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Evaluation of Demographic, Histopathologic and Radiological Features of Thyroid Cancer Patients

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Abstract
Aim: Our aim of this retrospective study was to evaluate the demographic, histopathologic and radiological features of thyroid cancer patients.
Material and Methods: In our study 129 thyroid cancer patients were divided into two groups: group 1 (tumor size <1cm) and group 2 (tumor size >1 cm). Parameters were age, gender, preoperative thyroid function test results, findings of nodule structure, nodule echogenicity and border features, presence of microcalcification and halo and anterioposterior diameter in preoperative thyroid ultrasonography, presence of radioactive iodine therapy, postoperative thyroglobulin values, postoperative diagnosis, histological type and size of the tumor, presence of multifocality and bilaterality, presence of invasion and recurrence after therapy.
Results: 27 (20.9%) of the patients were male and the remaining 102 (79.1%) patients were female. The preoperative average age was 44.8±14.4 years. There were no significant differences between two groups when compared to their age, fT3, fT4, TSH, TG, anti-TPO, anti-TG, supplementary operation, postoperative aphonia, hypocalcemia symptoms, multifocality of the tumor, bilateral tumor presence, nodule halo, anterioposterior diameter, recurrence, results of thyroid fine needle aspiration biopsy, structure and echogeneity of the nodule and pre- and postoperative diagnostic features. Most common preoperative histopathological diagnosis was suspicious malignancy (39.6%), whereas the most common postoperative diagnosis was papillary carcinoma (88.5%).
Conclusion: Extensive studies will enable the approaches with a result to minimize the disease related mortality and enable the early diagnosis of thyroid cancers.
Key Words: Thyroid Cancer; Patients; Demography; Histopathology; Epidemiology; Ultrasonography.

Tiroid Kanserli Hastaların Demografik, Histopatolojik ve Radyolojik Özellliklerinin Değerlendirilmesi

Özet
Amaç: Bu retrospektif çalışmada tiroid kanserli hastaların demografik, histopatolojik ve radyolojik özellikleri değerlendirildi.
Gereç ve Yöntemler: Tiroid kanserli 129 hastanın alındığı çalışmada hastalar 2 gruba ayrıldı: grup 1 tümör boyutu 1 cm'den küçük olan hastalar ve grup 2 tümör boyutu bir cm'den büyük olan hastalar. Yaş, cinsiyet, preoperatif tiroid fonksiyon test sonuçları, tiroid ultrasonografisinde nodül yapısı, nodül ekosu ve kenar özelliği, mikrokalsifikasyon ve halo varlığı, anteroposterior çapı, hastanın radyoaktif iyot tedavisi alıp almadığı, postoperatif tiroglobulin değerleri, postoperatif tanı, tümörün histolojik tipi, boyutu, multifokalite ve bilateralite durumu, invazyon varlığı ve tedavi sonrası nüks varlığı değerlendirildi.
Bulgular: Hastaların 27'si (%20.9) erkek ve 102'si (%79.1) kadındı. Hastaların preoperatif yaş ortalaması 44.8±14.4 yıl olarak saptandı. Her iki grup arasında yaş, fT3, fT4, TSH, TG, anti-TPO, anti-TG, tamamlayıcı operasyon, postoperatif ses kısıklığı ve hipokalsemi belirtileri, tümörün multifokal olması, tümörün bilateral yerleşimi, nodül halosu, nodül anteroposterior çapı, nüks, tiroid ince iğne aspirasyon biyopsi sonuçları, nodül yapısı ve nodül ekosu, bakımından anlamlı fark saptanmadı. En sık görülen preoperatif histopatolojik tanı şüpheli malignite (%39.6) iken, postoperatif en sık tanı papiller karsinom (%88.5) olarak rapor edildi.
Sonuç: Geniş çaplı araştırmalar tiroid kanserlerinin erken tanıları ve hastalığa bağlı mortalitelerini en az düzeye indirebilecek tedavi yaklaşımlarının gelişmesine imkan sağlayacaktır.
Anahtar Kelimeler: Tiroid Kanseri; Hastalar; Demografi; Histopatoloji; Epidemiyoloji; Ultrasonografi.

