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ORIGINAL ARTICLE

Multifocality related factors in papillary thyroid carcinoma

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Summary *Background:* Papillary thyroid carcinoma (PTC) is the main type of the well-differentiated thyroid carcinomas. Multifocality is regarded as a poor prognostic factor for PTC.
Methods: Documents of 777 patients who underwent thyroidectomy were reviewed retrospectively. A total of 305 PTC patients were included. Patients with multifocal PTC were included in Group 1, and patients with unifocal PTC were included in Group 2.
Results: There were 165 patients (54.0%) in Group 1 and 140 patients (46%) in Group 2. The pathological mixed variant of PTC was significantly higher in Group 1 ($p = 0,005$). Lymph node metastasis (LNM) was detected at 9.6% and 3.5% in Group 1 and Group 2, respectively ($p = 0,028$). **Micro PTC** rates were 28.4% and 40.7% in Group 1 and Group 2, respectively ($p = 0,017$). Tumor size and pathologically mixed-type and fine-needle aspiration biopsy (FNAB) results were significantly different between multifocal and unifocal **Micro PTC** ($p < 0.05$).
Conclusions: Multifocality is more frequent in patients with tumors ≥1 cm and mixed-type tumors. LNM is found more often in multifocal tumors. The presence of micropapillary tumors can be predicted preoperatively by ultrasound-guided FNAB. Mixed-type pathology is also a predictive factor for multifocality.

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1. Introduction

Papillary thyroid carcinoma (PTC) is the main type of the well-differentiated thyroid carcinomas, and its incidence has been detected increasingly in recent decades because of the wide **spread** use of ultrasound (US) and ultrasound-guided fine-needle aspiration biopsy (US-guided FNAB).[1] The long-term prognosis for PTC is excellent, with survival rates for adults 92–98% at 10-year follow-up. However, 5–20% of patients develop local or regional recurrence requiring further treatment, and 10–15% go on to develop distant metastases. **There are many** factors influencing prognosis **and some of these are** gender, age at presentation, histology, and tumor stage.[1]

PTC may occur in one focus or more. It is labeled multifocal PTC if two or more foci are detected following surgery.[2] Multifocality is a poor prognostic factor for PTC.[3] The frequency of **multifocal PTC** in PTC patients ranges from 18 to 87% in several series.[4] The risk of local recurrence, lymph-node metastasis, and distant metastasis **are** increased in **multifocal PTC** patients.

The sizes of the additional foci are smaller than the main focus, and these additional foci are generally detected in pathology specimens following surgery. Preoperative imaging methods can't detect multifocal or bilateral malignant nodules, so multifocality of the PTC may be diagnosed postoperatively.[5] There are no predictive factors for the preoperative diagnosis of **multifocal PTC**.

Micro PTC is a subtype of PTC. The largest size of the tumor focus is equal to or smaller than 1 cm in **Micro PTC**. **Micro PTC** accounts for 39% of the cases of thyroid cancer in the United States.[6] The incidences of multifocal **micro PTC** were 13.4%[7] and 36.1%[8] in all **micro PTCs** detected in two recent similar studies.

We aimed to evaluate the features of **multifocal** PTC and the differences between **multifocal** PTC and unifocal PTC in this study. We also intended to research the specific features of **multifocal** and unifocal **micro PTC.**

2. Materials and methods

This study was approved by the ethical committee of **the** hospital, and written informed consent was given by participants for their clinical records to be used in relation to this study. In all, 777 total or near-total thyroidectomies were performed between January 2015 and January 2017 at our clinic; of these, 305 patients were included in the study because of PTC. **Total thyroidectomy was performed on all patients by 6 different surgeons or under the supervision of them. Total thyroidectomy was performed because of multinodular bilateral disease or diagnosed PTC with FNAB. PTC which was diagnosed after surgery with main pathology was accepted as incidental PTC. Central lymph node dissection was performed if there was an evidence about the lymph node metastasis or detected palpable lymph node in the operation (i.e. in therapeutic manner).** The file charts of the patients who were included in the study were reviewed retrospectively. The age and gender of each patient was recorded. In addition, the size of the tumor focus, pathological subtypes of the tumors, lymph-node metastasis (LNM), US findings, FNAB pathology reports, extrathyroidal spreading of the tumor, surgical margins, capsule invasion, and lymphovascular invasion (LVI) of all tumors were recorded. The pathological subtypes of the tumors included papillary variant, follicular variant, oncocytic variant, and mixed (follicular and papillary together) variant. **Mixed variant means that two or more different pathological types were detected in the same nodule both for unifocal and multifocal PTCs**.

