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Preoperative predictors and prognosis of bilateral multifocal papillary thyroid carcinomas

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ABSTRACT

Background: The characteristics of multifocal PTC remain controversial. Surgical approach to multifocal tumor changes between centers. This study aimed to evaluate the incidence of bilateral involvement, predictive factors for bilaterality and whether bilaterality was related with more aggressive histopathologic features or prognosis in patients with multifocal PTC.

Method: Medical records and pathologic data of 914 patients who underwent total thyroidectomy and diagnosed with PTC were retrospectively reviewed. The patients with multifocal disease were detected and divided into two subgroups as unilateral-multifocal PTCs and bilateral multifocal PTCs. Those two groups were compared regarding to demographic, clinical and histopathological features.

Result: Multifocal disease was detected in 294 patients (32.7%). Of all, 102 patients (36.7%) had unilateral whereas 192 cases (65.3%) had bilateral involvement. As a result of univariate analysis, bilaterality was significantly associated with the number of tumor foci ($p < 0.001$), tumor size ($p = 0.008$), TSH ($p = 0.002$) and capsule invasion ($p = 0.018$). Multivariate analysis demonstrated that the number of tumor foci and TSH level were independent risk factors for bilaterality in multifocal PTC ($p < 0.001$ and $p = 0.006$, respectively). Bilateral and unilateral tumors had similar local/regional and distant recurrence rates.

Conclusion: Incidence of bilateral tumors is high and increases with the number of tumor foci in multifocal PTC. Bilateral involvement in multifocal PTC is not associated with worse prognosis.TSH can be taken as a preoperative indicator able to predict multifocal cancers and guide clinical decision making and surgical management.

1.1. Introduction

Thyroid carcinoma is the most common endocrine tumor and is associated with favorable prognosis although the long-term mortality rate can be as high as 10% [1]. Papillary thyroid carcinoma (PTC) accounts for approximately 75% of all thyroid malignancies and its frequency is increasing in all countries due to advances in diagnostic techniques [1–3].

Papillary thyroid carcinomas may occur as two or more separate foci within the thyroid gland. The frequency of such multifocal PTCs was reported as 18%–87%, varying depending on the diagnostic techniques [4]. The characteristics of multifocal PTC and the prognostic significance remain debatable [5,6]. In the recent reports it is suggested that different tumor foci in multifocal disease are independent from each other with an inherent predisposition to develop PTC where as other findings suggest that the multiple foci in multifocal PTC represent intraglandular metastasis from a single focus and such tumors are likely to be aggressive and therefore require more extensive treatment [7,8]. In addition to that, multifocal PTC may develop due to radiation exposure or genetic mutations and has more recurrence rates [9,10]. There are controversies about the best surgical approach and the indication of ^{131}I ablation after total thyroidectomy in patients with multifocal PTC [11,12]. Most [13,14] but not all [15] studies of papillary cancer have reported a higher rate of cancer in the opposite lobe when multifocal disease was compared with unifocal disease. Although surgical approach to multifocal tumor varies between centers, most accepted one is total thyroidectomy. In cases that the initial procedure was lobectomy, most clinicians would recommend completion

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thyroidectomy since the risk of PTC in the contralateral lobe is significant [16]. Multifocality and bilaterality was also reported to be correlated with lymph node metastasis that represents aggressive biological behavior [17].

In this report, we evaluated the incidence of multifocal tumors in a large series of patients with PTC. Moreover, we aimed to determine the incidence of bilateral involvement and predictive factors for bilaterality that would help the clinicians to choose the patients who would benefit from total thyroidectomy precisely. We also aimed to search whether bilaterality is related with more aggressive histopathologic features in multifocal PTC and compare the prognosis of bilateral tumors with unilateral ones.

1.2. Material and method

After obtaining the approval from local ethics committee, we reviewed the database for 2910 patients who underwent thyroidectomy in our hospital between January 2007 and December 2014 retrospectively. Cases whose histopathology was reported as PTC were included.

Our database also included demographic data such as age at the time of surgery and gender, surgical procedure, clinical characteristics, preoperative ultrasonography, fine needle aspiration biopsy (FNAB) results and final histopathological examination of the thyroid carcinoma, including multifocality, bilaterality, histologic subtype, tumor capsule or vascular invasion, cervical lymph node (LN) involvement, extrathyroidal extension, radioactive iodine treatment details. Cytological results were classified as benign, non-diagnostic, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm, suspicious for malignancy or malignant. After the operation thin sections of 4 μm thickness were stained by hematoxylene-eosine and examined histopathologically. American Joint Committee on Cancer (AJCC) system was used for staging.

