lateral neck lymph node dissection is also recommended. After surgery, radioactive iodine (RAI) therapy must be considered according to American Thyroid Association (ATA) risk stratification to treat persistent disease or to decrease the risk of recurrence. RAI is not indicated in patients with the low-risk PTC category, TSH suppressive-levothyroxine treatment is recommended for this group of patients (8).

Despite these features, the limited available data suggest that children with thyroid cancer generally have an excellent prognosis with appropriate management (9,10). This study aimed to assess the long-term oncological outcomes of pediatric PTC.

MATERIAL and METHODS

We retrospectively screened available medical records of patients who had PTC diagnosed in childhood and adolescence and followed up in the Istanbul Faculty of Medicine between 1980 and 2023.

Clinical characteristics of patients, age at diagnosis, gender, risk factors (such as radiation exposure, family history), surgical procedure, pathological findings (tumor diameter, histological type, microscopic subtype, invasion, lymph node metastasis), tumor stage, postoperative evaluation, and radioiodine treatment, presence of persistent disease or recurrence at follow-up, time to recurrence, the number of patients underwent reoperation, total RAI dose administered, presence of postoperative complications (recurrent nerve palsy and permanent hypoparathyroidism), duration of follow-up and oncological outcomes were evaluated.

PTC staging was made according to the American Joint Committee on Cancer/Tumor, Node, Metastasis (TNM) staging system (AJCC 8th.edition) (11).

The dose of administered activities of RAI was as follows: 30-100 mCi for tumors limited to the thyroid; 150 mCi for tumors that invaded the tissues surrounding the thyroid capsule and/or with metastasis to the neck or mediastinal lymph nodes; 175-200 mCi for distant metastases. In younger children, dose adjustments were made on a per kg basis using doses for a standard 70 kg person as a reference point.

An excellent response is defined as the absence of clinical, biochemical, or structural evidence of disease after RAI therapy.

BRAF mutation analysis was performed in thyroid tumor specimens and by using the QIAamp DNA tissue kit (Qiagen, Hilden, Germany) for genomic DNA preparation. The mutation was determined by pyrosequencing using the Qiagen PyroMark Q24 pyrosequencer (Qiagen, Venlo, Netherlands).

The Ethics Committee of the Istanbul Faculty of Medicine approved the study protocol (Date 28.04.2023, No: 09). The written informed consent was waived because of the nature of this retrospective study. For the statistical analyses, SPSS version 21.0 was used. Continuous and categorical variables were represented by mean±standard deviation, and frequency/percentage values, respectively. Categorical variables were compared with the chi-square test. The independent sample t-test was used to compare the baseline laboratory data.

RESULTS

The cohort included all patients who were transitioned from the pediatric to the adult endocrinology department and therefore who were followed up at the same tertiary center throughout the the entire process. In this study, a total of 30 patients were evaluated. The mean age at diagnosis was 14.7±2.3 years (range, 7 to 18). There were 21 females (70.0%) and 9 males (30.0%). The female-to-male ratio was 2.3:1. Among the patients, five had a history of radiation exposure to the neck and the mean duration from radiation exposure to the diagnosis of PTC was 7.2±2.4 years (range, 5 to 11). Only one patient had a family history of PTC (Figure 1). Ultrasound imaging was performed because of neck swelling in 18 patients, hypothyroidism in eight patients, and a history of lymphoma in two patients. The mean nodule size was 1.5±1.3 cm. According to Bethesda Classification fine-needle aspiration biopsy findings were as follows: Bethesda II category: 6.6% (n=2), Bethesda III category: 6.6% (n=2), Bethesda IV category: 10.0% (n=3), Bethesda V category: 26.6% (n=8), and Bethesda VI category: 46.6% (n=14). All of the patients underwent total thyroidectomy. Total thyroidectomy was combined with central lymph node dissection in 30.0% of the patients (n=9), and central and lateral lymph node dissection in 40.0% (n=12).

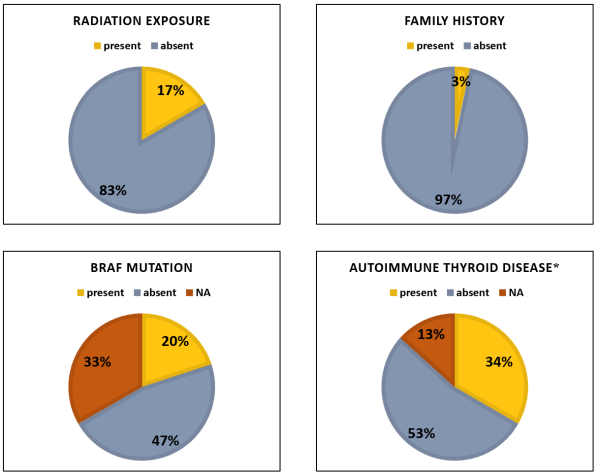

Figure 1: Presence of risk factors for papillary thyroid cancer. * Controversial risk factor

