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RESEARCH

Factors associated with resistant disease in pediatric differentiated thyroid carcinomas

Pediatrik diferansiye tiroid karsinomlarinda dirençli hastalık ile ilişkili faktörler

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Abstract

Purpose: Thyroid carcinoma is the most common carcinoma that originated from endocrine tissue in pediatric patients. Pediatric thyroid carcinomas are more prone to reveal lymph node or lung metastasis and recurrence. In this study, clinical, pathological and genetic features that may be related with resistant differentiated thyroid carcinoma in pediatric patients were investigated.

Materials and Methods: Thirty-nine pediatric patients who were 18 years old and below and were given ^{131}I Radioactive Iodine (RAI) therapy were included to the study. ^{131}I RAI therapy was planned in accordance with the American Thyroid Association (ATA) Guideline. Clinical and postoperative pathological features of patients were retrospectively determined and the patients who received single or multiple RAI therapy due to resistant disease compared statistically in terms of these features. Genetic analysis was also made in the patients who received multiple therapies.

Results: Thirty-one patients were female and 8 patients were male. Thirty-four patients had papillary thyroid carcinoma, 4 had follicular thyroid carcinoma and 1 had mixed papillary-oncocytic carcinoma of patients. Eight patients received multiple I-131 RAI therapy cycles due to resistant disease. Any clinical, pathological feature and genetic mutation that would indicate resistant disease was not found in these patients.

Conclusion: Although pediatric thyroid carcinoma is rarely seen, it has an increasing incidence in recent years. We were not able to reveal any feature related to resistant disease in our limited group. Clinical, pathological and genetic characteristics related to poor prognosis must be investigated with larger study groups.

Keywords:. Thyroid neoplasms, iodine radioisotopes, radiation therapy, genetics, pediatrics

Öz

Amaç: Pediatrik hasta grubunda, endokrin dokudan köken alan karsinomlar içinde en sık tiroid karsinomu görülür. Pediatrik tiroid karsinomları hem lenf nodu ya da akciğer metastazına hem de tekrarlamaya daha çok meyillidir. Bu çalışmada, dirençli pediatrik diferansiye tiroid karsinomları ile ilişkili olabilecek klinik, patolojik ve genetik özellikler araştırıldı.

Gereç ve Yöntem: I-131 radyoaktif iyot (RAİ) tedavisi almış 18 yaş ve altı 39 hasta çalışmaya dahil edildi. I-131 RAI tedavisi Amerika Tiroid Derneği (ATA) Rehberi'ne göre belirlendi. Hasta grubunun klinik ve postoperatif patolojik özellikleri geriye dönük olarak belirlenerek bu özellikler bakımından tek ve dirençli hastalık nedeniyle birden fazla tedavi almış hastalar istatistiksel olarak karşılaştırıldı. Birden fazla tedavi almış hastalarda ayrıca genetik analiz yapıldı.

Bulgular: Hasta grubunun 31'i kadın, 8'i erkekti. Otuz dört hastada papiller tiroid karsinomu, 4 hastada folliküler tiroid karsinomu, 1 hastada mikst papiller-onkositik karsinom saptandı. Sekiz hasta dirençli hastalık nedeniyle birden fazla I-131 RAI tedavisi aldı. Bu hastalarda dirençli hastalık ile ilişkili olabilecek herhangi bir klinik ve patolojik özellik ile genetik mutasyon saptanmadı.

Sonuç: Pediatrik tiroid karsinomu ender görülmesine rağmen sıklığı son yıllarda artış göstermektedir. Sınırlı sayıdaki hasta grubumuzda dirençli hastalık ile uyumlu olabilecek herhangi bir özellik izlenmemiştir. Kötü prognoz ile ilişkili olabilecek klinik, patolojik ve genetik özellikler daha geniş hasta serilerinde araştırılmalıdır.

Anahtar kelimeler: Tiroid neoplazmları, iyot radyoizotopları, radyasyon tedavisi, genetik, pediatri

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INTRODUCTION

Thyroid carcinoma is the third most common type of solid tumors and the most common type of endocrine tissue cancers in the pediatric group[1-3]. It was estimated that approximately 52070 patients would be diagnosed as thyroid cancer in 2022, and 2% of this patients would be under 20 years old[4]. At the time of diagnosis, pediatric patients are more prone to regional lymph node or lung metastasis and recurrence than adults, but have a better prognosis and lower mortality rates[1]. Thyroid cancers usually occur with a solitary nodule. There are several risk factors for the development of thyroid nodules such as radiation exposure, autoimmune thyroid disorders and genetic syndromes. Some studies showed that thyroid nodules in pediatric patients have risk of malignancy four times more than adults. In addition, the probability of malignancy increases in patients under 10 years old, history of head and neck radiation or iodine deficiency[5,6].