Among patients whose histopathology was positive for PTC, we determined cases with multifocal disease. Primary tumor were defined as the tumor focus with the largest diameter. Patients with multifocal PTC were then divided in two groups as" unilateral" or "bilateral" disease. Bilateral disease was defined as the presence of PTC foci in the right and left lobes of the thyroid gland.

The follow-up period for each patient was defined as the length of time from the initial therapy until the last known contact documented by a review of the medical record. Postsurgical physical examinations were performed every 3–6 months. During the follow-up visits, all patients underwent US examinations of the neck and thyroglobulin measurements.

Outcome data included local, regional or distant recurrence. The presence of local or regional recurrence following treatment was based on cytological or histopathological confirmation of structurally identifiable disease. Local recurrence was defined as recurrent disease located in the thyroid bed confirmed by cytological sampling or histological analysis following further surgery. Regional recurrence was defined as recurrent disease found in the cervical lymph nodes, confirmed again by cytological sampling or histopathology following subsequent surgical resection. Distant recurrence was determined by imaging studies, including radioiodine uptake scans, computed tomography (CT) scans, positron emission tomography scans, or cytological and histopathological evidence where available. We also considered Tg changes in Anti-Tg negative patients as an indicator of recurrence. In the recent years patients with previously undetectable Tg (< 0.2) who develop detectable levels are investigated with ultrasound, fine-needle aspiration of suspicious nodes or nodules, and CT scanning of the neck and chest in an attempt to identify evidence of structural disease.

Preoperative serum thyrotropin (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) levels were measured within at least 3 months prior to surgery in all patients. Chemiluminescence methods (Immulite 2000, Diagnostic Products Corp., Los Angeles, CA, USA and UniCel DXI 800, Beckman Coulter, Brea, CA) were used for measurement of serum TSH, fT3, fT4 and anti-TPOAb levels. The normal ranges for TSH, fT3, fT4 and anti-TPOAb were 0.4–4 μIU/mL, 1.57–4.71 pg/mL, 0.61–1.12 ng/dl and < 10 U/mL, respectively. The thyroid antibody level over the upper range was accepted as positive.

1.3. Statistical analysis

All statistical analyses were performed with the SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA). Descriptive analyses were presented using mean ± standard deviation (SD) for normally distributed variables, median and range (min-max) for non-normally distributed variables and as number of cases and (%) for nominal variables. Chi-square test was used to investigate the difference between the groups regarding the categorical variables. The comparisons between groups were performed by the student's *t*-test for parametric variables, and the Mann-Whitney *U* test for non-parametric variables determining the best predictor(s) which discriminate unilateral and bilateral groups from each other was analyzed by multiple logistic regression analysis. Any variable whose univariable test had a p value < 0.25 was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Odds ratios, 95% confidence intervals were calculated for each variable. A p value less than 0.05 was accepted as statistically significant.

A receiver operator characteristics curve (ROC curve) analysis was performed to identify the sensitivity and specificity of cut-off value of TSH measurements to discriminate unilateral and bilateral group from each other.

1.4. Results

Of 914 operated patients with PTC, multifocal disease was detected in 294 (32.7%) cases. Indications for surgery in multifocal PTC patients were listed on Table 1.

Initial surgery was total thyroidectomy in 280 patients and lobectomy in 14 patients. All patients with initial lobectomy underwent completion thyroidectomy. Eight patients found to have contralateral tumor. All of the contralateral tumors were microcarcinomas with the maximum size of 8 mm.

In 102 patients (36.7%) with multifocal PTC, all tumor foci were localized in one lobe whereas in 192 cases (65.3%) there was bilateral involvement. Demographic features and laboratory data of unilateral and bilateral multifocal PTCs were listed on Table 2. There was no difference between unilateral and bilateral multifocal PTC groups in regard to sex, age, free T3 and T4 levels and presence of Hashimoto thyroiditis on histopathological examination (p > 0.05) (Table 1). TSH was higher in the "bilateral" group (p = 0.002). (Table 2).

There were 714 papillary thyroid carcinoma foci reported in the final histopathology of 294 patients. Total number of tumor foci was 229 in unilateral whereas it was 485 in bilateral carcinomas. Of 714 tumor foci 526 (73%) were microcarcinomas (diameter less than 10 mm).

