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Interplay and clinicopathological correlates of tumor size, multifocality and aggressive variants in patients with operated differentiated thyroid carcinoma: A retrospective cohort study

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ABSTRACT

Objectives: To investigate the interplay and clinicopathological correlates of tumor size, cancer foci (multifocality/bilaterality), and aggressive variants in patients with operated differentiated thyroid cancer (DTC).

Methods: A total of 596 patients with operated DTC (median age: 47.0 (range: 18.0-87.0 years, 77.5% were females) were included in this retrospective cohort study. Data on patient demographics, cancer foci, concomitant Hashimoto's thyroiditis, surgery type, DTC subtype (papillary thyroid cancer [PTC], follicular thyroid cancer [FTC]) and variants, tumor size, lymph node metastasis, tumor invasion were recorded.

Results: PTC aggressive variant (21.9%, P=0.045), extrathyroidal invasion (24.6%, P=0.012), tall cell PTC variant (60.3%, P=0.043), and widely invasive FTC variants (60.0% P=0.002) rates were significantly higher in the bilateral multifocal tumors than in the unifocal and unilateral multifocal tumors. The rates of Hashimoto's thyroiditis (59.8%, P<0.001) and PTC subtype (99.6%, P<0.001) were significantly higher, while the rates of lymph node metastasis (5.8%, P<0.001), capsule invasion (11.6%, P<0.001), vascular invasion (0.4%, P<0.001) and extrathyroidal invasion (4.5%, P<0.001) were significantly lower in <10 mm than in >10 mm tumors. Presence vs. absence of PTC aggressive variant was associated with significantly higher greatest tumor size (12 mm, P=0.013) and higher rates of multifocal tumor (50.5%, P=0.013) and extrathyroidal invasion (33.0%, P<0.001).

Conclusions: Our findings revealed the presence of bilaterality/multifocality and aggressive variants in a considerable proportion of patients with operated DTC, and a multifaceted interplay between bilaterality/multifocality, tumor size, and PTC aggressive variants, in addition to their individual effects on increased risk of tumor invasion, particularly the extrathyroidal invasion.

Keywords: Differentiated thyroid cancer, cancer foci, tumor size, multifocality/bilaterality, aggressive variants.

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy, while papillary thyroid cancer (PTC) is the main subtype accounting for over 85% of DTC cases [1, 2]. Although PTC usually has a favorable prognosis, up to 20% of patients develop loco-regional recurrence with

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worse clinical outcomes requiring further treatment, and distant metastasis occurs in 10-15% of patients [3, 4].

Tumor size, extrathyroidal extension, and multifocality of tumor are considered amongst the clinicopathological factors used to differentiate patients at high risk of recurrence [5]. Multifocality is a frequent pathological feature of PTC generally detected in pathology specimens postoperatively [6], which may occur as multicentric independent synchronous neoplastic foci or as intrathyroidal spread from the primary tumor [5-7]. Multifocal lesions, particularly those with bilateral involvement, are associated with a higher degree of malignant characteristics and a more aggressive disease with an increased risk of lymph node metastasis and extrathyroidal extension [2, 6, 8, 9]. Accordingly, multifocality is involved in the PTC risk stratification systems as a poor prognostic factor associated with increased risk of local recurrence, lymph-node metastasis, and distant metastasis [10, 11].

However, there are conflicting results in the literature on the prognostic significance of multifocality in PTC. Some studies indicated more aggressive features and worse outcome in multifocal versus unifocal tumors, whereas others reported no such differences based on cancer foci or aggressive features [6, 8]. Hence, the clinical and prognostic implications of multifocality/bilaterality have been highly controversial, which contributes to uncertainty regarding the choice of appropriate treatment [5, 6, 11].

Therefore, this retrospective cohort study aimed to comparatively investigate the interplay and clinicopathological correlates of tumor size, cancer foci (multifocality/bilaterality), and aggressive variants in patients with operated DTC.

METHODS

Study Population

A total of 596 patients with operated DTC (median(min-max) age: 47.0(18.0-87.0) years, 77.5%