INTRODUCTION

Thyroid cancer that derives from follicular epithelial cells is a common endocrine malignancy and its incidence has been increasing in many regions of the world. Its major histological types are papillary, follicular and anaplastic cancers (1, 2). Papillary thyroid cancers (PTC) that are the most commonly encountered thyroid cancer type comprises approximately 50 to 90% of all differentiated thyroid cancers worldwide (3). Thyroid cancer accounts for approximately 94.5% of all thyroid cancers and is responsible for 65.9% of all endocrine cancer related deaths. Radiation exposure during childhood, advanced age, female gender and family history are risk factors that are known to increase the incidence of well differentiated thyroid cancers. Relative risk of thyroid cancer increases depending on the age exposure takes

place. The younger the subjects are, the higher is the risk. New data shows that there is no correlation between increase in fish consumption and increased thyroid cancer risk (4). Epidemiological studies have shown that individuals with a well differentiated thyroid cancer history in a first degree relative have a 4 to 10 fold increase in malignancy risk (5).

Generally, 5–10% of all thyroid nodules in the population have a possibility to be malignant, whereas this possibility is increased to 33–37% when individuals who were exposed to radiation are concerned (6). Microcalficiations in the thyroid nodules, irregular borders and punctate intranodular hypervascularized flow is in favor of malignancy although it is not diagnostic (7). Cytological diagnostic accuracy of thyroidal fine needle aspiration biopsy (TFNAB) varies between 70 to 97% (8). By reviewing the clinical, histopathologic and demographic features of the thyroid cancer patients that were diagnosed and followed up as part of our study group; our aim was to obtain current data on the etiology of thyroid cancers, diagnosis and treatment and response to various treatment models along with the study of clinical and pathological features that imply malignancy, prognostic features and incidence.

MATERIAL AND METHODS

In this study, 129 thyroid cancer patients that were followed up by Endocrinology and Metabolism Department were reviewed retrospectively by examining medical records, scintigraphy and radiological results and patients were evaluated along with clinical signs and necessary blood work. Patients were divided into two groups: group 1 (tumor size <1cm) and group 2 (tumor size >1 cm). Age, gender, preoperative thyroid function test results (Beckmancoulter kıt), postoperative anti-TPO, anti-TG and globuline levels, preoperative TFNAB results (if performed), complementary operation (if performed), pre and postoperative diagnoses, postoperative aphonia and hypocalcemia symptoms, size of the tumor, type of the tumor, multifocality of the tumor, bilateral tumor presence, nodule halo and anteroposterior diameter of the nodule, presence of extrathyroidal dissemination, presence of invasion recurrence, results of TFNAB, structure, borders and echogenity of the nodule, presence of microcalcifications by using SHIMADZU brand 7.5 MHz high resolution linear probe, previous RAI therapies, whole body iodine screening following therapy, recurrence were the parameters that were used.

RESULTS

Kolmogorov Smirnov test was used to determine the normal distribution of continous variables (p>0.05) . When evaluating the inter-groupal average data for significance unpaired t test was used and Pearson chi–square test and Fisher's chi–square test were used to evaluate categorical variables. Results of continous variables were given as mean ± Standart Deviation (SD). Results of categorical variables were given as number and percent. P values of < 0.05 were accepted as statistically significantIn our study 27 of the patients (20.9%) were male and the remaining 102 (79.1%) were female. Average preoperative age was 44.8±14.4. Free T3 values were between 0.40 and 4.30 pg/ml (mean 3.18±1.20 pg/ml). Free T4 values were between 0.40 and 4.30 ng/dl (mean 0.98±0.48 ng/dl), and TSH values were between 0.00 and 9.5 µIU (mean 2.43.±8.7 µIU).

In the preoperative period 32 (24.8%) of the patients were receiving antithyroidal or L-thyroxin treatment, whereas 97 (75.2%) did not receive any treatment at all. Those who had complementary therapy were 61 (47.7%) and those who did not have complementary therapy were 67 (52.3%) patients. There was no data for 1 patient. Preoperative and postoperative diagnostic features of 129 thyroid carcinoma patients are shown in Tables 1 and 2.

Table 1. Preoperative clinical diagnostic features of the patients

Diagnosis	Number of the Patients	%
Euthyroid multinodular goiter	82	63.5
Euthyroid nodular goiter	25	19.3
Graves Disease	3	2.3
Toxic multinodular goiter	11	8.5
Toxic nodular goiter	1	0.7
Subclinical hyperthyroidism + multinodular goiter	6	4.6
Subclinical-clinical hypothyroidism	1	0.7
Total	129	100

Table 2. Postoperative diagnostic features of the patients.

