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Comparison of Clinicopathological Features in Differentiated Thyroid Carcinomas at 55 Age Cut-Off Point: A Single Center Experience

Diferansiye Tiroid Karsinomlarında 55 Yaş Kesim Noktasında Klinikopatolojik Özelliklerin Karşılaştırılması: Tek Merkez Deneyimi

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ABSTRACT

Aim: The incidence of differentiated thyroid cancer (DTC) has been increasing rapidly in recent years. Patient age at diagnosis is a good prognostic factor for thyroid cancer. DTC is the only malignancy that includes age as part of its staging system. The current 8th edition American Joint Committee on Cancer (AJCC) staging system uses age 55 as a cut-off point for risk stratification. In this study, we aimed to compare the clinicopathological features of DTC in patients <55 and ≥55 years old in our series.

Material and Methods: In total, 920 patients with DTC were retrospectively reviewed. Thyroid functions, ultrasonographic features of malignant nodules, cytological and histopathological findings, and recurrence and persistence rates were compared in patients <55 and ≥ 55 years old.

Results: There were 605 (65.76%) patients <55 years old and 315 (34.24%) patients ≥55 years old. Of all cancer types, 95.79% in <55 years old patients and 94.46% in ≥55 years old were papillary thyroid cancer (PTC) (p = 0.269). The mean tumor diameter was 10.53±10.72 mm in patients <55 years old and 12.65±12.72 mm in patients >55 years old (p=0.009). Extrathyroidal extension (ETE) was detected in 8.42% of <55 years old patients and 12.79% of patients ≥55 years old (p=0.011). Capsular invasion was detected in 19.11% of <55 years old patients and 23.24% of patients ≥55 years old (p=0.032). The rate of chronic lymphocytic thyroiditis in the <55 years old patients was higher than in the ≥55 years old patients (p<0.001). Lymphatic invasion, vascular invasion, lymph node metastasis, distant metastasis, persistence, and recurrence rates were similar.

Conclusion: DTC in patients ≥55 years old is associated with larger tumors, higher risk of ETE, and higher risk of capsular invasion compared to patients <55 years old.

Keywords: Differentiated thyroid carcinoma, Clinicopathological features, Age

ÖZ

Amaç: Diferansiye tiroid kanseri (DTK) insidansı son yıllarda hızla artmaktadır. Tanı anındaki hasta yaşı, tiroid kanseri sağkalımı için iyi bir prognostik faktördür. DTC, evreleme sisteminin bir parçası olarak yaşı içeren tek malignitedir. Mevcut 8. Baskı Amerikan Ortak Kanser Komitesi (AJCC) evreleme sistemi,

risk sınıflandırması için bir kesim noktası olarak 55 yaşı kullanmaktadır. Bu çalışmada, serimizdeki <55 ve ≥55 yaş hastalarda DTK'nın klinikopatolojik özelliklerini karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Toplamda DTK tanılı 920 hasta retrospektif olarak incelendi. <55 ve ≥55 yaş hastalarda tiroid fonksiyonları, malign nodüllerin ultrasonografik özellikleri, sitolojik ve histopatolojik bulgular, nüks ve persistans oranları karşılaştırıldı.

Bulgular: Çalışmamızda <55 yaş grubunda 605 (%65,76) hasta ve ≥55 yaş grubunda 315 (%34,24) hasta vardı. Tüm kanser türlerinin <55 yaş hastalarda %95,79'u ve ≥55 yaş hastalarda %94,46'sı papiller tiroid kanseri (PTK) idi (p=0,269). Ortalama tümör çapı <55 yaş hastalarda 10,53±10,72 mm ve >55 yaş hastalarda 12,65±12,72 mm idi (p=0,009). <55 yaş hastaların %8,42'sinde ve ≥55 yaş hastaların %12,79'unda ekstratiroidal yayılım (ETY) saptandı (p=0,011). <55 yaş hastaların %19,11'inde ve ≥55 yaş hastaların %23,24'ünde kapsüler invazyon saptandı (p=0,032). <55 yaş hastalarda kronik lenfositik tiroidit oranı ≥55 yaş hastalara göre daha yüksekti (p<0,001). Lenfatik invazyon, vasküler invazyon, lenf nodu metastazı, uzak metastaz, persistans ve rekürens oranları benzerdi.