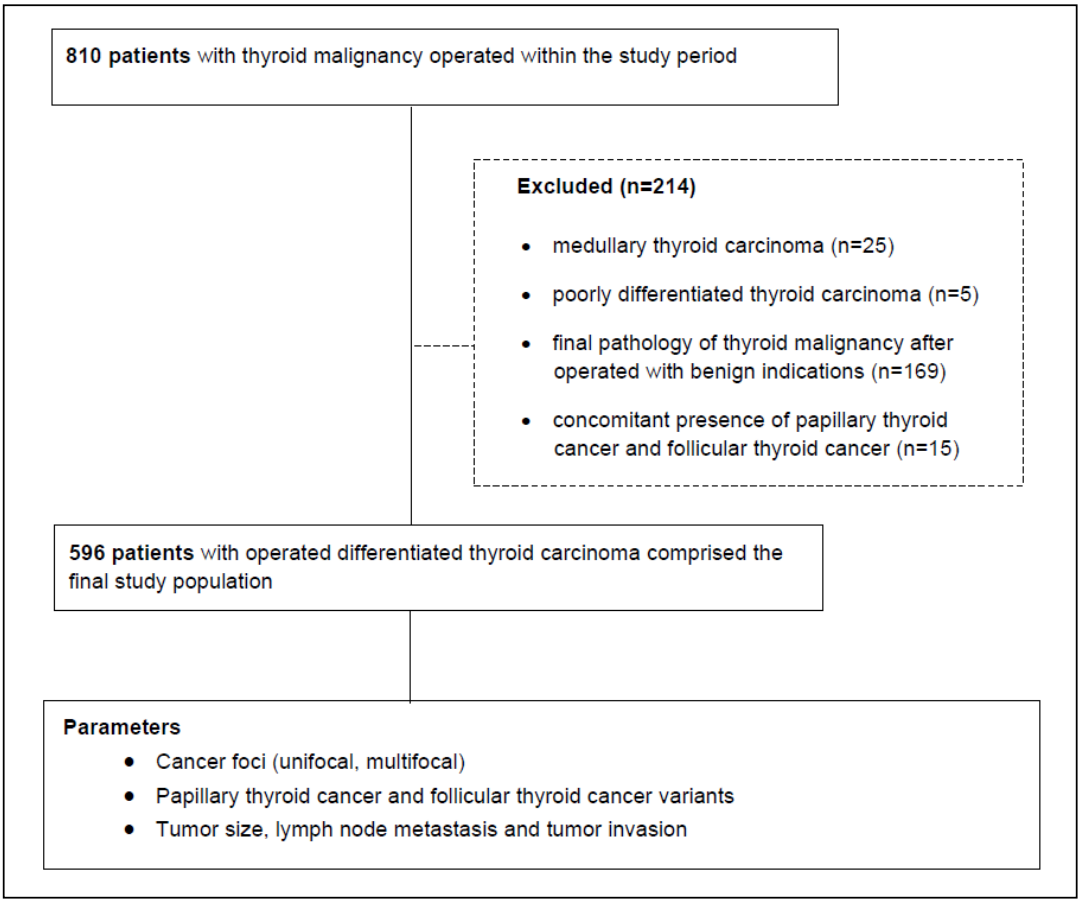

Fig. 1. Study flowchart.

were females) were included in this retrospective cohort study conducted at a tertiary care center between January 2011 and August 2023. Adult (age >18 years) patients who operated with the suspected diagnosis of DTC and had the final pathological diagnosis confirming the DTC were included in the study. Concomitant presence of PTC and FTC subtypes, recurrence, and final pathology of thyroid malignancy after being operated on with benign indications such as multinodular goiter or treatment-resistant Graves' disease were the exclusion criteria of the study. Accordingly, while overall 810 patients with thyroid malignancy were operated on within the study period, the final study population comprised 596 patients with exclusion of 214 patients due to medullary thyroid carcinoma (n=25), poorly differentiated thyroid carcinoma (n=5), final pathology of thyroid malignancy after operated with benign indications such as multinodular goiter or treatment-resistant Graves' disease (n=169), concomitant presence of PTC and FTC (n=15) (Fig. 1).

Written informed consent was obtained from each participant. This study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Bursa Uludag University Clinical Research Ethics Committee (Date of Approval: 12/12/2023; Protocol No: 2023-27/20).

Assessments

Data on patient demographics (age, gender), cancer foci (unifocal, multifocal), concomitant Hashimoto's thyroiditis, surgery type, DTC subtype (PTC, follicular thyroid cancer [FTC]) and variants, tumor size, lymph node metastasis, tumor invasion (capsule, vascular and extrathyroidal) were recorded in each patient. Study parameters were also evaluated across cancer foci (unilateral unifocal, unilateral multifocal, and bilateral multifocal) and tumor size (<10 mm, 10-39 mm, and ≥40 mm) subgroups, while cancer foci and tumor invasion status were also evaluated with respect to PTC and FTC variants.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY). The conformity of the variables to the normal distribution was examined using the Kolmogorov-Smirnov method. The chi-square (X^2) test and Fisher's exact test were used to compare categorical data. Mann-Whitney U test was used to analyze two independent non-normally distributed variables. Data were expressed as median (minimum-maximum), and percent (%) where appropriate. $P<0.05$ was considered statistically significant.

RESULTS

Patient Demographics, Surgery Type, and Tumor Characteristics

Median patient age was 47.0 years (range, 18.0 to 87.0 years) and females comprised 77.5% of the study population. Concomitant Hashimoto's thyroiditis was noted in 52.7% of patients (Table 1). Total thyroidectomy (88.9%) was the leading operation and PTC (94.8%) was the most common DCT subtype. Multifocal cancer was noted in 38.1% (bilateral in 30.7%) of patients and PTC aggressive variants were noted in 17.1% of patients. Papillary thyroid microcarcinoma (PTMC; tumor size <10 mm) was evident in 37.6% of patients. Lymph node metastasis, capsule invasion, vascular invasion, and extrathyroidal invasion were noted in 13.4%, 19.1%, 7.4% and 17.6% of patients, respectively (Table 1).