Differentiated thyroid carcinomas (DTC) which include papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) originate from thyroid follicle cells. Of the DTCs, about 80% are diagnosed as PTC and 20% are diagnosed as FTC[2]. In addition, there are some subtypes of these pathological types and the most common subtype is follicular variant of PTC in the pediatric population. Other rare subtypes of PTC are tall cell, diffuse sclerosing and columnar variant, and rare subtypes of FTC are Hürthle cell, clear cell and insular variant. For pediatric patients diagnosed as DTC, total/subtotal thyroidectomy with or without cervical lymph node dissection depending on metastasis presence, and following ^{131}I radioactive iodine (RAI) and thyroid-stimulating hormone (TSH) suppression therapy is recommended[7].

Poor clinical or pathological prognostic factors in pediatric DTC were represented by some recent studies. According to the long-term results of a high volume center from Germany, event-free survival was found 78.1% and negatively affected by presence of metastasis, both biochemical and structural incomplete response, invasion of capsule or lymphatic vessels, extrathyroidal extension, multifocality and age below 10.[8] In another study including less participants revealed event-free survival as 79.2% similarly. However, the authors only found >4 cm of tumors in addition to lymph node or distant metastasis as negative effectors.[9] Some genetic mutations were also described in pediatric group like RET/PTC, and BRAF. While RET/PTC rearrangements are presented with younger age and high rates of lymph node metastasis, BRAF V600E mutations are not associated with poor prognosis or invasive behaviour in contrast to adults.[10,11]

In the study, pediatric patients who were treated in our department between 2007-2020 were retrospectively evaluated and clinical, pathological and genetic features that might be related to resistant disease were investigated. The aim of the study was to reveal any feature that may be associated with resistant disease in a pediatric group in Southern Anatolian region.

MATERIALS AND METHODS

Sample

After the total thyroidectomy and pathological diagnosis of DTC, thirty-nine patients who were 18 years old and below and were given one or more ^{131}I RAI therapy at the Cukurova University Balcali Hospital Department of Nuclear Medicine between 2007 and 2020 were included to the study. Data collecting process was done by authors in accordance with principles of Helsinki Declaration. The informed consent was accepted and signed by all participants or their custodians. Because it is a retrospective study, ethical approval from the board was waived.

^{131}I RAI therapy planning and preparation

^{131}I RAI therapy was planned according to American Thyroid Association (ATA) Pediatric Risk Classification for Differantiated Thyroid Carcinoma[7] by considering neck ultrasonography (US), thyroid scintigraphy, pathology report of surgical specimen and serum thyroglobulin (Tg) values of the patients with pathologically proven DTC. RAI treatment evaluation was not performed earlier than first month after surgery. The appropriate radioactivity dose was determined empirically according to the risk status of disease. Then, the dose was adjusted for paediatric group (Appropriate ^{131}I RAI dose = weight of patient x appropriate dose for adults / 70). Appropriate radioactivity dose for adults must be about 1,1 GigaBecquerel (GBq) for low risk DTC patients, up to 5.55 GBq for in intermediate risk patients and about 7.4 GBq high risk patients with distant organ

metastasis[7]. Whole body iodine scan (WBS) at 5th – 7th day following RAI therapy was performed to all of the patients. Levothyroxine therapy that was initated following surgery is stopped approximately 3 weeks prior to the RAI therapy to reach a thyrotropin (TSH) level above 30 mIU/L and to enhance the uptake of ^{131}I in thyroid gland. After the day withdrawal of levothyroxine, short-acting L-triiodotironin was started until 14th day before therapy. Serum TSH value was checked whether it is above 30 mIU/L on the previous day of hospitalization.