Sonuç: 55 yaş ve üzerindeki hastalarda DTK, 55 yaşın altındaki hastalara kıyasla daha büyük tümörler, daha yüksek ETY riski ve daha yüksek kapsüler invazyon riski ile ilişkilidir.

Anahtar Sözcükler: Diferansiye tiroid karsinomu, Klinikopatolojik özellikler, Yaş

INTRODUCTION

There is an ongoing increase in the incidence of differentiated thyroid cancer (DTC) in recent years (1). DTC accounts for more than 95% of all thyroid cancers and includes papillary (PTC) and follicular (FTC) histopathological subtypes. Patient age at diagnosis is a good prognostic factor for thyroid cancer and has long been associated with survival. Although the association between advanced age and poor survival is common for many types of cancer, DTC is the only human malignancy to include age as part of its staging system. The biology of DTC is highly dependent on age and younger patients outperform older patients in terms of survival (2). It has been reported that there is no specific age limit that predicts prognosis and that the relationship between advancing age and worse outcomes is continuous (3,4). However, most thyroid cancer staging systems include patient age as a binary variable (5,6). Patient age is used as part of current DTC risk stratification algorithms, such as the American Joint Committee on Cancer (AJCC) staging system and the MACIS (metastases, age, completeness of resection, invasion, and size) score (5,7).

Given the results of previous studies investigating the relationship between patient age and disease-specific survival, data on the use of age threshold in DTC staging are conflicting. In the AJCC thyroid cancer staging system, a patient age of 45 years was used as the cut-off point from 1983 to 2018. However, with the recognition of the overall good prognosis of DTC, the eighth edition of the AJCC staging system entered clinical practice on January 1, 2018, to provide more appropriate risk stratification. Compared with the seventh edition, age, tumor size and extrathyroidal extension were revised. In the eighth edition of AJCC thyroid cancer staging, the threshold for age was increased from 45 to 55 (5).

It has long been known that DTC has a poor prognosis in older people. In previous studies, it was reported that more aggressive pathological features were observed more frequently in elderly patients and their cancers were less frequently completely resectable (8). Clinical experience reveals that younger patients have better remission rates and disease-specific survival than older ones, even if they are initially classified at high risk of recurrence.

In this study, we aimed to compare the clinical and pathological features of DTC patients <55 and ≥55 years old, based on the current AJCC staging system.

MATERIAL and METHODS

The medical records of the patients who were operated in Ankara Yıldırım Beyazıt University Faculty of Medicine, Atatürk Training and Research Hospital between December 2006 and September 2014 and diagnosed with DTC histopathologically were reviewed retrospectively. Patients with a previous history of thyroidectomy and radiotherapy to the head and neck region, incomplete clinical or histopathological data, and secondary malignancy were excluded from the study. Local ethics committee approval was obtained in accordance with the ethical standards of the Declaration of Helsinki.

Age, gender, ultrasonographic features, cytological results, type of surgery and final histopathological diagnosis were obtained from medical records. Patients were divided into two groups as <55 and ≥55 years old according to their age at diagnosis of DTC, and the demographic and histopathological features of the patients were compared.

Serum thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), antithyroid peroxidase (anti-TPO), anti-Tg antibody, and Tg measurements were made by chemiluminescence methods (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA, and the UniCel DxI 800, Beckman Coulter, CA, USA). Reference ranges for TSH, fT3, fT4, Tg were 0.4-4.0 μIU/mL, 1.57-4.71 pg/mL, 0.61-1.12 ng/dL, and 0-78 ng/mL, respectively. Anti-TPO higher than 10 U/mLand anti-Tg higher than 30 U/mL were interpreted as positive. Thyroid antibody lev-

el exceeding the upper limit of normal was evaluated as positive. Patients were classified according to their thyroid functions as euthyroidism (both TSH and fT4 within normal limits), hypothyroidism (increased TSH with low fT4) and hyperthyroidism (suppressed TSH with high fT4).