Study Parameters in Cancer Foci Subgroups

Bilateral multifocal tumors were associated with significantly higher total thyroidectomy (99.5% vs. 84.6% and 81.8%, respectively, P<0.001), PTC aggressive variant (21.9% vs. 13.6% and 15.9%, respectively, P=0.045) and extrathyroidal invasion (24.6% vs. 14.4% and 15.9%, respectively, P=0.012) rates, compared to the unifocal and unilateral multifocal tumors (Table 2). PTC subtype was significantly more common in the unilateral multifocal (100.0%) and bilateral multifocal (98.4%) tumors compared to the unifocal tumors (92.4%, P=0.003). The largest tumor size was significantly lower in the unilateral multifocal tumors than in unifocal tumors and bilateral multifocal tumors (median (min-max): 8.5 (1.0-45.0) vs. 12.0 (1.0-180.0) and 12.0 (2.0-105.0) mm, respectively, P=0.024). Patient demographics, and the presence of Hashimoto thyroiditis, lymph node metastasis, and capsular and vascular tumor invasion were similar across cancer foci subgroups (Table 2).

Table 1. Patient demographics, surgery type and tumor characteristics (n = 596)

Age (year), median (min-max)	Total	47.0 (18.0-87.0)
	Females	46.5 (18.0-82.0)
	Males	49.5(20.0-87.0)
Gender, n (%)		
Female		462(77.5)
Male		134(22.5)
Concomitant Hashimoto's thyroiditis, n (%)		
No		282 (47.3)
Yes		314 (52.7)
Surgery type, n (%)		
Total thyroidectomy		530(88.9)
Lobectomy		62(10.4)
Other		4(0.7)
DTC subtype, n (%)		
PTC		565(94.8)
FTC		31(5.2)
Cancer foci, n (%)		
Unifocal		369(61.9)
Unilateral multifocal		44(7.4)
Bilateral multifocal		183(30.7)
PTC aggressive variants, n (%)		
Absent		468 (82.9)
Present		97 (17.1)
Lymph node metastasis, n (%)		
Absent		516 (86.6)
Present		80 (13.4)
Central		*27 (4.5)*
Lateral		*38 (6.4)*
Both		*15 (2.5)*
Largest tumor size (mm), median (min-max)		12.0 (1.0-180.0)
Tumor size groups, n (%)	<10 mm (PTMC)	224 (37.6)
	10-39 mm	329 (55.2)
	≥40 mm	43 (7.2)
Capsule invasion, n (%)		
Absent		482 (80.9)
Present		114 (19.1)
Vascular invasion, n (%)		
Absent		552 (92.6)
Present		44 (7.4)
Extrathyroidal invasion, n (%)		
Absent		491 (82.4)
Present		105 (17.6)

DTC=Differentiated thyroid carcinoma, PTC=Papillary thyroid cancer, FTC=Follicular thyroid cancer, PTMC=Papillary thyroid microcarcinoma

Table 2. Study parameters according to cancer foci

	Cancer foci			
	Unifocal (n = 369)	**Unilateral multifocal (n = 44)**	**Bilateral multifocal (n = 183)**	**P value**
Age (year), median (min-max)	47.0 (18.0-82.0)	47.5 (24.0-81.0)	47.0 (18.0-87.0)	0.962
Gender, n(%)				
Female	282 (76.4)	35 (79.5)	145 (79.2)	0.716
Male	87 (23.6)	9 (20.5)	38 (20.8)	
Hashimoto's thyroiditis, n(%)				
No	181 (49.1)	15 (34.1)	86 (47.0)	0.170
Yes	188 (50.9)	29 (65.9)	97 (53.0)	
Surgery type, n(%)				
Total thyroidectomy	312 (84.6)[a]	36 (81.8)[a]	182 (99.5)	**<0.001**
Lobectomy	55 (14.9)	7 (15.9)	0 (0.0)	
Other	2 (0.5)	1 (2.3)	1 (0.5)	
DTC subtype, n(%)				
PTC	341 (92.4)	44 (100.0)[b]	180 (98.4)[b]	**0.003**
FTC	28 (7.6)	0 (0.0)	3 (1.6)	
PTC aggressive variants, n(%)				
Absent	319 (86.4)	37 (84.1)	143 (78.1)	**0.045**
Present	50 (13.6)[a]	7 (15.9)[a]	40 (21.9)	
Lymph node metastasis, n(%)				
Absent	324 (87.8)	40 (90.9)	152 (83.1)	0.208
Present	45 (12.2)	4 (9.1)	31 (16.9)	
Central	14 (31.1)	1 (25.0)	12 (38.7)	0.812
Lateral	21 (46.7)	3 (75.0)	14 (45.2)	
Both	10 (22.2)	0 (0.0)	5 (16.1)	
Largest tumor size (mm), median (min-max)	12.0 (1.0-180.0)	8.5 (1.0-45.0)	12.0 (2.0-105.0)	**0.024**
Tumor size groups, n(%) <10 mm	143 (38.8)	23 (52.3)	58 (31.7)	0.097
10-39 mm	198 (53.7)	20 (45.5)	111 (60.7)	
≥40 mm	28 (7.6)	1 (2.3)	14 (7.7)	
Capsule invasion, n(%)				
Absent	299 (81.0)	36 (81.8)	147 (80.3)	0.967
Present	70 (19.0)	8 (18.2)	36 (19.7)	
Vascular invasion, n(%)				
Absent	337 (91.3)	43 (97.7)	172 (94.0)	0.214
Present	32 (8.7)	1 (2.3)	11 (6.0)	
Extrathyroidal invasion, n(%)				
Absent	316 (85.6)	37 (84.1)	138 (75.4)	**0.012**
Present	53 (14.4)	7 (15.9)	45 (24.6)	