The result of the FNAB was accepted as positive if it was **Bethesda III, IV, V or VI (atypia of undetermined significance, follicular neoplasia, suspicious for malignancy,** malign).[9] The benign **or nondiagnostic** results of FNAB were accepted as negative. Similarly, the US results were accepted as positive if there were irregular margins, multifocality, central vascularization, or calcification. US findings were accepted as negative if the result was "not suspicious" or "unknown."

The result was accepted as a multifocal tumor if there were two or more foci in the pathological specimen. The patients were divided into two groups according to the presence or absence of multifocality; those who had multifocal tumors were included in Group 1, and patients with unifocal tumors were included in Group 2. The largest tumor focus was accepted as the tumor size in Group 1. The number of foci, average tumor size, and bilaterality are also reviewed in Group 1. **Micro PTCs** were recorded in both groups. Demographic parameters including age and gender, pathological parameters including tumor size, LNM, capsular invasion, LVI, extrathyroidal extension (ETE), pathological subtypes, US findings, and FNAB findings were analyzed and compared in both groups.

The **micro PTC** patients were also divided into two groups as **multifocal micro PTC** and **unifocal micro PTC**, and the same parameters noted above were compared in these subgroups as well.

2.1. Statistical analysis

The two groups were compared for continuous variables (age, size of tumor, LNM) by using independent samples t test and chi-square test or Fisher's exact test if an observed value was <5 for the categorical variables. Multiple logistic regression analysis was used for the multivariate analysis. SPSS v. 22.0 (IBM Corp., Armonk, NY) was used for all analyses. All statistical tests were two-sided, and a P value of <0.05 was considered statistically significant.

3. Results

The descriptive characteristics of the 305 consecutive patients are summarized in Table 1. The mean age of the 305 patients was 48.39 ± 12.62 (21–85) years, and 241 patients (79.0%) were female. The smallest tumor size was 0.01 cm, and the largest tumor was 6.6 cm; the average tumor size was 1.56 ± 1.27 (0.01–6.6) cm.

There were 165 patients (54.0%) in Group 1 and 140 patients (46.0%) in Group 2. Age, gender, the sizes of the tumors, ETE, and capsular invasion were statistically similar in both groups ($p < 0.05$). The pathological mixed variant of the PTC was significantly higher in Group 1 ($p = 0,005$).

Table 1 Descriptive characteristics of the 305 patients.

	N	(%)
Gender		
Female	241	%79.0
Male	64	%21.0
Multifocality		
Multifocal	165	%54.1
Unifocal	140	%45.9
LNM		
Positive	21	%6.9
Negative	284	%93.1
Pathologic subtype		
Classic	127	41.6
Follicular	82	26.9
Oncocytic	30	9.8
Mixed	64	21.0
Unknown	2	0.6
Total	305	
FNAB		
Positive	142	46.6
Negative	163	53.4
US		
Positive	197	64.6
Negative	81	26.6
Unknown	27	8.9
Papillary (>10 mm)	201	65.9
Micropapillary (≤10 mm)	104	34.1

LNM: lymph node metastasis, FNAB: fine needle aspiration biopsy (positive: Bethesda III-VI; negative: Bethesda I-II), US: ultrasound.

LNM was detected at 9.6% and 3.5% in Group 1 and Group 2, respectively; the difference was significant between the two groups (p = 0,028). In Group 1, 47 (28.4%) patients had **micro PTC**, and in Group 2, the **microPTC** rate was 40.7% (57 patients) (p = 0,017). The average number of foci was 2.9 (2—7) in Group 1; 16 patients with LNM in Group1 had an average of 3.1 tumor foci. The average number of foci was 3.1 in the patients with mixed-variant tumors and 3 in the group with tumors >1 cm. In Group 1, 49 (29.6%) of the tumors were bilateral. The prediction rates of US and US-guided FNAB for malignancy were 73.0% and 50.3%, respectively in Group 1. The findings were not statistically different from Group 2 [Table 2].

We used multivariate analysis to evaluate the significant parameters between the multifocal and unifocal groups. The odds ratio of pathological mixed-type PTC was 7.93 (CI: 3.62—17.44) on multifocality according to the logistic regression test. LNM and tumors larger than 10 mm did not affect factors on multifocality after multivariate analysis [Table 3].

We analyzed **micro PTC** as a subgroup analysis. There were 104 **micro PTCs** in our study; 47 (45.1%) were **multifocal micro PTCs** and 57 (54.9%) were **unifocal micro PTCs**. The largest size in the multifocal group was 0.56 ± 0.22 cm. The tumor size is significantly larger than in the unifocal group (p = 0.0002). Of the mixed-type micropapillary tumors, 93.6% were multifocal. This rate was significantly higher than the other pathological subtypes (p = 0.0001).