Thyroid US was performed with a superficial probe (Model LA523 13-4, 5.5-12.5 MHz) using Esaote color Doppler US (Model 796FDII; MAG Technology Co. Ltd., Yung-Ho City, Taipei, Taiwan). The localization, diameter, anterior posterior-transverse diameter (AP/T) ratio, echogenicity, texture, marginal regularity, presence of microcalcification and macrocalcification, and peripheral halo of the nodules were evaluated.

US-guided Fine Needle Aspiration Biopsy (FNAB) was performed by an experienced endocrinologist. FNAB was applied to all nodules with an ultrasonographic nodule diameter ≥1 cm. It was also performed in <1 cm nodules when there were suspicious US features and/or clinical risk factors. Cytological findings were classified according to nondiagnostic (ND), benign, atypia of undetermined significance / follicular lesion of undetermined significance (AUS / FLUS), follicular neoplasm / suspected follicular neoplasm (FN / SFN), and according to the Bethesda System (9).

Pathological specimens were evaluated by two experienced thyroid pathologists. Tumor size, presence of lymphocytic thyroiditis, number of tumors (unifocal/multifocal), lymph node metastasis (LNM), distant metastasis, vascular invasion, capsular invasion, and extra thyroidal extension (ETE) were recorded from histopathology reports. It was accepted that the thyroid capsule was invaded in patients whose thyroid capsule was infiltrated by the tumor but without surrounding soft tissue and muscle involvement. If the tumor was invaded to the surrounding soft tissue or muscle, it was accepted as ETE. Histological variants of PTC have been grouped into classical, follicular, tall cell, oncocytic, and others (diffuse sclerosing, encapsulated, columnar cell, solid/trabecular, Warthin-like). Multifocality was defined as the presence of two or more tumor foci. All patients diagnosed with PTC were routinely evaluated with nuclear medicine specialists for possible adjuvant therapy with radioactive iodine (RAI). Remission was defined as serum thyroglobulin levels <2 ng/mL during TSH suppression and absence of anti-Tg and no clinical or imaging evidence of tumors. The definition of persistence was used for patients who never met the criteria for remission. If a patient in remission developed evidence of disease at follow-up, it was defined as a recurrence.

In this study, sample size and power analysis were calculated using G*Power software (latest version 3.1.9.7). The effect size was 0.22, type 1 error was 0.05, type 2 error was 0.20, and the N2/N1 ratio was 0.50. All statistical analyzes were performed with a software package program (SPSS, version 11.5 for Windows; SPSS Inc., Chicago, IL, USA). The normality of the distribution of continuous variables was tested with the Kolmogorov-Smirnov test. Descriptive statistics were presented as mean ± SD with medians (minimum-maximum) for continuous variables and percentages (%) for categorical variable. Differences in groups were compared with Student's t test for parametric variables and Mann-Whitney U test for non-parametric variables. Chi-square test was used to investigate the difference between groups in terms of categorical variables. A value of $p < 0.05$ was accepted to indicate statistical significance.

RESULTS

The data of 920 patients who were diagnosed with DTC histopathologically were analyzed. 605 (65.76%) patients were <55 years old and 315 (34.24%) were ≥ 55 years old. There were 488 (80.66%) female and 117 (19.34%) male in the <55 years old, and 238 (75.56%) female and 77 (24.44%) male patients in the ≥55 years old (Table 1) (p=0.072). Mean age was 42.25±8.56 and 62.43±6.28 years in <55 years old patients and ≥55 years old patients, respectively (p< 0.001). Serum TSH, fT4, fT3 and anti-Tg antibody positivity at the time of diagnosis were similar in both groups (p=0.093, p=0.499, p=0.254 and p=0.223, respectively). Anti-TPO antibody positivity was significantly higher in patients <55 years old (p=0.044). The rate of chronic lymphocytic thyroiditis in the <55 years old patients was higher than in the ≥55 years old (p<0.001). Anteroposterior and longitudinal diameters of malignant nodules were larger in the ≥55 years old than in patients <55 years old (p=0.007 and p=0.014, respectively), but other preoperative US features were similar in both groups (Table 2).