Patient follow-up

Serum TSH, free triiodothyronin (fT3), free thyroxine (fT4), Tg and Tg antibody (Anti Tg) values and cervical ultrasonography were evaluated three or six month intervals according to the risk status. All patients underwent diagnostic WBS with 37 MegaBecquerel (MBq) ^{131}I on 6th month and the results were compared with the post-treatment WBS. The levothyroxine therapy was ceased and short-acting L-triiodotironin was initiated before WBS same as therapeutic ^{131}I. WBS was performed in third day following administiration of diagnostic ^{131}I. On 6th month follow up, patients with no positive focus on WBS and negative Tg (<0.04 ng/ml accepted negative in our hospital) and Anti Tg values were considered in biochemical and clinical complete remission. Then, their follow up intervals were extended to six months.

Resistant disease

Biochemically incomplete remission (high serum Tg levels) in 6th month follow-up or structural incomplete remission in cervical region or distant metastasis in 6th month WBS suggested resistant disease. ^{131}I RAI therapy were repeated to these patients according to board decision. The period between two therapy was not less than 6 months. The patients with lung metastasis were administered oral corticosteroid in order to prevent side effects and pulmonary function tests were performed before and after treatment. Genetic analysis was also performed in Genetics Department of Cukurova University Balcali Hospital to all the patients who have resistant disease.

Genetic analysis

All the resistant patients were studied for the identification of actionable somatic variants in the formaline-fixed embedded tissue samples for possible drug sensitivity and resistance through a multi-gene solid tumors related panel including KRAS, NRAS, KIT, BRAF, PDGFRA, ALK, EGFR, ERBB2, PIK3CA, ERBB3, ESR1 and RAF1 genes. All the genes were next-generation sequenced by GeneReader NGS Systems and analyzed via QCI bioinformatics tools.

Moreover, the patients who have resistance to the treatment were also analyzed for germline mutations of SDHA, SDHB, SDHC, CDC73, CASR, PDGFRA, RET, SDHAF2, MEN1, SDHD, MAX, PRKAR1A and KIT genes to evaluate the association between genetic alterations, cascade and disease perpetuation. The multi-gene panel was designed by QIASeq NGS Solutions and next-generation sequencing was performed by Illumina MiSeq System (San Diego, CA, USA). Bioinformatic analysis was performed using QCI-Analyze and QCI-Interpret bioinformatics tools which was customized for our genetic diagnosis center's pipelines.

Statistical analysis

The characteristics of the patients to whom single or multiple therapy were given were compared statistically. IBM SPSS Statistics Version 20.0 package program[12] was used for statistical analysis. Categorical measurements were summarized as numbers and percentages, and numerical measurements were summarized as mean and standard deviation. Chi-square test was used to compare categorical measurements between groups. Statistical significance was taken as 0.05 in all tests.

RESULTS

Thirtyone patients (79.5%) were female and eight (20.5%) were male. The mean age at diagnosis was 15 ± 2.5. Out of 39 patients, 34 (87.2%) were diagnosed as PTC and four (10.3%) were diagnosed as FTC and one (2.6%) was diagnosed as papillary+oncocytic (Hürthle cell) carcinoma. Nine patients in the PTC group had follicular variant (fvPTC), three had tall cell variant (tcvPTC) and twenty-two had classical variant (cvPTC). No subtype was reported in patients with FTC.

The mean tumor diameter in the total group was 2.09 centimeter (cm) ± 1.15. At the time of diagnosis, tumor diameter was less than 1 cm in five patients and more than 5 cm in one patient. 15 patients

(38.5%) had metastasis to the regional lymph nodes. The clinicopatholgical features of patient group are presented in Table 1.

Table 1. Demographical and histopathological features of patients

Variable		n, (%)
Gender	Male Female	8 (20.5) 31 (79.5)
Diagnosis Age	Mean < 15 ≥ 15	15 ± 2.5 15 (38.5) 24 (61.5)
Pathological Type	Papillary thyroid carcinoma Follicular thyroid carcinoma Papillary + Oncocytic carcinoma	34 (87.2) 4 (10.3) 1 (2.6)
Pathological Subtype of Papillary Carcinoma	Classical variant Follicular variant Tall cell variant	22 (64.7) 9 (26.5) 3 (8.8)
Multicentricity	Negative Positive	24 (61.5) 15 (38.5)
Lymphovascular Invasion	Negative Positive	19 (48.7) 20 (51.3)
Tumor Capsule Invasion	Negative Positive	20 (51.3) 19 (48.7)
Metastatic Cervical Lymph Node	Negative Positive	24 (61.5) 15 (38.5)
Received RAI Therapy	Single Multiple	31 (79.5) 8 (20.5)

All the patients with FTC and fvPTC, one of the patients with tcvPTC (1/3; 33.3%) and 29 of 34 patients (85.2%) with cvPTC were considered in clinical and biochemical complete remission at the 6th month follow up and WBS.