The tumor was bilateral in 43.3% of the patients, was located in the left lobe in 30.0%, in the right lobe in 20.0%, and in the isthmus region in 3.3%. The mean tumor size was 1.6±1.5 cm (range, 0.1 to 6), and the tumor was microcarcinoma (maximum diameter of 1 cm or less) in 12 of the patients. Histopathological subtype was available in 29 patients, and distribution was as follows; follicular variant in 13, classic variant in nine, encapsulated follicular variant in three, tall cell variant in one, macrofollicular variant in one, hobnail variant in one, diffuse sclerosing variant in one. The tumor was multicentric in 19 patients (63.3%). Histopathological examination revealed chronic lymphocytic thyroiditis in 10 patients. BRAF mutation could be analyzed in 20 patients and was detected in 30.0% of them (Table 1).

Most of the patients presented with a T1 disease (T1a, n=12; T1b, n=9; T2, n=5; T3, n=2). At diagnosis, half of the patients had lymph node metastases to the neck or upper mediastinum. Five patients had metastases to the central lymph nodes (N1a), and ten patients had metastases to the lateral lymph nodes (N1b). Seven of the patients with N1b had multicentric disease and vascular invasion, and six had lymphatic invasion. Lung metastases were detected in two patients (6.7%).

There was no difference between the metastasic and non-metastatic groups in terms of age at diagnosis and nodule size (p=0.68 and p=0.264 respectively). There was no association between the BRAF mutation and metastatic disease (p=0.051). However, radiation exposure was significantly higher in the non-metastatic group (p=0.014)

The mean duration of follow-up was 10.6±3.8 years. Eight low-risk patients still in remission were treated with only TSH-suppressive levothyroxine. Post-operative RAI treatment was administered to 22 patients [median number of administration was one (range 1-7), and the median cumu-

Table 1: Stage at diagnosis, treatment modalities and response to therapy

Patients	Gender	Age at diagnosis	BRAF	pT	pN	pM	No. of surgery	No. of RAI therapy	Total RAI dose	Persistent/ Recurrent disease	Response to therapy (Surgery and RAI)	Response to therapy (Only surgery)
Case 1	M	12.4	NA	T1a	N0	M0	1	-	-	-		Remission
Case 2	F	13.5	Positive	T2	N1b	M0	2	2	200	Recurrent	Excellent	
Case 3	F	15.7	Negative	T2	N0	M0	2	2	300	Persistent	Structural incomplete	
Case 4	F	16.3	NA	T1a	N0	M0	1	-	-	-		Remission
Case 5	F	13.7	Negative	T3a	N1b	M0	2	1	150	-	Excellent	
Case 6	F	13.6	NA		N1b	M0	4	4	750	-	Excellent	
Case 7	F	14.5	Positive	T1b	N1b	M0	1	1	150	-	Excellent	
Case 8	F	12.7	Negative	T1b	N0	M0	2	1	50	-	Excellent	
Case 9	F	15.6	Positive	T2	N1a	M0	1	1	150	-	Indeterminate	
Case 10	M	15.6	NA	T1b	N1b	M0	1	1	150	-	Excellent	
Case 11	F	15.8	Negative	T1b	N0	M0	1	1	100	-	Excellent	
Case 12	M	11.6	NA	T2	N1b	M1	1	5	605	-	Excellent	
Case 13	F	16.8	Negative	T1a	N0	M0	1	-	-	-		Remission
Case 14	M	17.7	Negative	T1a	N0	M0	1	-	-	-		Remission
Case 15	F	14.6	NA	T1b	N0	M0	1	1	100	-	Excellent	
Case 16	F	16.9	Negative	T1a	N0	M0	1	1	100	-	Excellent	
Case 17	F	15.2	NA	T1a	N0	M0	1	-	-	-		Remission
Case 18	F	14.7	Negative	T1a	N0	M0	1	-	-	-		Remission
Case 19	F	14.4	NA	T1b	N1b	M0	4	3	450	Persistent	Structural incomplete	
Case 20	F	7.3	Negative	T2	N1a	M0	1	1	50	-	Excellent	
Case 21	F	14.5	Positive	T1b	N1b	M0	5	3	450	Persistent	Indeterminate	
Case 22	F	17.5	Positive	T1a	N0	M0	1	-	-	-		Remission
Case 23	M	10.7	NA	T1a	N0	M0	1	1	50	-	Excellent	
Case 24	F	17.3	Negative	T1b	N0	M0	1	1	150	-	Excellent	
Case 25	F	15	Negative	T1a	N1a	M0	1	1	75	-	Excellent	
Case 26	M	18	Negative	T1a	N0	MO	1	-	-	-		Remission
Case 27	M	17.3	Negative	T1b	N1a	M0	1	1	150	-	Excellent	
Case 28	M	12.8	Positive	T1a	N1a	M0	1	1	150	-	Excellent	
Case 29	M	15.2	Negative	T3a	N1b	M0	3	2	250	Persistent	Structural incomplete	
Case 30	F	14	NA	NA	N1b	M1	4	7	1100	Persistent	Indeterminate	