Cytological and histopathological features in <55 and ≥ 55 years old patients are compared in Table 3. There were a total of 1348 malignant foci, and 879 (65.21%) were in <55 years old patients and 469 (34.79%) were in ≥55 years old patients. Tumor diameter was 10.53 ± 10.72 mm in the <55 years old patients and 12.65 ± 12.72 mm in the ≥55 years old patients (p=0.009). While 415 (47.21%) of tumors in <55 years old patients were incidental, 232 (49.47%) of tumors in the ≥55 years old patients were incidental (p=0.431). LNM, vascular invasion, lymphatic invasion, and distant metastasis rates were similar in two groups (p=0.931, p=0.539, p=0.984 and p=0.638, respectively) (Table 1 and 3). Capsular invasion was detected in 168 (19.11%) of <55 years old patients and 109 (23.24%) of patients ≥55 years old (p=0.032). ETE was detected in 74 (8.42%) of the tumors of the <55 years old patients and in 60 (12.79%) of the tumors of the patients ≥55 years old (p=0.011).

The histopathological tumor type distribution was similar in both groups. 842 (95.79%) of tumors in patients <55 years old and 443 (94.46%) of tumors in patients ≥55 years old were PTC. Classical variant, follicular variant PTC (FVPTC),

Table 1: Demographical, clinical and histopathological features of patients with differentiated thyroid cancer <55 and ≥ 55 years old.

Parameters	<55 years (n= 605)	≥55 years (n= 315)	p
Age (year±std)	42.25±8.56	62.43±6.28	**<0.001**
Sex*			
Male	117 (19.34)	77 (24.44)	0.072
Female	488 (80.66)	238 (75.56)	
TSH (μIU/mL)	1.61±1.92	1.50±1.35	0.093
fT4 (ng/dL)	1.16±0.32	1.18±0.34	0.499
fT3 (pg/mL)	3.35±1.34	3.25±1.19	0.254
Anti TPO positivity*(n =747)	131 (27.12)	54 (20.45)	**0.044**
Anti-Tg positivity*(n = 737)	124 (25.83)	56 (21.79)	0.223
Functional status*			
Euthyroid	439 (72.56)	217 (68.89)	0.085
Hypothyroid	57 (9.42)	23 (7.30)	
Hyperthyroid	109 (18.02)	75 (23.81)	
Nodule number in US	3.75±2.94	5.29±3.69	**<0.001**
Surgical approach*			
BTT/NT	556 (91.90)	303 (96.19)	**0.013**
Hemithyroidectomy	49 (8.10)	12 (3.81)	
Operation indications*			
Giant nodule	108 (17.85)	59 (18.73)	0.246
Hyperthyroidism	54 (8.93)	38 (12.06)	
Cytology			
Malignant	104 (17.19)	57 (18.10)	
Suspicious for malignancy	106 (17.52)	33 (10.48)	
FN/SFN	44 (7.27)	19 (6.03)	
AUS/FLUS and suspicious ultrasonography features	114 (18.84)	65 (20.63)	
Non-diagnostic	52 (8.60)	30 (9.52)	
Parathyroid pathology	2 (0.33)	1(0.32)	
Other	21 (3.47)	13 (4.13)	
Multifocality*	189 (31.24)	109 (34.60)	0.301
Lymph node metastasis*	49 (8.10)	25 (7.94)	0.931
Distant metastases*	1 (0.17)	1 (0.32)	0.638
Lymphocytic thyroiditis*	234 (38.68)	85 (26.98)	**<0.001**

TSH: thyrotropin, **fT3:** free triiodothyronine, **fT4:** free thyroxine, **anti-TPO:** antithyroid peroxidase antibodies, **anti-Tg:** anti-thyroglobulin antibodies, **US:** ultrasonography, **BTT/NT:** bilateral total thyroidectomy/near-total thyroidectomy, **FN/FNS:** follicular neoplasm/suspicious for follicular neoplasm, **AUS/FLUS:** atypia of undetermined significance/follicular lesion of undetermined significance.

Significant p values are indicated as bold in the table

*Data are presented n (%)

oncocytic and tall cell variant PTC were similar in both groups (p=0.723, p=0.798, p=0.723 and p=0.544, respectively). Mean follow-up period was similar in two groups (p = 0.874). RAI ablation was performed in 514 (78.71%) of <55 years old patients and 259 (71.94%) of ≥55 years old (p = 0.282). 194 (37.74%) <55 years old patients and 115 (44.40%) ≥55 years old patients were ablated with a RAI dose greater than 100 mCi. Persistence and recurrence rates were similar in two groups (p=0.348 and p=0.630, respectively) (Table 3).