DTC=Differentiated thyroid carcinoma, PTC=Papillary thyroid cancer, FTC=Follicular thyroid cancer

Table 3. Study parameters according to tumor size

	Tumor size			
	<10 mm (n = 224)	**10-39 mm (n = 329)**	**≥40 mm (n = 43)**	**P value**
Age (year), median (min-max)	47.0 (20.0-81.0)	48.0 (18.0-87.0)	45.0 (20.0-82.0)	0.995
Gender, n (%)				
Female	186 (83.0)*	249 (75.7)	27 (62.8)*	**0.007**
Male	38 (17.0)	80 (24.3)	16 (37.2)	
Hashimoto's thyroiditis, n (%)				
No	90 (40.2)	160 (48.6)	32 (74.4)	**<0.001**
Yes	134 (59.8)*	169 (51.4)	11 (25.6)*	
Surgery type, n (%)				
Total thyroidectomy	190 (84.8)	305 (92.7)*	35 (81.4)	**0.006**
Lobectomy	32 (14.3)	23 (7.0)	7 (16.3)	
Other	2 (0.9)	1 (0.3)	1 (2.3)	
DTC subtype, n (%)				
PTC	223 (99.6)*	310 (94.2)	32 (74.4)*	**<0.001**
FTC	1 (0.4)	19 (5.8)	11 (25.6)	
PTC aggressive variants, n (%)				
Absent	201 (89.7)	262 (79.6)	36 (83.7)	**0.007**
Present	23 (10.3)	67 (20.4)*	7 (16.3)	
Lymph node metastasis, n (%)				
Absent	211 (94.2)	269 (81.8)	36 (83.7)	**<0.001**
Present	13 (5.8)*	60 (18.2)	7 (16.3)	
Central	3 (23.1)	22 (36.7)	2 (28.6)	0.812
Lateral	8 (61.5)	27 (45.0)	3 (42.9)	
Both	2 (15.4)	11 (18.3)	2 (28.6)	
Capsule invasion, n (%)				
Absent	198 (88.4)	263 (79.9)	21 (48.8)	**<0.001**
Present	26 (11.6)*	66 (20.1)	22 (51.2)	
Vascular invasion, n (%)				
Absent	223 (99.6)	297 (90.3)	32 (74.4)	**<0.001**
Present	1 (0.4)*	32 (9.7)	11 (25.6)	
Extrathyroidal invasion, n (%)				
Absent	214 (95.5)	244 (74.2)	33 (76.7)	**<0.001**
Present	10 (4.5)*	85 (25.8)	10 (23.3)	
Cancer foci, n (%)				
Unifocal	143 (63.8)	198 (60.2)	30 (69.8)	0.392
Multifocal	81 (36.2)	131 (39.8)	13 (30.2)	

DTC=Differentiated thyroid carcinoma, PTC=Papillary thyroid cancer, FTC=Follicular thyroid cancer
*P<0.01 or P<0.001 compared to other groups

Study Parameters in Tumor Size Subgroups

In patients with PTMC (tumor size <10 mm), compared to those with tumor size of 10-39 mm and tumor size of >40 mm, percentage of females were significantly higher (83.0% vs. 75.7% and 62.8%, P=0.007) along with higher rate of concomitant Hashimoto's thyroiditis (59.8% vs. 51.4% and 25.6%, P<0.001) and PTC (99.6% vs. 94.2% and 74.4%, P<0.001) but lower rates of lymph node metastasis (5.8% vs. 18.2% and 16.3%, P<0.001), capsule invasion (11.6% vs. 20.1% and 51.2%, P<0.001), vascular invasion (0.4% vs. 9.7% and 25.6%, P<0.001) and extrathyroidal invasion (4.5% vs. 25.8% and 23.3%, P<0.001) (Table 3). The rates of total thyroidectomy (92.7% vs. 84.8% and 81.4%, P=0.006) and PTC aggressive variants (20.4% vs. 10.3% and 16.3%, P=0.007) were significantly higher in tumors of 10-39 mm in size than in tumors of <10 mm and >40 mm in size (Table 3).