Table 1
Clinical and biochemical characteristics of patients with bilateral versus unilateral multifocal PTC.

	Unilateral (n = 102)	Bilateral (n = 192)	p
Sex (F/M)	81/21	36/156	0.704
Age (years)	56.61 ± 11.82	49.18 ± 11.80	0.095
TSH (μIU/mL)	1.27 ± 0.90	1.79 ± 1.48	**0.002**
fT3 (pg/ml)	3.19 ± 0.42	3.21 ± 0.59	0.785
fT4 (ng/dl)	1.18 ± 0.24	1.17 ± 0.33	0.846
Anti TPO positivity (n)	16 (15.7%)	43 (22.4%)	0.177
Hashimato thyroiditis (n)	39(38.2)	54(28.1)	0.076

Table 2
Comparision of FNA results of unilateral and bilateral PTC groups.

Side	FNA Cytology						
	ND	Benign	FLUS/AUS	FN/FNS	SUS	Malign	Total
unilateral	14 (19.2%)	12 (16.4%)	14 (19.2%)	1(1.4%)	11 (15.1%)	21 (28.8%)	73
bilateral	22 (12.9%)	34 (19.9%)	28 (16.4%)	7 (4.1%)	41 (24%)	39 (22.8%)	171
Total	36	46	42	8	52	60	244

No significant difference between the groups, p = 0.39.

Table 3
Comparison of unilateral and bilateral multifocal PTCs according to tumor characteristics and histopathologic features.

	Unilateral (n = 229)	Bilateral (n = 485)	p
Number of carcinoma foci	2.26 ± 0.57	2.56 ± 0.76	**0.001**
Tumor size (mm)	5.0 (0.5–60)	6.0 (0.5–70)	**0.002**
Number of microcarcinomas	183 (79.9%)	344 (70.9%)	**0.009**
PTC variant			0.780
Classical	181 (79%)	388(80%)	
Follicular	30 (13.1%)	60 (12.4%)	
Oncocytic	4 (1.7%)	8 (1.6)	
Tall cell	2 (0.9%)	8 (1.6)	
Other	12 (5.2%)	21(4.3%)	
Capsular invasion	28 (12.2%)	84 (17.3%)	0.203
Vascular invasion	4 (1.7%)	6 (1.2%)	0.681
Extrathyroidal extension	12 (5.2%)	45 (9.3%)	0.160
Lymph node metastases	9 (3.9%)	28 (5.8%)	0.152
Incidental	134 (%58.5)	279 (%57.5)	0.915

Number of carcinoma foci and the largest tumor size was significantly higher in the bilateral compared to the unilateral multifocal PTC group (p = 0.001 and p = 0.002, respectively). There was no difference between the groups according to the histologic subtypes of PTC, capsular invasion, vascular invasion, extrathyroidal extension, lymph node metastasis at surgery and incidentality **(p > 0.05).** Number of microcarcinomas was higher in the bilateral disease group (Table 3). The initial tumor stage according to AJCC, number of local, regional and distant metastasis was also similar in between the groups (Table 3). Death during follow up occurred in only one patient in the unilateral group and the difference was not statistically significant. The mean follow up was 47.7 ± 18.3 months in the unilateral group while it was 44.15 ± 17.1 in the bilateral group and there wasn't any significant difference.

Multivariate analysis was performed for any variable whose univariable test had a p value < 0.25 and demonstrated that the number of tumor foci and TSH level were independent risk factors for bilaterality in multifocal PTC (p < 0.001and p = 0.006, respectively) (Tables 4 and 5). In the ROC analysis the area under curve was significant for TSH in differentiating bilateral tumors from unilateral ones (AUC = 0.595, 95% CI = 0.529–0.661 and p = 0.008). Best cut-off value for TSH for predicting bilaterality was determined as 1.905 μIU/mL (sensitivity 37.4%, specifity 85.4%, PPV and NPV; 82.6% and 40.8%, respectively) (Fig. 1).

1.5. Discussion

Multifocality was reported in 18–87% of patients with PTC [4,18,19], and was seen in 32.1% of patients in the present study which was compatible with the literature. Despite multifocality was not considered as a risk factor making the patient “high risk” in the guidelines, some studies claim that multifocality is related with more aggressive features as well as poor prognosis in PTC [20]. One of the reasons for the conflicting results of the studies may be due to different behavior of unilateral and bilateral tumors.