DISCUSSION

Our study revealed that DTC is associated with larger tumors and higher risk of ETE and capsular invasion in patients ≥55 years old than in patients <55 years old. Our findings support the hypothesis suggested by the eighth edition of the AJCC classification that patients ≥55 years old with DTC have a higher incidence of histopathological features associated with the aggressive course and that the risk of locally advanced disease is relatively higher than patients <55 years old.

Table 2: Ultrasonography features of malignant thyroid nodules in patients <55 and ≥ 55 years old.

Ultrasonography features	<55 years (n= 605)	≥ 55 years (n= 315)	p
Diameters (mm) Anteroposterior	11.82 (3.21-56)	12.91 (4.3-41.1)	**0.007**
Transverse	12.43 (3.4-92.4)	13.45 (5.3-68.4)	0.124
Longitudinal	14.15 (3.9-88.2)	17.18 (4.2-93)	**0.014**
AP/T	0.89± 0.24	0.91 ± 0.26	0.521
Localization*			
Right	334 (55.21)	173 (54.92)	0.953
Left	254 (41.98)	132 (41.91)	
Isthmus	17 (2.81)	10 (3.17)	
Texture*			
Solid	593 (98.02)	309 (98.10)	0.935
Cystic/mixed	12 (1.98)	6 (1.90)	
Echogenicity*			
Isoechoic	218 (36.03)	115 (36.51)	0.990
Hypoechoic	151 (24.96)	78 (24.76)	
Iso-hypoechoic	236 (39.01)	122 (38.73)	
Microcalcification*	266 (43.97)	141 (44.76)	0.818
Macrocalcification*	198 (32.72)	102 (32.38)	0.915
Hypoechoic halo*	151 (24.96)	62 (19.68)	0.072
Irregular margins*	365 (60.33)	194 (61.59)	0.711

AP/T: ratio of anterior posterior to transverse diameter

Significant *p* values are indicated as bold in the table

*Data are presented n (%)

DTC is the fastest increasing malignancy in the world and the prognosis is generally excellent with appropriate therapy. The patient's age at presentation clearly affected the prognosis, and the AJCC has included age in tumor staging since 1983 (5). Unlike other types of cancer, thyroid cancer staging is based on age. In the eighth edition of the AJCC staging system, patients with DTC under the age 55 are considered low risk and have a favorable prognosis even in the presence of regional advanced disorders. Generally, age above 55 years is regarded as a poor prognostic marker in DTC, using the AJCC staging system; the mortality rate climbs gradually starting at age 55 years and above (5). Previous studies have reported some clinicopathological features in elderly patients (≥55 years), such as large primary tumors at diagnosis, more aggressive histopathological variants of DTC, higher risk of distant metastases at presentation, and higher recurrence rates (10,11).

The relationship of age to thyroid cancer outcome is still unclear, but there may be some reasons why elderly patients at the time of diagnosis have a worse prognosis than younger patients. DTC is a slow-growing tumor, and tumors that are usually diagnosed at a younger age are more likely to be confined to the thyroid gland. Sometimes it may have spread only to the central compartment of the neck or, less frequently, to the regional lymph nodes. However, over the years, these tumors may develop distant metastases with local invasion and regional involvement associated with poor prognosis. It has also been suggested that well-differentiated tumors may mutate and dedifferentiate over time, becoming both more aggressive and less susceptible to RAI, thus having a worse prognosis. In an age-related mutation study, the BRAF (V600E) mutation correlated with the worst outcome for PTC patients, who were not only at a higher risk not to be cured but also for death. In particular, the BRAF (V600E) mutation was demonstrated to be a poor prognostic factor independent from other clinicopathological features (12). Furthermore, TERT promoter mutations have been reported as the major predictor of poor outcomes in DTC such as recurrence and disease related mortality (13).