PTC and FTC Variants According to Cancer Foci

Overall, PTC variants were noted in 724 foci (59.5% were classical variants), and FTC variants were noted in 31 foci (74.2% were minimally invasive variants) among 596 patients (Table 4). Classical PTC variants (56.4% vs. 43.6%, P=0.043) and minimally invasive FTC variants (100.0% vs. 0.0%, P=0.002) were associated with significantly higher rates of unifocal tumor than multifocal tumor, while tall cell PTC variants (60.3% vs. 39.7%, P=0.043) and widely invasive FTC variants (60.0% vs. 40.0%, P=0.002) were associated with significantly higher rate of multifocal tumor than unifocal tumor (Table 4).

PTC and FTC Variants According to Tumor Invasion

Capsule invasion was less common in classical (14.8%) and tall cell (15.5%) PTC variants, but more common in follicular PTC variants (24.9%) (P=0.026). No significant difference was noted in vascular invasion rates concerning PTC variants. Extrathyroidal invasion was more common in PTC aggressive variants (columnar cell: 44.4%, diffuse sclerosing: 88.9%), P<0.001) (Table 5). Capsule invasion was more common in minimally invasive

Table 4. PTC and FTC variants according to cancer foci

	Total	Cancer foci		
		Unifocal	Multifocal	P value
PTC variants, n (%)	724			
Classical	431 (59.5)	243 (56.4)	188 (43.6)	**0.043**
Follicular	177 (24.4)	85 (48.0)	92 (52.0)	
Tall cell[a]	58 (8.0)	23 (39.7)	35 (60.3)	
Solid[a]	13 (1.8)	8 (61.5)	5 (38.5)	
Hobnail[a]	12 (1.7)	9 (75.0)	3 (25.0)	
Oncocytic	10 (1.4)	7 (70.0)	3 (30.0)	
Columnar cell[a]	9 (1.2)	6 (66.7)	3 (33.3)	
Diffuse sclerosing[a]	9 (1.2)	4 (44.4)	5 (55.6)	
Clear cell	4 (0.6)	4 (100.0)	0 (0.0)	
Cribriform-morular	1 (0.1)	1 (100.0)	0 (0.0)	
Warthin-like	0 (0.0)	0 (0.0)	0 (0.0)	
FTC variants, n (%)	31			
Minimally invasive	23 (74.2)	23 (100.0)	0 (0.0)	**0.002**
Widely invasive	5 (16.1)	2 (40.0)	3 (60.0)	
Hurtle cell carcinoma	3 (9.7)	3 (100.0)	0 (0.0)	

PTC=Papillary thyroid cancer, FTC=Follicular thyroid cancer
[a]aggressive PTC variants, Fisher exact test

Table 5. PTC and FTC variants according to tumor invasion

	Capsule invasion		Vascular invasion		Extrathyroidal invasion	
PTC variants, n (%)	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Classical	367 (85.2)	64 (14.8)	408 (94.7)	23 (5.3)	351 (81.4)	80 (18.6)
Follicular	133 (75.1)	44 (24.9)	167 (94.4)	10 (5.6)	148 (83.6)	29 (16.4)
Tall cell[a]	49 (84.5)	9 (15.5)	57 (98.3)	1 (1.7)	42 (72.4)	16 (27.6)
Solid[a]	9 (69.2)	4 (30.8)	11 (84.6)	2 (15.4)	11 (84.6)	2 (15.4)
Hobnail[a]	10 (83.3)	2 (16.7)	11 (91.7)	1 (8.3)	9 (75.0)	3 (25.0)
Oncocytic	7 (70.0)	3 (30.0)	10 (100.0)	0 (0.0)	8 (80.0)	2 (20.0)
Columnar cell[a]	7 (77.8)	2 (22.2)	7 (77.8)	2 (22.2)	5 (55.6)	4 (44.4)
Diffuse sclerosing[a]	9 (100.0)	0 (0.0)	7 (77.8)	2 (22.2)	1 (11.1)	8 (88.9)
Clear cell	3 (75.0)	1 (25.0)	4 (100.0)	0 (0.0)	3 (75.0)	1 (25.0)
Cribriform-morular	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
Warthin-like	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
P value	**0.026**		0.086		**<0.001**	
FTC variants, n (%)	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Minimally invasive	4 (17.4)	19 (82.6)	18 (78.3)	5 (21.7)	21 (91.3)	2(8.7)
Widely invasive	5 (100.0)	0 (0.0)	1 (20.0)	4 (80.0)	4 (80.0)	1(20.0)
Hurtle cell carcinoma	0 (0.0)	3 (100.0)	1 (33.3)	2 (66.7)	3 (100.0)	0(0.0)
P value	**0.001**		**0.019**		0.606	

PTC=Papillary thyroid cancer, FTC=Follicular thyroid cancer.
[a]Aggressive PTC variants, Fisher exact test

(82.6%) and Hurtle cell carcinoma (100.0%) variants of FTC but less common in widely invasive FTC variants (P=0.001). Vascular invasion was less common in the minimally invasive FTC variant (21.7%) but more common in the widely invasive FTC variant (80.0%) (P=0.019). No significant difference was

Table 6. Tumor characteristics according to presence of PTC aggressive variant

	PTC aggressive variant		
	No	**Yes**	**P value**
Tumor characteristics			
The greatest tumor size (mm), median(min-max)	10.5 (1.0-77.0)	12.0 (3.0-105.0)	**0.013**
Concomitant Hashimoto's thyroiditis, %	53.4	55.7	0.686
Multifocal tumor, %	37.0	50.5	**0.013**
Lymph node metastasis, %	13.2	18.6	0.172
Capsule invasion, %	16.0	17.5	0.726
Vascular invasion, %	5.6	7.2	0.526
Extrathyroidal invasion, %	15.0	33.0	**<0.001**

PTC=Papillary thyroid cancer

noted in extrathyroidal invasion rates concerning FTC variants (Table 5).