Diagnosis	Number of Patients	%
Papillary carcinoma	114	88.5
Follicular carcinoma (hurthle–oncocytic carcinoma)	9	6.9
Medullary carcinoma	4	3.1
Anaplastic carcinoma	2	1.5
Total	129	100

Histopathological features and tumor type determined after postoperative pathological analyses of the 86 patients who had preoperative TFNAB and available results are given in Tables 3 and 4. Out of the 129 thyroid carcinoma patients, TFNAB data was not available for 43. 28.7% (n=33) of the tumors were multifocal, 71.3% (n=82) were unifocal, 25.2% (n=29) were bilateral and 74.8% (n=86) were unilateral. Fifteen(12,9%) patients had extrathyroidal involvement, whereas 101 (87,1%) did not have extrathyroidal involvement. Tumors had a minimum size of 4 mm, a maximum size of 100 mm and a mean of 17.7±16.7 mm.

Table 3. Histopathological features of thyroidal fine needle aspiration biopsy results of patients with thyroid carcinoma

TFNAB	Number of the Patients	%
Benign	16	18.6
Suspicious malign	34	39.5
Malign	17	19.8
Non-diagnostic	12	14.0
Hurthle cell neoplasia (follicular lesion)	7	8.1
Total	86	100

Table 4. Postoperative histopathological results of the tumors

Diagnosis	Number of patients	%
Papillary carcinoma, classical type	58	44.97
Papillary carcinoma, follicular variant	43	33.34
Papillary carcinoma, follicular variant and classical type	7	5.43
Papillary carcinoma, oncocytic variant	4	3.10
Papillary carcinoma, diffuse sclerosant variant	1	0.77
Papillary carcinoma, tall cell variant	1	0.77
Follicular carcinoma (hurthle cell-oncocytic carcinoma)	9	6.97
Medullary carcinoma	4	3.10
Anaplastic carcinoma	2	1.55
Total	129	100

When nodule structures were reviewed ultrasonographically in patient; it was seen that 79.1% were solid, 1.1% was cystic and 19.8% were mix nodules. 66.3% of these nodules were hypoechogenic, 26.7% were isoechogenic and 7.0% were hyperechogenic nodules. 91.7% had microcalcifications and 8.3% had no microcalcifications. 33.3% of the patients had regular borders of the nodules, whereas the borders of the nodules were irregular in 66.7% of the patients. The biggest nodule diameter was bigger than 1 cm in 96.5% of the patients, and smaller than 1 cm in 3.5%.

In the 1-20 year follow up of the patients, recurrence was seen in 4.0% (n=5) of the patients and there was no recurrence in the remaining 96.0% (n=121). There was inadequate information concerning recurrence in 3 patients. 86.5% of the patients (n=109) had previous RAI (radioactive iodine) therapies, 13.5% (n=17) had not received any treatment and there was no data for 3 patients. 85.7% (n=108) of the patients had whole body scintigraphic screening with Iodine-131, 14.3% (n=18) were not screened previously and 3 patients did not have adequate information. Invasion characteristics are given in Table 5. Fourteen (10.8%) of the patients did not have any evidence of invasion in their pathology report.

When pathological features of the patients with papillary carcinoma were assessed; it was observed that 28.8% (n=30) had multifocal nodules, 71.2% (n=74) had unifocal, 25.0% (n=26) had bilateral and 75.0% (n=78) had unilateral nodules. Moreover, there were 10 (9.5%) papillary carcinoma patients with extra-thyroidal involvement and 95 (90.5%) who did not have any extra-thyroidal involvement. When pathological features of patients with follicular carcinoma were reviewed, it was seen that 77.8% (n=7) had unifocal and 77.8% (n=7) had unilateral nodules. In addition to this, there was 1 (14.3%) follicular carcinoma patient with extrathyroidal involvement and 6 (85.7%) with no extrathyroidal involvement.

When pathological features of medullary carcinoma patients were assessed, it was observed that 25% (n=1) had multifocal nodules and 25% had (n=1) unifocal, 25% (n=1) had bilateral and another 25% (n=1) had unilateral nodules. 2 (50%) medullary carcinoma patients had extrathyroidal involvement and there were not enough data on the remaining 2 patients.

When pathological features of patients with anaplastic carcinoma were assessed; it was determined that both patients had multifocal and bilateral disease. Moreover, both had extrathyroidal involvement. None of them had satisfactory data about recurrence. There was no statistical significance between two groups when age, fT3, fT4, TSH and other values were compared (Table 6).

In our study; 66% (n=67) of the patients with PTC, 88% (n=8) of the patients with FTC,75% (n=3) of the patients with MTC and 100% (n=2) of the patients with ATC were in group 2. There were no statistically significant differences between both groups when tumor types were compared (p=0.003). When presence of invasion was compared between group 1 and 2, it was documented that all invasion types were more commonly encountered in group 2 and this difference was found to be statistically significant (p=0.038).