Changes in the expression of the sodium-iodine transporter play a critical role in RAI uptake, and previous studies have shown that these changes are related to patient age (14,15). More functional sodium iodine symptom expression in younger patients is another hypothesis that explains the higher probability of younger patients having radioiodine-avid cancer and a better prognosis (2). Also, the increase in serum TSH level with aging may support both the increase in the incidence of thyroid cancer and the acceleration of tumor growth progression (16). In addition, the immune system may play an important role in controlling cancer forma-

Table 3: Cytological and histopathological features of malignant thyroid nodules in patients <55 and ≥55 years old and follow-up data of patients.

	<55 years (n= 605)	≥55 years (n= 315)	p
Cytological diagnosis*	n=479	n=235	
Nondiagnostic	52 (10.86)	30 (12.77)	0.452
Benign	59 (12.32)	31 (13.19)	0.741
AUS/FLUS	114 (23.80)	65 (27.66)	0.263
FN/SFN	44 (9.19)	19 (8.09)	0.626
Suspicious for malignancy	106 (22.13)	33 (14.04)	**0.010**
Malignant	104 (21.71)	57 (24.26)	0.445
Histopathological features*	n=879	n=469	
Tumor diameter	10.53±10.72	12.65±12.72	**0.009**
Microcarcinoma	100 (11.38)	64 (13.64)	0.225
Incidentality	415 (47.21)	232 (49.47)	0.431
Tumor type*	n=879	n=469	
Papillary	842 (95.79)	443 (94.46)	0.269
Follicular	26 (2.96)	14 (2.98)	0.978
Hurthle cell	11 (1.25)	12 (2.56)	0.078
PTC variants*	n=859	n=459	
Classical	674 (78.46)	364 (79.30)	0.723
Follicular	147 (17.11)	76 (16.56)	0.798
Oncocytic	18 (2.09)	11 (2.39)	0.723
Tall cell	15 (1.75)	6 (1.31)	0.544
Other	5 (0.59)	2 (0.44)	0.728
Capsular invasion*	168 (19.11)	109 (23.24)	**0.032**
Vascular invasion*	23 (2.62)	15 (3.20)	0.539
Extrathyroidal extension*	74 (8.42)	60 (12.79)	**0.011**
Lymphatic invasion*	13 (1.48)	7 (1.49)	0.984
Follow-up period (month)	41.25 ± 21.78	39.38 ± 11.04	0.874
RAI treatment*	514 (78.71)	259 (71.94)	0.282
RAI dose (mCi)*			
≤100	320 (62.26)	144 (55.60)	0.074
>100	194 (37.74)	115 (44.40)	
Persistence*	13 (2.15)	4 (1.27)	0.348
Recurrence*	4 (0.66)	3 (0.95)	0.630

AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance, **FN/SFN:** follicular neoplasm/suspicious for follicular neoplasm, **PTC:** papillary thyroid cancer, **RAI:** radioactive iodine.

Significant *p* values are indicated as bold in the table

*Data are presented n (%)

tion and invasion, and there may be a decline in immune response with aging. The worsening prognosis with age can be explained by the reduced immune system response with aging. On the other hand, all-cause mortality increases with aging, and this may contribute to the overall increase in older age mortality in thyroid cancer patients.

Several clinicopathological features, such as age, gender, tumor size, ETE, LNM and distant metastasis, are well-known prognostic factors in DTC patients (17). ETE is defined as the spread of the tumor beyond the thyroid capsule to adjacent soft tissue. It is generally accepted that advanced ETE adversely affects the prognosis of DTC. Ito et al. reported that recurrence free survival was significantly worse in patients with tumors with massive extension compared to those with minimal or no extension (18). On the other hand, some previous studies have shown worse survival rates even in patients with minimal extension (19). Previous studies have shown that tumor size and older age are independent risk factors for ETE and patients with ETE are more likely to have positive surgical margins (20,21). That is, sustained tumor growth will increase the likelihood of the tumor extension beyond the thyroid capsule, especially in peripheral tumors. Aging restrains adaptive immunity and

makes the tumor microenvironment more immunosuppressive, which may facilitate the invasion process (22).