Tumor Characteristics According to the Presence of PTC Aggressive Variant

Presence vs. absence of PTC aggressive variant was associated with significantly higher value of the greatest tumor size (median(min-max) 12.0(3.0-15.0) vs. 10.5(1.0-77.0), P=0.013), higher rate of concomitant Hashimoto's thyroiditis (50.5 vs. 37.0%, P=0.013) and extrathyroidal invasion (33.0% vs. 15.0%, P<0.001) (Table 6).

Overall Correlates of the Bilateral Multifocal Tumor, <10 mm Tumor Size, and PTC Aggressive Variant

Total thyroidectomy (99.5%, P<0.001), PTC aggressive variant (21.9%, P<0.05) and extrathyroidal invasion (24.6%, P=0.012), tall cell PTC variant (60.3%, P=0.043) and widely invasive FTC variants (60.0% P=0.002) rates were significantly higher in the bilateral multifocal tumors than in unifocal tumors and unilateral multifocal tumors (Fig 2). Percentage of females (83.0%, P=0.007), rate of Hashimoto's thyroiditis (59.8%, P<0.001) and PTC subtype (99.6%, P<0.001) were significantly higher, while the rates of lymph node metastasis (5.8%, P<0.001), capsule invasion (11.6%, P<0.001), vascular invasion (0.4%, P<0.001) and extrathyroidal invasion (4.5%, P<0.001) were significantly lower in <10 mm tumors than in >10 mm tumors. Presence vs. absence of PTC aggressive variant was associated with significantly higher greatest tumor size (12 mm, P=0.013) and higher rates of multifocal tumor (50.5%, P=0.013) and extrathyroidal invasion (33.0%, P<0.001) (Fig 2).

DISCUSSION

Our findings in a retrospective cohort of patients with operated DTC revealed a potential interplay between the cancer foci, tumor size, and tumor variants, along with the significant adverse impact of multifocality, larger tumor size, and PTC aggressive variants on the extent of tumor invasion.

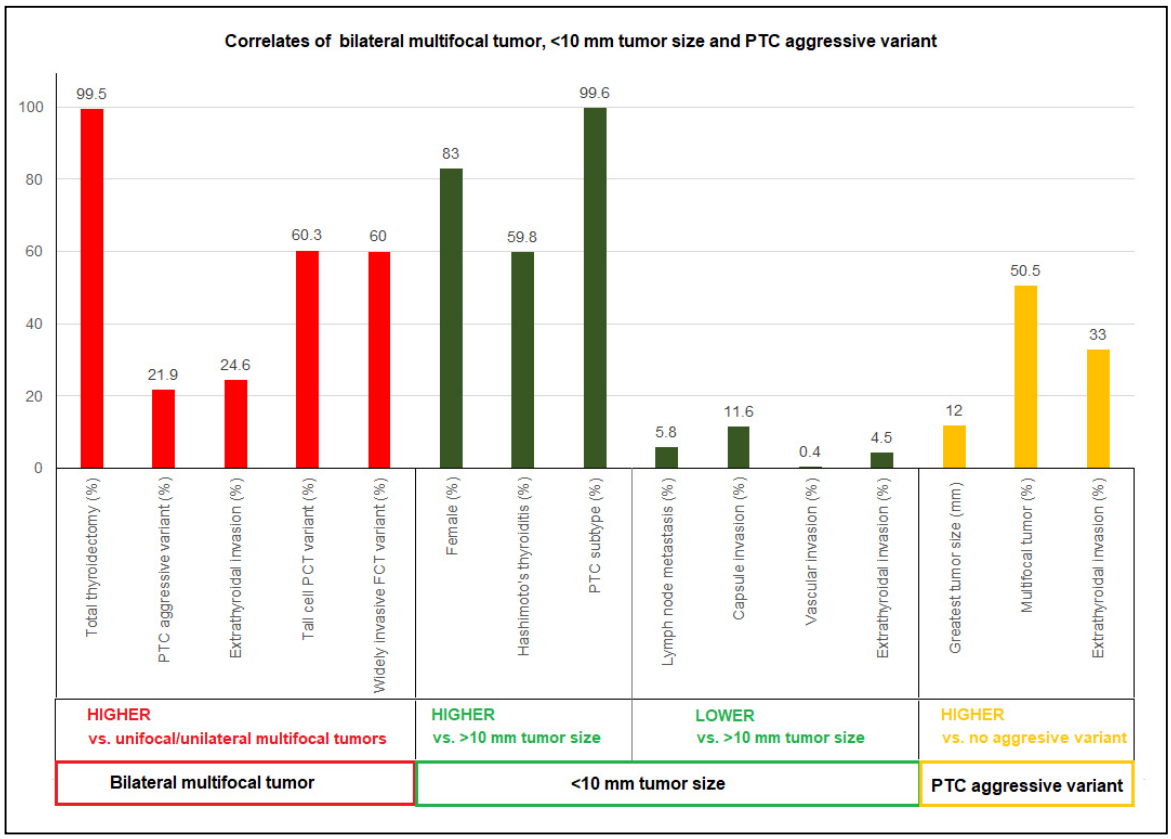

Fig. 2. Correlates of bilateral multifocal tumor, <10 mm tumor size and PTC aggressive variant.