Eight patients with positive WBS or high Tg values at the 6th month follow-up were considered with resistant disease and new RAI therapy was planned. None of the resistant patients had high Anti Tg value in 6th month follow-up. Of the 8 patients who received multiple cycles, 3 were male (37.5%) and 5 were female (62.5%). There was no significant relationship between gender and resistant disease (p=0.323). Seven of the resistant patients were diagnosed with PTC, two of them had tall cell variant, the rest five had classical variant. A patient was diagnosed as papillary + oncocytic carcinoma. In addition, all resistant patients had lymphovascular invasion, seven of them had tumour capsule invasion, and seven of them had metastatic cervical lymph nodes. Table 2 summarizes the characteristics of patients that resistant to therapy (Table 2).

Patient no 1 and 2 who were diagnosed as cvPTC received second cycle of ^{131}I therapy due to minimal rising of Tg value (<10 ng/ml) without showing any focus on WBS. After second cycle, these patients were considered in biochemical complete remission with falling of Tg to the negative values at follow-ups (<0.04 ng/ml).

However, Patient no 3, 4 and 5 with cvPTC had very aggresive clinical status. In the time of diagnosis, both Patient no 3 and 4 had multiple regional metastatic lymph nodes and multiple milimetric metastatic pulmonary nodules. The Tg value of Patient no 3 was 1457 ng/ml and of Patient no 4 was 93720 ng/ml before first ^{131}I therapy. Both patients underwent total thyroidectomy and bilateral cervical lymph node dissection prior to RAI therapy. Patient no 3 has multiple milimetric nodules that do not show iodine uptake and at the 12th month follow up after second cycle, his supressed Tg value was 34 ng/ml.

The uptake of both lungs of Patient no 4 decreased significantly but some pathologically proven metastatic calcified lymph nodes showing iodine uptake were detected in parapharyngeal and

paratracheal region on 6th month WBS after the third cycle. Subsequently, all the nodes were excised by accomplished surgery. Last measured Tg value was 1755 ng/ml with stimulated TSH and fourth cycle will be planned (Figure 1).

Patient no 5 recieved second cycle following a successful surgery that was performed due to relapse tumoral mass which invaded trachea. Her stimulated Tg value had progressed from 14.83 to 73.91 ng/ml before surgery. She is being followed with supressed Tg value of <1 ng/ml.

Patient no 6 was diagnosed as mixt papillary and oncocytic carcinoma with multiple regional lymph node metastasis. Due to high Tg values after first therapy (91.95 ng/dl) and metastatic lymph nodes, three cycles have been given in total. His last supressed Tg value was 3.72 ng/dl without any uptake in WBS. He is being followed closely for any change of Tg values pathological lymph node that may appear in US.

Patient no 7 and 8 who both were diagnosed as tcvPTC with presenting regional metastatic lymph nodes and high Tg values had aggressive disease. In the 6th month WBS after first therapy, both had metastatic pulmonary uptakes. Second cycle was given and they are following with supressed Tg values (<10 ng/dl).

There was no significant relationship between resistant disease and parameters such as age group (prepubertal (<15 years) and postpubertal (>15 years), p>0.05), pathologic type (p>0.05), pathological subtype (p>0.05), multicentricity of tumor (p>0.05), presence of tumor capsule invasion (p>0,05), lymphovascular invasion (p>0.05), metastatic lymph node (p>0.05) and residual tissue in WBS (p>0.05).

None of the testings identified any clinical relevant or actionable pathogenic variants according to the American College of Medical Genetics criteria. There might be possible other genetic backgrounds that needs larger multigene panels or the whole-exome-sequencing.