Table 5. Invasion characteristics of the tumors

Invasion	Number of the Patients	%
Lenfovascular	7	6.0
Capsule	12	10.5
Capsule + vascular	3	2.6
Lymph node metastasis	10	8.7
Skeletal muscle	3	2.6
Perineural	1	0.9
Extra thyroidal invasion	4	3.5
Tumor confined to thyroid	75	65.2
Total	115	100

Table 6. Comparison of the clinical and laboratory findings between group 1 and 2

	Group 1 (n=49)	Group 2 (n=80)	P
Age (mean ± SD)	46.08±11.10	44.23±16.24	0.44
fT3 (mean ± SD)	3.22±1.51	3.16±0.92	0.78
fT4 (mean ± SD)	1.00±0.45	0.97±0.51	0.73
TSH (mean ± SD)	1.18±1.29	3.26±12.13	0.28
TG (mean ± SD)	1.85±3.99	14.69±47.97	0.04
Gender (% (n))			
Male	12.2 (6)	26.9 (21)	0.058
Female	87.8 (43)	73.1 (57)	
Anti-TPO			
Positive	7.4 (2)	15.6 (7)	0.311
Negative	92.6 (25)	84.4 (38)	
Anti-TG			0.662
Positive	9.4 (3)	6.2 (4)	
Negative	90.6 (29)	92.3 (60)	
Complementary therapy			0.749
Performed	45.8 (22)	47.4 (37)	
Not performed	54.2 (26)	52.6 (41)	
Postoperative aphonia			0.182
Present	14.3 (7)	24.7 (19)	
Non present	85.7 (42)	75.3 (58)	
Postoperative hypocalcemia symptoms			
Present	55.1 (27)	57.1 (44)	0.948
Non present	44.9 (22)	42.9 (33)	
Multifocality			0.568
Present	25.6 (11)	31.0 (22)	
Non present	74.4 (32)	69.0 (49)	
Bilaterality	23.3 (10)	26.8 (19)	0.708
Unilaterality	76.7 (33)	73.2 (52)	
Extrathyroidal invasion			
Present		20.8 (15)	0.001
Non present	100.0 (43)	79.2 (57)	
Microcalcification			0.021
Present	71.4 (5)	100.0 (17)	
Non present	28.6 (2)		
Nodule halo			
Present	75.0 (6)	78.6 (11)	0.848
Non present	25.0 (2)	21.4 (3)	
Recurrence			
Present	2.1 (1)	5.3 (4)	0.395
Non present	97.9 (47)	94.7 (72)	
RAI			
Performed	87.5 (42)	86.8 (66)	0.798
Not performed	12.5 (6)	13.2 (10)	
Iodine screening			
Performed	87.5 (42)	85.5 (65)	0.653
Not performed	12.5 (6)	14.5 (11)	

DISCUSSION

Recently, age and gender related thyroid cancer prevalence has increased more rapidly when compared to other malignancies (9). When cancer statistical data between 1973 and 2002 is reviewed, an increase in PTC incidence to 7.7 from 2.7 in each hundred thousand patients (2.9 times) was observed (1). Prevalence of thyroid cancer of small size seems to be increasing and this seems to be related to the fact that 49% of the papillary carcinomas are smaller than 1 cm and 87% of them are smaller than 2 cm (3,10). Our results were in accordance with the literature. Although papillary thyroid cancer can be seen in all ages, most of the cases are between the ages of 30 and 50 (average 45). It affects mostly women with a percentage of 60 to 80% of the cases are seen in females. PTC is commonly multifocal and limited to one lobe and are seen bilaterally in 20% to 80% of the cases (11). In our study, we observed that 28.8% of the patients with papillary carcinoma had multifocal disease whereas 71.2% of the patients had unifocal disease. There were no significant differences between two groups in regards to this classification.

Ultrasonographic microcalcification rate in the nodule or nodules were significantly higher in group 2 when compared to the other group. It was hypothesized that this was due to having more PTC patients in group 2 and that microcalcification was encountered more in PTC. Extra-thyroidal involvement in PTC is seen in 15% of the

patients during primary surgery and one third of the cases are diagnosed clinically by presence of lymphadenopathies (3,12) Extrathyroidal involvement was less in our cases when compared to the literature (9.5%).