Table 2 The affecting factors on the multifocality of the papillary thyroid cancer.

	Group 1 (multifocal) (165)	Group 2 (unifocal) (140)	p
Age			
Gender	48.18 ± 13,17	48,64 ± 11,98	NS
Female	125	116	NS
Male	40	24	
The largest size (cm)	1.61 ± 1.21	1.51 ± 1.33	NS
Average size (cm)	0.92 ± 0.66		
ETE			
Yes	24 (14.5%)	17 (12.1%)	NS
No	141 (85.5%)	123 (87.9%)	
LNM			
Yes	16	5	0.028
No	149	135	
CI			
Yes	38	26	NS
No	127	114	
Pathologic subtype			
Classic (127)	59	68	
Follicular (82)	36	46	
Oncocytic (30)	14	16	
Mixed (64)	56	8	0,005
FNAB			
positive (142)	83	59	NS
negative (163)	82	81	
LVI			
Yes (35)	22	13	NS
No (270)	143	127	
Surgical margin			
Yes (64)	39	25	NS
No (241)	126	115	
US			
Significant (197)	111	86	NS
Nonsignificant (81)	41	40	
Size			
Papillary (201)	118	83	0.017
Micropapillary (104)	47	57	

ETE: extrathyroidal extension, LNM: lymph node metastasis, CI: capsule invasion, FNAB: fine needle aspiration biopsy (**positive: Bethesda III-VI; negative: Bethesda I-II),** LVI: lymphovascular invasion, US: ultrasound.

Table 3 Multivariate analysis between multifocal and unifocal papillary thyroid cancers.

	p	OR	95% CI
Pathologic mixed type*	0,0005	7,93	3,62—17,44
Lymph node metastasis	0,1222	0,42	0,14—1,2
Tumor size	0,125	0,66	0,41—1,11

OR: Odds ratio, CI: Confidence interval, *: significant.

FNAB was a significant test for the detection of malignancy in **multifocal micro PTC** (p = 0.009). The other parameters were similar in both groups [Table 4].

Table 4 The affecting factors on the multifocality of the micropapillary thyroid cancer.

	Group 1 (multifocal) (47)	Group 2 (unifocal) (57)	p
Age	48.77 ± 12.178	50.02 ± 12.03	NS
The largest size	0.56 ± 0.22	0.41 ± 0.24	0,002
Gender			
Female	35	50	
Male	12	7	NS
ETE			
Yes	4	1	NS
No	43	56	
LNM			
Yes	3	0	NS
No	44	57	
CI			
Yes	6	3	NS
No	41	54	
Pathologic subtype			
Classic	20	28	0,0001
Follicular	10	23	
Oncocytic	2	4	
Mixed	15	1	
FNAB			
positive	20	11	0,009
negative	27	46	
LVI			
Yes	2	0	NS
No	45	57	
Surgical margin			
Yes	8	3	0,05
No	39	54	
US			
Significant	26	32	NS
Nonsignificant	18	22	

ETE: extrathyroidal extension, LNM: lymph node metastasis, CI: capsule invasion, FNAB: fine needle aspiration biopsy (**positive: Bethesda III-VI; negative: Bethesda I-II**), LVI: lymphovascular invasion, US: ultrasound.

4. Discussion

The surgical treatment of PTC is controversial because PTC frequently has a good prognosis. A 10-year, disease-free survival rate for PTC is approximately 96—98%. The factors that affect the prognosis are age, gender, histology, and tumor stage.[1] Multifocality of PTC is a poor prognostic factor. Wang et al.[10] evaluated the features of PTC and demonstrated that the multifocality rate was 27.1% and that multifocal tumors had more frequent LNM in comparison to unifocal tumors (49.4% and 38.4%, respectively). Additionally, tumor size was larger in the multifocal group than in the unifocal group in the same study.

Another study also evaluated the features of patients with MPC[11]; the authors found multifocal tumors in 37.2% of the patients. Tumor size and LNM, as poor prognostic criteria for PTC, were advanced in the multifocal group in comparison to the unifocal group in the same study. By contrast, male gender and follicular variants were also found to be poor prognostic factors. The authors also evaluated the foci number and found a correlation between the foci number and LNM.

The MPC rate was found to be 33.8% in a study published in 2016.[12] The authors researched capsular invasion, extrathyroidal extension, and LNM as poor prognostic factors; they found that these parameters were more advanced in the multifocal group than in the unifocal group.