pTNM: Pathological Tumor-Node-Metastasis, RAI: Radioactive Iodine, No. of surgery: Number of surgery, No. of RAI therapy: Number of radioactive iodine therapy NA: Not available

lative dose was 150 mCi (range 50 to 1100)]. Sixteen patients had excellent response following single (n=13) or multiple (2 for persistent and 1 for recurring disease after 100 months) RAI administrations. The remaining three patients had structural incomplete and three had indeterminate response. Data regarding the clinical characteristics and the follow-ups of the patients are summarized in Table 1.

DISCUSSION

In this study, the clinical features of PTC diagnosed in childhood and adolescence including stage at diagnosis, therapy modalities, response to treatment, and course of the disease were evaluated.

As in similar studies in the literature, our patients were predominantly female (12,13). Specific risk factors for thyroid cancer are ionizing radiation and genetic predisposition (14). There were five patients with a history of radiotherapy and one patient with a family history in our study.

In the literature, it was reported that the presence of autoimmune thyroid disease might be a risk factor for the development of thyroid cancer (15). However, in the study of Anil et al, it was found that Hashimoto's thyroiditis was not a risk factor for thyroid cancer in patients with thyroid nodules (16). On the pathological examination, histopathological characteristics of non-tumor thyroid tissues were available in 26 patients, and autoimmune thyroid disease was detected in 10 of them (38.4%, n:10/26). No other identified risk factors were detected for the remaining patients.

Children with PTC tend to have bilateral and more advanced disease at presentation compared with adults. Hay et al., reported the presence of regional lymph node metastases at initial surgery in 75.0% of patients (7). It was detected in 50.0% of the patients in our study. In the study of Cherella et al., bilateral disease was reported in 41.0% of the patients, and similarly, it was detected in 43.3% of the patients in our study (17). Total thyroidectomy is recommended as the first surgical procedure due to the risk of bilateral disease. After surgery, RAI treatment should be considered according to risk assessment (8).

Despite more advanced disease at presentation, the prognosis of PTC in children is excellent, and the survival rate is better than in adults (7). In our study, an excellent response was obtained in 16 of 22 patients who received RAI therapy. One of the patients with lung metastases (case 12) had an excellent response after repeated RAI therapies (total dose of 605 mCi). In the study of van de Berg et al., it was reported that the recurrence rate was 19.0% and the median duration of follow-up was 11.3 years (10). In our study, recurrence occurred in only one patient and the time from the initial surgery to recurrence was 8.3 years. The patient had lymph node metastasis at the time of diagnosis, and multicentricity and vascular invasion were present in the microscopic examination.

BRAF mutations are associated with lymph node metastases and advanced-stage at presentation (18). However, in the study of Poyrazoğlu et al., it was stated that BRAFV600E mutation was found in 25% of patients, and no relation was found between BRAFV600E mutation and lymph node or pulmonary metastasis at diagnosis (19). In the study of Senyurek et al., it was found that the locoregional recurrence rate was higher in BRAFV600E positive patients than in negative patients nevertheless BRAFV600E mutation had no role in the achievement of the excellent response to treatment (20). Six of our patients had BRAF mutations. Five of the 6 patients with BRAF mutations had lymph node metastases at the time of diagnosis, and one of them recurred during follow-up. However, no association between the BRAF mutation and metastatic disease was found.

Patients with a history of radiation exposure were diagnosed before the development of metastasis and these patients had smaller nodules (the mean nodule diameter 1.2±1.1 cm) at the time of diagnosis. This result may be related to the closer follow-up of the patients due to the risk of radiation exposure.

Postoperative complications developed in 12 patients; recurrent nerve palsy in one of them and permanent hypoparathyroidism in 11 patients. According to the literature, the risk of second primary cancer increases in children who receive RAI (21). Second primary cancer did not occur in our patients who received RAI, but the duration of follow-up might be short to assess.

The limitation of the study is the number of patients, but a small sample size is an unavoidable limitation in rare diseases like pediatric thyroid cancer.

CONCLUSION

In conclusion, pediatric PTC, the most common endocrine cancer in childhood and adolescence, had a tendency to present at a more advanced stage, but the response to treatment was fairly good with appropriate management.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date 28.04.2023, No: 09).

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