Bilaterality means that both lobes of the thyroid gland are affected by the tumor. In previous reports incidence of bilateral PTC was ranged from 13% to 65% [21–23]. In our study rate of bilaterality in multifocal papillary thyroid cancer was 65%.

To date there are only few studies investigated the affect of bilaterality on the prognosis of multifocal PTC. Results of our study shows that bilaterality is not associated with poor outcomes regarding to local/regional recurrence or distant metastasis and death. Our results are consistent with the report by Kim et al. showed that the clinicopathologic parameters did not differ significantly between the patients with multifocal-unilateral and multifocal-bilateral PTC [24]. Inconsistent with our findings, in a previous report the bilateral-multifocality was proved to be an independent risk factor for neck recurrence ((HR) = 4.052, 95% CI: 2.070–7.933), distant metastasis (HR = 3.860, 95% CI 1.507–9.884), and cancer death (HR = 7.252, 95% 2.189–24.025) [25]. In addition to that Wang et al. showed worse prognosis and higher prevalence of BRAF mutations in bilateral PTC [26].

In the current study we evaluated clinical and histopathological features such as age, initial tumor stage, vascular invasion and capsule invasion of the tumor in unilateral and bilateral disease groups. Bilaterality was not associated with extrathyroidal invasion, advanced T stage, capsule invasion or vascular invasion in our study. Our findings

Table 4
Clinicopathological predictors of multifocality and bilaterality (univariate analysis).

	Univariate logistic regression	
	OR (95% CI)[a]	p-value
Age	0.983 (0.963–1.004)	0.110
Gender	1.123 (0.616–2.050)	0.704
N.of carcinoma	2.045 (1.353–3.093)	< **0.001**
Tumor size [b]	1.205 (1.051–1.389)	**0.008**
TSH	1.434 (1.138–1.806)	**0.002**
Lymph node metastases	1.764 (0.798–3.899)	0.161
Vascular invasion	1.070 (0.262–4.372)	0.925
Capsular invasion	1.943 (1.120–3.368)	**0.018**
Presence of thyroiditis	0.640 (0.130–3.138)	0.582

OR: Odds ratio, CI: Confidence interval.
[a] Crude odds ratios.
[b] The effect of each 5 mm-increased in tumor size.

Table 5
Independent risk factors for bilaterality in multifocal PTC (multivariate analysis).

	Multiple logistic regression	
	OR (95% CI)[a]	p-value
Age	0.986 (0.963–1.009)	0.221
Number of carcinoma	2.088 (1.338–3.258)	< **0.001**
Tumor Size	1.126 (0.975–1.295)	0.105
TSH	1.399 (1.100–1.779)	**0.006**
Lymph node metastasis	1.072 (0.451–2.549)	0.875
Capsular invasion	1.614 (0.881–2.956)	0.121

[a] Adjusted odds ratios.

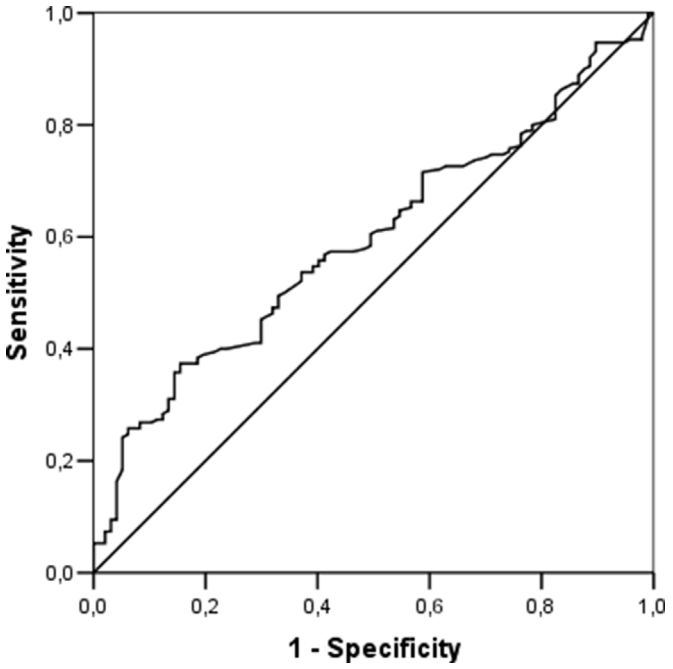

Fig. 1.

was inconsistent with Hwang et al. who reported that bilateral PTC was more commonly found in patients with extrathyroidal invasion, advanced T stage, and at least one multifocal lobe [22]. Similarly In another report by Wang et al., patients who had bilateral PTCs had larger tumors and higher rates of extrathyroidal extension compared to ones with unilateral disease [27]. However in a recent study it was detected that neither vascular nor capsule invasion wasn't correlated with bilateral disease in the logistic regression model that was consistent with our results [28].