The multifocality rate was found to be 54.0% in our study, and that rate was higher in comparison to the literature. In addition, the average size of the tumors was larger in the multifocal group in the present study. LNM, which is an important prognostic factor, was significantly higher in the multifocal group (9.6%), similar to the literature. The pathological features of the tumors did not differ between the two groups except for the subtype of the tumors. The multifocality rate was significantly higher if the tumor included both the papillary and follicular variant. The multivariate analysis showed that the mixed variant of PTC was more likely to be multifocal. The odds ratio (OR) of mixed-type PTC was 7.93 (95% CI 3.61—17.44) for multifocality. The size of the tumor, which was a significant factor with univariate analysis, showed no differences between the two groups in multivariate analysis.

In recent research, programmed death-ligand 1 (PD-L1) expression was studied in PTC.[13] PD-L1 has been studied in various malignancies in order to predict prognoses. The study showed that PD-L1 was a poor prognostic factor for PTC and that the expression of PD-L1 was elevated in multifocal tumors. This was one of the reasons for the poor prognosis related to multifocal papillary thyroid carcinomas.

MPC is generally detected incidentally. A study that featured a large patient series (3241 patients) researched the characteristics of incidental and non-incidental PTC.[14] The authors included 235 patients in the study, and 31.91% were diagnosed incidentally. Solitary tumors were more often diagnosed preoperatively than multifocal tumors to a significant degree in the same study. The researchers concluded that preoperative diagnosis of multifocal tumors was difficult using current diagnostic methods. The most valuable preoperative diagnostic methods for diagnosing the malignant thyroid nodules are US and FNAB, according to the guidelines.[1] With our patients, we performed both methods preoperatively. Multifocal tumors were diagnosed preoperatively by US and FNAB in 67.2% and 50.5% of the patients, respectively. US was more valuable in our study, but the difference between the solitary group and the multifocal group was not significant.

The bilaterality of MPC is a poor prognostic factor, according to the literature. A study that compared the 10-year, disease-free survival in PTC patients found the rate of bilaterality to be 19.2%, and this group had a poorer prognosis than the other group.[15] In the present study, 16.0% of all patients and 29.6% of the multifocal group had bilateral tumor foci. The number of foci was not compared statistically between patients with poor and good prognostic parameters, but the number of foci was higher in patients with LNM, mixed-variant tumors, and average tumor sizes >1 cm.

The present study showed that micropapillary tumor rates were 22.9% and 40.7% in the multifocal group and the solitary group, respectively. The difference was significant in univariate analysis, but there was no difference in multivariate analysis.

MPC has a good prognosis and generally incidental tumors, according to the literature. Some authors have proposed that MPC should be accepted as a benign disorder,[16] but others have described cases with LNM and distant metastasis in patients with MPC.[17] It is considered that multifocality could be an important factor for recurrence in MPC. In cases of incidental MPC, completion of primary surgery and lymph node dissection may be necessary. Moreover, the extent of surgery in unilateral MPC has not yet been clearly defined.[5,18]

Kaliszewski et al.[7] studied 246 patients with PTC and found that 39.6% of them had MMPC. They compared solitary and multifocal MPC according to the demographic and pathological features. At the conclusion of the study, there was no difference between the parameters. Preoperative US-guided FNAB was the single parameter used to decide on surgery.

The other study showed that MMPC was more frequent in the multinodular goiter and that patients did not require additional surgery following total thyroidectomy.[19] A meta-analysis detected that central lymph-node metastasis was higher in male patients younger than 45 years of age with MMPC.[20]

In the present study, patients with MMPC and UMPC were compared. Tumor size was a significant factor for multifocality in micropapillary tumors. Age and gender were similar in both groups. US findings were not a good predictor for multifocal micropapillary tumors, while US-guided FNAB was a predictive factor for multifocality in micropapillary thyroid tumors. Tumors that had a mixed-type pathology were multifocal in the micropapillary group. Similar to the literature, multifocality of micropapillary thyroid tumors was more frequent in our study in patients with positive US-guided FNAB and tumors with larger sizes.

5. Conclusion

In conclusion, multifocality can be detected in papillary and micropapillary thyroid carcinomas. Multifocality is more frequent in patients with tumors $\geq$1 cm and mixed-type tumors. Lymph-node metastasis is present more often in multifocal tumors. Micropapillary tumors can be multifocal and their presence can be predicted preoperatively by US-guided FNAB. Mixed-type pathology is also a predictive factor for multifocality in micropapillary thyroid cancer.

Ethics committee approval

This study was approved by the ethical committee of our hospital and written informed consent was given by participants for their clinical records to be used in this study.

Financial disclosure

All of the authors declare that there are no financial disclosure in connection with this paper.

Conflict of interest

The authors report no conflicts of interest.

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