There is evidence of histological involvement in the cervical lymph nodes in 35% to 50% of PTC patients whose lymph nodes were removed. These patients are majorly 17 years old or younger and more than 90% of them present with nodal involvement (13,14). In 1% to 7% of the patients, there is distant metastasis at time of diagnosis (3,12). Lymph node metastasis was also higher in PTC patients when compared to follicular carcinoma patients in our study. Advanced age and presence of extrathyroidal invasion at time of diagnosis are shown as independent risk factors in all studies. Extrathyroidal invasion is not seen in minimal invasive FTCs but are seen frequently in invasive FTCs. Five% to 20% of FTC patients exhibit distant metastasis at time of diagnosis (15). In our study, there were no patients with extra-thyroidal involvement in group 1, there were a fair amount in group 2. This may be related to the fact that the number of papillary carcinoma patients is high in both groups and that extrathyroidal involvement is seen more in PTC. In the same manner, all invasion types were observed more than group 1 and this supports the studies that as tumor size increases invasion rate increases. In accordance with our study, average tumor size in FTCs was found to be bigger in PTCs in most studies (15,16). In many studies, distant metastasis at the time of diagnosis and large tumor diameter were regarded as prognosis changing variables and histopathologic grade was regarded as an independent variable in some studies. Tumor's complete removal at the start was seen as the biggest determining factor of mortality in the postoperative period. Presence of nodal metastasis at the time of diagnosis has been found to be related to nodal recurrence and it has been observed that it does not affect case-specific mortality (17). In FTC patients, thyrotoxicosis can be observed due to large tumor mass and following metastasis of FTC (18). Although the number of FTC patients was limited in our study, we encountered TMNG in preoperative stage in 1 (11.1%) patient and in 7 (7.9%) patients with TMNG. Nodal metastasis or extrathyroidal involvement are seen in patients with age 45 or higher, approximately 4% of these patients have FTC and a 9% have Hurthle cell carcinoma. More than 17% of the patients with FTC (non–oxipholic) have distant metastasis at the time of diagnosis (17) . Nodal metastasis is rarely seen in FTC patients and there is only a 2% nodal recurrence rate when a 20 year postoperative follow up period is reviewed (15). In our study, there were no nodal or distant metastases in FTC patients. Distant metastasis at the time of diagnosis, advanced age, large tumoral mass and exdtrathyroidal invasion are regarded to be poor prognostic risk factors in patients with FTC. Male gender and poorly differentiated tumor are not as effective. In addition to this, vascular invasion and lymphatic involvement are potential risk factors for FTC (17). Medullary thyroid cancer can invade the intraglandular lymphatics and can spread to the other parts of the gland and to the pericapsular and regional lymph nodes in addition. Distant metastasis and lymph node metastasis are common. In more than 60% of the patients, it is found in both lobes (bilateral) (17). In our series, 2 out of 4 patients with medullary thyroid carcinoma had extrathyroidal involvement. Moreover; one patient (25%) with medullary thyroid carcinoma had lymphovascular invasion and one patient (25%) had lymph node metastasis (18).

In Salvador et al's. study that consisted of 325 patients that were diagnosed with differentiated thyroid carcinoma between the years of 1987-2003, it was observed that 78.46% of the patients were either stage 1 or 2 (19). In a study by Hundahl et al which comprised 53.856 patients who were diagnosed with thyroid cancer between the years of 1985-1995, 93% of the patients were diagnosed as having PTC whereas 85% had FTC as the diagnosis and 76% were diagnosed as Hurthle cell carcinoma. In this study, 75% had MTC and a 14% were diagnosed with ATC. Moreover, 71.3% of the patients with PTC and 67.9% of the patients with FTC were found to be stage 1 or 2. A majority of patients with MTC were found to be stage 2 or 3 (20). Although the total patient number was limited in our study; we have found that 79.85% (n=103) of our patients were stage 1, 6.20% (n=8) were stage 2, 9.3% (n=12) were stage 3 and a 4.6% of the patients (n=6) had stage 4 disease.

TG values (14.69 ± 47.97 ng/ml) were recorded to be significantly higher in group 2 in our study. This may be because of the fact that number of PTC patients was more in group 2 and TG secretion secondary to TSH stimulus is higher in these patients. The fact that TG values were higher in FTC and ATC patients in this group when compared to PTC patients may be explained by the fact that tumor sizes are larger and that the frequency of extrathyroidal involvement and metastasis are higher.

It is evident that early diagnosis, proper treatment and close monitoring is a must, although it is an advantage that differentiated thyroid cancers have a good prognosis and a long life expectancy. In those patients with persistent or metastatic disease, therapy modalities involving systemic chemotherapy and/or radiotherapy are being applied. Extensive research will enable the therapeutic approaches that will minimize the disease related mortality and contribute to early diagnosis.

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