Table 2. Features of the patients with resistant disease

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Gender	Female	Female	Male	Female	Female	Male	Female	Male
Diagnosis Age	17	13	6	10	16	10	15	9
Pathological type	PTC¶	PTC¶	PTC¶	PTC¶	PTC¶	PTC¶+OC§	PTC¶	PTC¶
Pathological Subtype	Classical	Classical	Classical	Classical	Classical		TCV‖	TCV‖
Tumor Capsule Invasion	+	-	+	+	+	+	+	+
Lymphovascular Invasion	+	+	+	+	+	+	+	+
Multicentricity	+	+	+	-	+	-	+	-
CLNM*	-	+	+	+	+	+	+	+
6.mn WBS**	-	-	LM†	LM†	LR‡	LR‡	LR‡+LM†	LR‡+LM†
Cycle 1	125	75	75	75	125	75	100	75
Cycle 2	150	85	85	85	150	100	150	100
Cycle 3				100		125		

*CLNM: Cervical lymph node metastasis, †LM: Lung metastasis, ‡LR: Local recurrence, §OC: Oncocytic carcinoma, ||TCV: Tall Cell Variant, ¶PTC: Papillary thyroid carcinoma,**WBS: Whole body scan

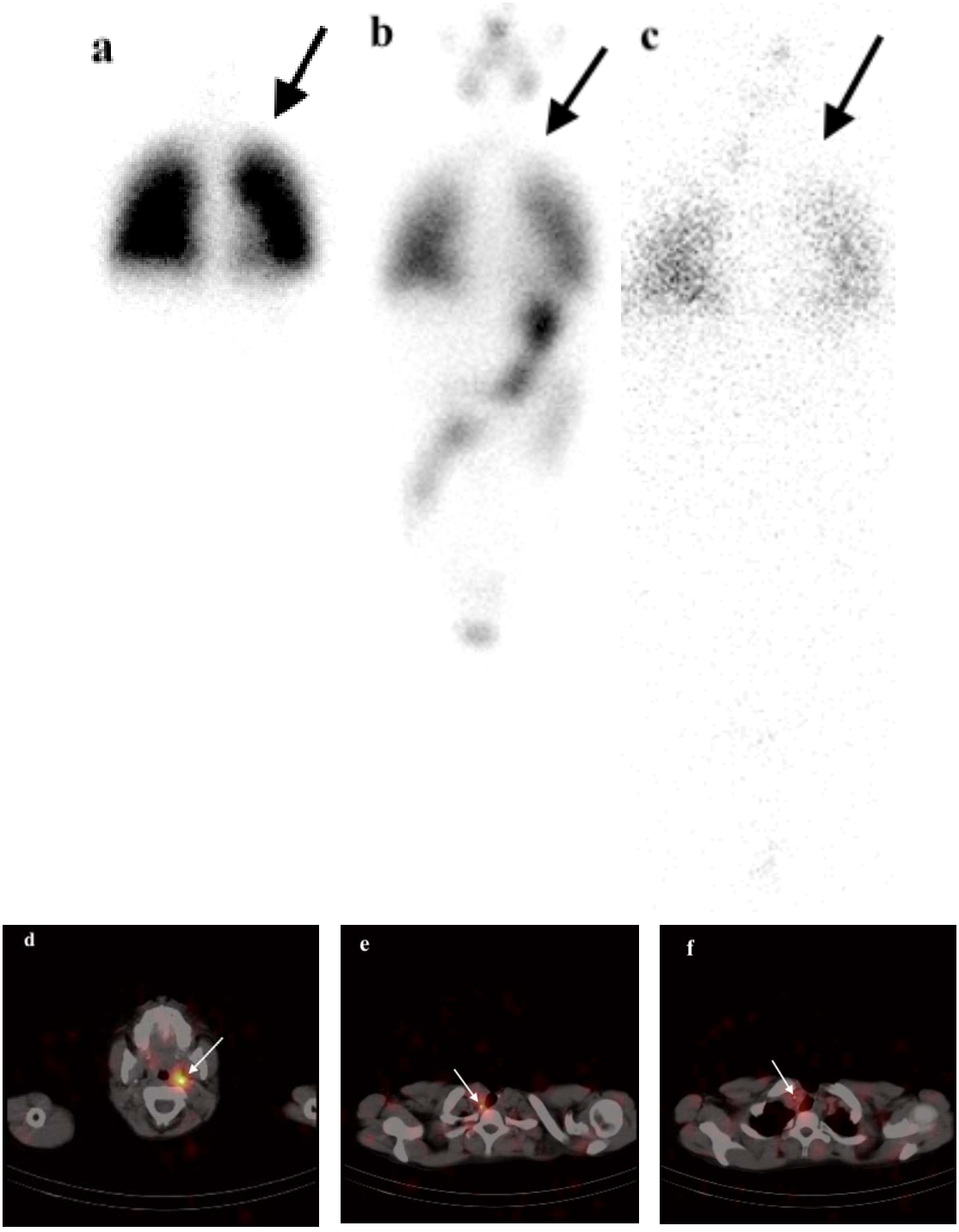

Figure 1. Planar WBS images of Patient no 4 after first (a), second (b) and third (c) cycle.