Another clinical parameter evaluated was the age of the patients. There are reports suggesting that patients with multifocal cancer has older age compared to ones with solitary tumors [29]. In our study mean age of the unilateral and bilateral groups were similar and above 45 years. Mazeh et al. found that patients under and over the age of 40 years had similar rate of multifocality although younger patients had a higher rate of unilateral disease [30]. In contrast to previous study, Pacini found that bilateral tumors were as frequent among low-risk patients ($\leq$45 years) and high-risk patients ($>$ 45 years) [31].

In the present study number of tumor foci was an independent indicator of bilateral disease in multifocal PTC. In a previous study it was detected that incidence of bilateral tumors was depending on the number of tumor foci but not tumor size in the dominant lobe supporting our results [32].

In our cohort 73% of all tumors were microcarcinoma and half of them were detected incidentally. All except 14 patients underwent total thyroidectomy as the initial procedure. In that 14 cases who had lobectomy, completion thrıoidectomy was performed and eight (57%) of the patients found to have bilateral disease. All tumors in the contralateral lobe were microcarcinomas. In one study among the patients undergoing completion thyroidectomy following hemithyroidectomy the rate of malignancy was 48 %and 90% of the tumors were microcarcinomas [33,34]. Our results are suggesting that total thyroidectomy is not indicated in all cases with multifocal cancer detected in one lobe since finding an incidental cancer in the contralateral lobe doesn't change the prognosis in long term.

In this study we found that TSH was positively correlated with presence of contralateral tumor in multifocal PTC patients and was an independent risk factor for bilateral disease. Every 1 mIU/L increase in the hormone level ended up with 1.434 fold increase in the risk of bilateral cancer (p = 0.002). Our best cut-off for discrimination of bilateral disease from unilateral disease was 1.9 IU/L. Risk of bilaterality increased above that limit even if the patients' TSH was within the normal range (0.4–4.5 IU/L). In humans serum TSH level increases with age and the mean TSH is higher in the thyroid cancer patients. Even though serum TSH is within the normal range (0.4–4 mIU/L) in most PTC patients, frequency of malignancy increases when TSH is greater than 0.9 mIU/L [35]. It is previously reported that incidence of $BRAF^{V600}$ mutation is higher in the bilateral multifocal PTCs [36]. In mouse models when PTC is induced by $BRAF^{V600}$ mutation TSH increases up to 100 fold. In humans we don't expect such significant increases since PTC develops from only minority of thyrocytes carrying $BRAFV600^{mutation}$ and the surrounding thyrocytes maintain the normal thyroid function [37]. In addition to that it was previously demonstrated that $BRAF^{V600}$ mutation cannot induce a tumor when it is expressed postnatatally in thyrocytes without TSH stimulation [37]. As a result of those studies it can be suggested that the development of PTC requires constant TSH stimulation. In our study TSH was higher in the bilateral group which was consistent with the study by Wang et al. [36].

One of the limitations of our study is the retrospective design of the study. Second limitation was that histopathology was not interpreted by one pathologist.

In conclusion, incidence of bilateral disease is high in multifocal PTCs. However bilateral disease isn't more aggressive than unilateral disease in regard to histopathologic features, tumor stage and prognostic outcomes. Surgeons can prefer lobectomy in multifocal carcinomas and completion thyroidectomy is not required if the patient doesn't have one of “high risk properties” or will not receive RAI treatment. TSH is found as an independent risk factor for bilateral disease in multifocal PTC. Although the roles of TSH in promoting metastasis within the gland and stimulating the cancer cells need to be supported with further studies, it may be taken as one of the clinical indicators able to predict bilaterality in multifocal cancers than 1 cm and completion thyroidectomy may be required.

Disclosure statement

Authors declare that there is no conflict of interest and we didn't receive any funding.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2018.12.004.

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