In our cohort, the multifocal tumor was noted in 38.1% (bilateral in 30.7%) of patients, PTC aggressive variants in 17.1% of patients, and PTMC (tumor size <10 mm) in 37.6% of patients. These findings are consistent with previously reported frequencies of multifocality (18%-87%), unilateral multifocality (30.1%), bilateral multifocality (13%-71%), PTMC (39.0%), multifocal PTMC (13.4%-36.1%) and PTC aggressive variants (5-28%) in DTC series [6, 9-13].

Multifocality, particularly the bilaterality of multifocal PTC, has been consistently reported to be a poor prognostic factor for PTC regarding its strong association with aggressive clinicopathological factors such as the increased risk of tumor size >1 cm, extrathyroidal extension, locoregional recurrence, lymph node metastasis, and distant metastasis [9-11, 13, 14].

In our cohort, bilateral multifocal tumor was associated with significantly higher rates of extrathyroidal invasion and total thyroidectomy and a more common presence of PTC aggressive variants, tall cell PTC variants, and widely invasive FTC variants compared to unifocal tumors and unilateral multifocal tumors. Lymph node metastasis and capsular and vascular tumor invasion rates were similar across cancer foci subgroups in our study. In a metanalysis of 15 studies comprising 9,665 patients with PTC, no significant differences were noted between unilateral multifocal and unilateral unifocal PTC in terms of age, gender, extrathyroidal extension, and tumor size but lymph node metastasis rates were higher in the unilateral multifocal group, emphasizing the role of multifocality in tumor aggressiveness and tumorigenesis [5].

Notably, in our cohort, the effect of cancer foci appeared to significantly differ between unifocal and bilateral multifocal groups, rather than between unifocal and unilateral multifocal groups. Apart from lower tumor size in unilateral multifocal tumors, no significant difference was noted between unifocal and unilateral multifocal groups in terms of patient demographics, lymph node metastasis or tumor invasion. Likewise, in a previous study with PTC patients, bilateral and unilateral multifocal PTC were reported to differ significantly concerning larger tumor size, higher frequency of gross extrathyroidal extension, and a more advanced T stage in bilateral multifocal PTC but were found to be similar in terms of aggressive PTC subtypes, cervical LN metastasis, BRAFV600E positivity, and lymphatic, vascular, and perineural invasion [8].

PTMC (tumor size <10 mm) was more common in our female patients and in those with concomitant Hashimoto's thyroiditis and was associated with favorable prognostic factors such as lower rates of lymph node metastasis and tumor invasion (capsule, vascular, and extrathyroidal) compared to larger tumor size (particularly >40 mm). Similarly, in previous PTC studies, tumor size >1 cm was associated with an increased likelihood of multifocality [10, 12, 15], while tumor size >4 cm was found to be an independent predictor for bilaterality in multifocal PTCs [11]. PTC (compared to PTMC) and >5 mm PTMC (compared to ≤5 mm PTMC) were reported to have more aggressive histopathological features such as capsule invasion, bilaterality, and lymph node metastasis [16]. It is also suggested that tumor multifocality is an important prognostic factor for PTCs larger than 1 cm but may have little or no prognostic significance for PTMC [17].

Multifocal and unifocal lesions were similar in terms of gender and Hashimoto's thyroiditis in our study, while some studies indicated a higher rate of multifocal lesions in male subjects and a lower incidence of Hashimoto's thyroiditis in multifocal patients compared with those in solitary lesions (41% vs 60%) [9, 18]. The association of Hashimoto's thyroiditis with <10 mm tumors but not with multifocality in our study supports the consideration of close follow-up performed for Hashimoto's thyroiditis to be associated with increased diagnosis rates of <10 mm thyroid malignancies with no relation to the clinical course [19]. Likewise, PTC subjects complicated with benign thyroid diseases were reported to present with relatively small tumors and a relatively low incidence of lymph node metastasis [9, 20].

In our cohort, patient age (median 47 years overall, 46.5 years in females, 49.5 years in males) was not associated with tumor size or multifocality, which seems notable given the consideration of age over 45 as an independent risk factor for recurrence and age over 55 as a risk factor for postoperative mortality in patients with thyroid malignancy [21]. However, some studies also reported no correlation between age and prognosis [18].