Decreasing of radioiodine uptake in lungs which is compatible with response to therapy can be seen (black arrows). A few new calcified lymph nodes which show radioiodine uptake at parapharyngeal (d) and right paratracheal (e,f) regions (white arrows) at sixth month whole body scan after third cycle were excised and the pathology report revealed metastasis. A new cycle was planned.

DISCUSSION

Although DTC is rarely seen in the pediatric group, metastasis and recurrence rates are higher than adults. There are few studies in the literature investigating the relationship between recurrence and clinical or pathological features of the patient probably due to limited number of pediatric DTC patients in centers.

Up to 34% of recurrence rates in the pediatric group were reported in the literature[13]. Lee et al. compared the survival and recurrence rates of 124 pediatric patients with 3071 adult patients and found that recurrence-free survival of the pediatric group was significantly lower compared to 20-54 years old adult group. In addition, the lowest recurrence-free survival time among all patients with multifocal tumor belongs to the pediatric group. The study also showed that tumor multifocality and size can predict recurrence in children[14]. Qu and his collagues found that the progression-free survival time was 23 months in a group of 34 patients. Tumor multifocality was the only parameter affecting progression-free survival[15]. Also, according to a study from Back et al., lateral metastatic lymph nodes presence is a significant prognostic factor for recurrence[16]. In our limited patient group, although 5 of 8 patient with resistant disease had tumor multifocality, statistically correlation was not found between tumor multifocality and resistant disease. We also were not able to find a significant difference in recurrence between localized and metastatic groups.

The cervical lymph node metastasis is more common in pediatric patients. Thus, careful neck evaluation with ultrasound is very important before and after total thyroidectomy. A study of Al-Qurayshi et al.[17] in which 644 pediatric patients and 43536 adult patients were compared, the rate of lymph node (31.5% vs. 14.7%) and lung metastasis (5.7% vs. 2.2%) in children and the rate of bone metastasis (0.3% vs 1.1 %) in adults was found higher significantly. In our study, 15 of 39 patients (38.5%) had metastatic cervical lymph nodes and none of them had bone metastases. Besides, four patients have lung metastasis in the time of diagnosis (10.2%).

There are some aggressive subtypes of PTC such as tall cell variant, columnar variant and hobnail variant which may be with persistent or metastatic disease with worse outcome. In a paper by Song et al.[18] in which genetic variants in adult population compared cvPTC and aggressive variants of PTC (avPTC, tall cell, columnar and hobnail variant) in terms of disease-free survival (DFS) and recurrence, the patients with cvPTC have higher DFS than others. Interestingly, when they evaluated the aggressive variants separately, there was no difference in DFS between classical and tall cell variant group. However, the patients with columnar variant have lower DFS and higher risk of recurrence compared to cvPTC. In another study by Borgers et al.[23], cvPTC and the patients with tall cell change which consists of focal tall cell change and tcvPTC were compared. Risk of persistent/recurrent disease, lymph node and distant metastasis were found higher in the group with tall cell change. In addition, 5-year disease-free survival was higher in cvPTC group. Similar to this findings, the rate of recurrent disease of tcvPTC (2/3 patients; 66.6%) was more than cvPTC (5/22 patients; 22.7%) in our study. Otherwise, all the patients with tcvPTC had lymphovascular and capsule invasion. Two of them who were resistant to therapy had also regional lymph node metastasis in the time of diagnosis. It can be concluded that tcvPTC comes with more significant pathological characteristics and is prone to be metastatic disease.