Tumor size and ETE appear to be major factors in classification of AJCC guideline tumor staging (5). One of the most important prognostic factors for DTC is tumor size. Generally, increased tumor diameter in DTC is associated with worse prognosis and increased mortality rates. Tumors larger than 4 cm have been reported to have a significantly higher rate of disease-specific mortality (23). Some previous authors have shown that vascular invasion, ETE, lymphatic invasion, and cervical lymph node metastasis are more common in patients with DTC >1 cm than in patients <1 cm (24). Tumor size has been shown to be an important determinant of survival, even in patients with clinically early stages (25). On the other hand, it has been reported that the prognostic effect of tumor size may vary according to the age of the patient at the time of diagnosis. Although it is an independent predictor of survival in patients ≥55 years old, it has been reported that it has no effect in patients <55 years old (26).

The prognostic significance of tumor capsular invasion in DTC is unclear. Previous publications considered angioinvasion to be the main prognostic factor, while considering capsular invasion of not much significance. However, some more recent studies seem to suggest that wide invasion, not specifically angioinvasion, is an adverse prognostic factor (27,28).

In our study, we confirmed that some histopathological features related to poor prognosis, such as ETE and capsular invasion, are more common in older patients (≥55 years old) than younger patients (<55 years old). In addition, tumor size was larger in older patients than in younger patients. We found no difference in the frequency of LNM and distant metastases in younger and older patients. Zhang et al. evaluated patients with PTC by age group and reported that bilateral LNM is more likely in older patients (45-65 years) than younger patients. They also found that tumors in the elderly group showed more capsular and extrathyroidal extension than those in the middle and young groups (29). In addition, another study reported that tumor diameter and LNM were independent predictors for recurrence in elderly patients with PTC (30).

Data on the effect of chronic lymphocytic thyroiditis on clinicopathological parameters of DTC are uncertain (31). Many previous studies have shown less aggressive disease and a better outcome at presentation in patients with DTC and chronic lymphocytic thyroiditis (32,33), but some studies have not supported these results (34,35). Borowczyk et al. showed that lymphocytic thyroiditis has a protective effect on the prognosis of DTC. Patients with DTC with chronic lymphocytic thyroiditis were younger than patients with DTC without chronic lymphocytic thyroiditis (36). In accordance with this result, in our study, the rate of chronic lymphocytic thyroiditis in the <55 years old patients were higher than in the ≥55 years old patients.

Our study has some limitations. The first is its retrospective design. Second, it is a single center analysis. Third, the follow-up period was relatively short in our study. Considering the slow course of DTC, a longer follow-up period is needed to fully evaluate the impact of clinical and pathological features on prognosis. In addition, the inability to perform molecular tests in our center during our study was another limitation. Finally, central lymph node dissection is not routinely performed in patients who underwent thyroidectomy in our center. This situation may have confused the nodal status of the patients. However, prophylactic central lymph node dissection is still controversial, and there is no definitive recommendation to support routine central lymph node dissection in the absence of evidence of metastasis (37).

In conclusion, patient age in DTC is an important prognostic indicator in most staging systems. Risk stratification for disease recurrence and survival is a critical component of DTC management and is based on the age of the patient at diagnosis and the clinical and pathological characteristics of the tumor. Our series revealed that DTC is associated with larger tumors, higher risk of ETE, and higher risk of capsular invasion in patients older than 55 years old compared to patients <55 years old. Our results support that, according to the eighth edition of the AJCC classification, patients ≥55 years old have a higher incidence of histopathological features associated with the aggressive course than patients <55 years old in DTC.

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Author Contributions

Concept: **Nagihan Bestepe,** Design: **Nagihan Bestepe, Oya Topaloglu,** Data collection or processing: **Nagihan Bestepe, Husniye Baser, Abdussamed Yalcin,** Analysis or Interpretation: **Nagihan Bestepe, Husniye Baser, Aysegul Aksoy Altinboga,** Literature search: **Nagihan Bestepe, Reyhan Ersoy, Bekir Cakir,** Writing: **Nagihan Bestepe, Husniye Baser,** Approval: **Nagihan Bestepe, Reyhan Ersoy, Bekir Cakir.**

Conflicts of Interest

The authors declare no conflict of interest.

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Ethical Approval

The present study was approved by the Ethics Commitee of Ankara City Hospital (REC number: E1-21-2081, Date:20.10.2021). Since the study was retrospective, informed consent was not obtained from the patients.

Review Process

Extremely peer-reviewed and accepted.

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