Although multifocality was indicated as an independent risk factor for lymph node metastasis (cervical and lateral) in previous meta-analyses [5], lymph node metastasis appeared to be associated with tumor size

(less common in the case of PTMC) but not with multifocality in our study. Also, there was a nonsignificant tendency for increased risk of lymph node metastasis in patients with vs. those without PTC aggressive variant (18.6 vs. 13.2%). These findings may relate to the low sensitivity and specificity of preoperative US in detecting lymph node metastasis [22]. Indeed, some studies indicated that multifocality "per se" was not independently associated with lymph node metastasis or worse clinical outcomes in PTC patients [6].

In our cohort, bilateral multifocality was associated with PTC aggressive variants, particularly the tall cell PTC variants, as well as with the widely invasive FTC variants. The relation of multifocality with aggressive variants was also reported in previous studies which indicated multifocality in all tall cell variants and increased likelihood of multifocality in mixed-variant tumors including both papillary and follicular variants [10,12,15]. Moreover, bilaterality itself was associated with a higher risk of capsule invasion and a higher incidence of the "tall-cells" variant when compared to unilateral tumors [16]. The association of PTC aggressive variants with significantly greater tumor size and higher rates of multifocal tumors are notable in this regard, given the adverse impact of tumor size >40 mm (capsular and vascular invasion) and bilateral multifocal tumor (extrathyroidal invasion) on tumor invasion, increasing the likelihood of a total thyroidectomy operation. Previous studies also indicated the association of the aggressive variants at the time of diagnosis with advanced stage and increased risk of postoperative recurrence and resistance to radioactive iodine ablation (RAI) therapy [14, 23].

Overall, more aggressive initial treatment (including total thyroidectomy and RAI) and closer follow-up are employed for patients with multifocal disease, given the higher incidence rate of recurrence/persistence than unifocal disease [5, 12, 17, 20]. Specifically, our total thyroidectomy rates were highest for bilateral multifocal tumors (99.5%), followed by unilateral unifocal tumors (84.6%) and unilateral multifocal tumors (81.8%). This seems consistent with the consideration of multifocality, increased tumor size and tumor invasion amongst the factors predicting the recurrence risk in patients with DTC and the association of bilateral PTC with multiple cancer foci and easy extrathyroidal extension [9, 12, 24].

Given the propensity for PTC to be multifocal (often bilateral, mostly in familial disease), a lower risk of loco-regional disease recurrence has been reported following total thyroidectomy as compared to thyroid lobectomy [6, 25, 26]. Also, occult carcinoma rates of 45.1% and 16.7% were reported in total thyroidectomy operations performed for solitary nodules and unilateral PTMC, respectively [27, 28]. Although the size of preoperatively undetected occult foci was <3 mm in majority of cases, given their association with increased risk of multifocality and recurrence, total thyroidectomy is considered a reasonable strategy in solitary nodules, regardless of the lesion size [9, 27].

Nonetheless, the implementation of active surveillance has also been suggested in patients with <1 cm lesion, N0 nodal status, and low-risk factors in the US [29, 30], given the very low rates of tumor growth >3 mm (8%) or lymph node metastasis (3.8%) at 10-year follow up [29], and low rates of surgery need (7%) during 5-year follow up of PTMC patients [30]. However, these findings should be justified with evidence-based data from large series, and currently, the active surveillance in low-risk PTMC seems to be considered a questionable strategy, given the loss to follow-up risk in the long-term, patients' perception of surgery needs during the surveillance period, and the reliability and accuracy of preoperative US.

Limitations

Although our results provide data on a comprehensive analysis of tumor size, cancer foci, and aggressive variants in DTC patients, certain limitations of this study should be considered. First, the retrospective single-center design and relatively small number of participants are the main limitations in terms of the risk of selection bias and the generalizability of our results. Second, the lack of data on other outcomes of interest such as family history or genetic mutation including BRAF mutation, or long-term follow-up data on recurrence and cancer-specific survival is another limitation.

CONCLUSION

In conclusion, our findings revealed the presence of bilaterality/multifocality and aggressive variants in a considerable proportion of patients with operated DTC, alongside a multifaceted interplay between bi-

laterality/multifocality, tumor size, and PTC aggressive variants, in addition to their individual effects on increased risk of tumor invasion, particularly the extrathyroidal invasion. Accordingly, while total thyroidectomy should be considered in the presence of >4 cm tumor with high-risk factors on preoperative ultrasound, the recurrence risk related to bilaterality/multifocality and aggressive variants besides the patients' preference and concerns regarding the close follow-up required after less extensive procedures should guide the decision of thyroidectomy, regardless of the tumor size.

Ethical Statement

This study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Bursa Uludag University Clinical Research Ethics Committee (Date of Approval: 12/12/2023; Protocol No: 2023-27/20).

Authors' Contribution

Study Conception: EG; Study Design: EG; Supervision: EG, AVÖ; Funding: N/A; Materials: EG, AVÖ; Data Collection and/or Processing: EG, AVÖ; Statistical Analysis and/or Data Interpretation: EG, AVÖ; Literature Review: EG, AVÖ; Manuscript Preparation: EG and Critical Review: EG, AVÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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