The genetic and molecular basis of DTC has been frequently investigated in recent years in both adult and pediatric groups. Researchers are investigating whether some gene mutations can be used for diagnosis, extension or resistance of disease. Approximately 45% positivity has been reported in the adult group for BRAF V600E mutation and is mostly seen in PTC patients with classical variant. RET/PTC and RAS gene mutations are more prominent in the pediatric group. In addition, RAS and PAX8/PPARG gene mutations are highly associated with FTC or PTC follicular variant in both groups[20-22]. Xing et al.[20] investigated the relationship between PTC recurrence and presence of BRAF V600E mutation in multicentered retrospective study which consists of 2099 patients and found that BRAF V600E mutation is related to tumor recurrence in whole PTC group, pathological subgroups (cvPTC and fvPTC) and even in the patients with low risk status. Presence of BRAF V600E also caused lower recurrence free survival not only in whole study group but also in subgroups such as the patients with lymph node metastasis, extrathyroidal tumor extension or advanced age. Henke et al.[21], found BRAF V600E mutation in 63% of 27 pediatric patients below 22 years old. It seems the highest rate

for pediatric group and may be due to high age cut-off. They did not find correlation between presence of BRAF mutation and progression free survival or pathological characteristics. A study from Giles Senyurek et al.[22] also revealed that in 55 pediatric patients in whom BRAFV600E mutation analysis was performed, excellent and incomplete/indeterminate responses did not show significant difference between BRAFV600E positive and negative results. Otherwise, in another study from Mostoufi-Moab et al.[23] presence of BRAF V600E or RET/PTC gene mutation is associated with malignancy and lymph node metastasis in a mixt group of adult and pediatric patients. RET/PTC was also correlated with invasive disease. Similarly, Mollen et al.[24] found that BRAF-like mutations are associated with higher rate of surgery for recurrence in addition to increased tumor stage, multifocality and lymph node metastasis. In the light of this results, the clinical importance of presence of BRAF mutations still seems controversial in pediatric group. In this study, any genetic mutation was not found in resistant patients. When 20.5% (8/39) rate of resistant disease is taken into consideration, some regional differences can exist in terms of gene mutations. Thus, it is quite obvious that larger study groups especially in Turkey or Middle Eastern region which investigate gene alterations and their effects to patient management are needed.

Our study has some limitations. Firstly, our patient group is a small population. All patients who treated in our center were included in the study. Pediatric DTC is not common and it is difficult to create a large patient group in one center. Secondly, the genetic analysis was only performed to resistant patients. For the reason it is a retrospective study, all patients was not been able to reached for genetic testing. Lastly, our single-centered study represents the results of small region. More accurate results can be obtained with a larger multi-centered patient groups.

Although pediatric DTC is seen rare, it has an increasing incidence in recent years. We were not able to find any correlation between resistant disease and clinical and pathological features in our limited pediatric group. Any gene alteration or pathological variant also could not be identified that might be related to resistant disease. Otherwise, presence of some clinical and pathological features such as lymphovascular invasion, capsule invasion, multicentricity, tall cell variant of PTC and cervical lymph node or lung metastasis at diagnosis may indicate persistent or recurrent disease in pediatric group.

In conclusion, in the region where the study was conducted, no genetic mutations that could predict resistant disease were detected in accordance with the literature. However, other clinicopathological features that may be compatible with resistant disease and were not found significant in our small study group may produce significant results in larger study groups.

Yazar Katkıları: Çalışma konsepti/Tasarımı: KAK, ZY; Veri toplama: KAK; Veri analizi ve yorumlama: KAK, İBG; Yazı taslağı: KAK, ZY; İçeriğin eleştirel incelenmesi: KAK, İBG, ZY; Son onay ve sorumluluk: KAK, İBG, ZY; Teknik ve malzeme desteği: KAK, İBG; Süpervizyon: İBG, ZY; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma retrospektif (geriye dönük) özellikte olduğundan etik kurul onayı alınmamıştır. Hastalardan veya yasal velilerinden ayıdınlatılmış onam alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
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Author Contributions: Concept/Design : KAK, ZY; Data acquisition: KAK; Data analysis and interpretation: KAK, İBG; Drafting manuscript: KAK, ZY; Critical revision of manuscript: KAK, İBG, ZY; Final approval and accountability: KAK, İBG, ZY; Technical or material support: KAK, İBG; Supervision: IBG, ZY; Securing funding (if available): n/a.
Ethical Approval: Since this study has a retrospective (retrospective) feature, ethics committee approval has not been obtained. Patient or legal guardian ayidinlatilm were taken as controls.
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