Original Article

The clinical importance of multifocality on tumor recurrence in papillary thyroid carcinoma

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Background: Although the origin of the multifocality of papillary thyroid carcinoma (PTC) is unclear, it is not unusual and has not been considered as an independent prognostic factor from several tumor staging systems. This study aims to evaluate whether the presence of multifocality is associated with PTC recurrence.

Methods: We reviewed retrospectively detailed histological reports of PTC patients who underwent thyroidectomy from January 2000 through December 2010 at a single institution. We assessed the relationship between multifocality and other possible prognostic factors using binary logistic regression analysis. We compared recurrence by the Kaplan-Meier method (the log-rank test). We analyzed a prognostic factor for recurrence using Cox's proportional hazard model (the stepwise forward method).

Results: We enrolled a total of 434 PTC patients (380 women and 54 men; mean age, 48 years). The median follow-up period was 10.2 years. Of all PTC patients enrolled, 135 patients (31%) had multifocal PTC. There was a significant association between multifocality and cervical lymph node (CLN) metastasis (P=0.01). Multivariate analyses showed a significant association between multifocality and CLN metastasis (P<0.001). Multifocal PTC patients had higher CLN metastasis and tumor recurrence than those with single PTC. There was a significant association between multifocality and tumor recurrence (P=0.03 by log-rank test), but it disappeared in multivariate analysis.

Conclusions: Multifocality of PTC might be related to CLN metastasis and tumor recurrence.

Keywords: Multifocality; papillary thyroid carcinoma (PTC); tumor recurrence

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Introduction

Multifocal papillary thyroid carcinoma (PTC) is defined as there are two or more. Multifocality is not a prognostic factor affecting TNM staging. It, however, is controversial to conclude multifocality is not a risk factor.

It is not sure that multifocality in PTC is multicentricity, which means independently arising PTCs. Multifocal PTC could be attributed to multicentricity or intrathyroidal spread of a single PTC (1,2); the latter might have a worse prognosis. The reasons multifocality is considered an important prognostic factor are as follow: (I) multifocality is associated with a cervical lymph node (CLN) metastasis (3,4), (II) multifocality is related to risk for recurrence (5), (III) multifocality is associated with BRAFV600E mutation (6). However, there are studies that multifocality is not related to increased recurrent or metastatic disease (7,8).

This study aimed to evaluate if multifocality in PTC is associated with a poor prognostic factor such as CLN metastasis, distant metastasis, or tumor recurrence.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/gs-20-603).

Methods

Patients & variables

We enrolled PTC patients sequentially who underwent thyroidectomy with or without CLN dissection and/or subsequent ^{131}I remnant ablation treatment (RIA-T) at Sanggye Paik Hospital, Seoul, Korea, from January 2000 through December 2010. Lobectomy was performed if tumor size is less than 1 cm and no clinical extrathyroid extension on the pre-operative imaging such as neck ultrasonography or neck computed tomography. CLN dissection was performed if macroscopic CLN metastasis was present on the pre-operative imaging such as neck ultrasonography or neck computed tomography or during surgery. We reviewed retrospectively detailed histological reports. They included maximal tumor diameter, extrathyroid extension (no/microscopic/macroscopic), bilaterality (no/yes), multifocality (no/yes), and CLN metastasis (N0/N1a/N1b/Nx using TMN staging system by the American Joint Committee on Cancer, 7th ed.). We analyzed the demographics (age and gender) and clinical outcomes (distant metastasis and recurrence). We excluded cases to include missing data.

When recurrence in clinical or biochemical data was suggested, we performed radiologic studies, including neck ultrasonography. Recurrence was confirmed by cytological or histopathological examination. Patients with distant metastasis at the time of initial diagnosis were excluded from the analysis of recurrence.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Inje University Sanggye Paik Hospital (No. SGPAIK 2020-09-019) and individual consent for this retrospective analysis was waived.

Statistics

We presented categorical variables as numbers and percentages and compared using chi-square or Fisher's exact test. We presented continuous variables as mean ± SD and range. We assessed the relationship between multifocality and other possible prognostic factors using binary logistic regression analysis. We compared recurrence by the Kaplan-Meier method (the log-rank test). The endpoint for the analysis of disease-free survival was a recurrence. We analyzed a prognostic factor for recurrence using Cox's proportional hazard model (the stepwise forward method). P value of <0.05 was considered significant. We performed all statistical analyses using SPSS (version 25.0; IBM Corp., Armonk, NY, USA).

Results

Clinicopathological characteristics (Table 1)

We enrolled a total of 434 PTC patients (380 women and 54 men; mean age, 48 years). The median follow-up period was 122 (range, 1–240) months. A total of 434 patients with PTC, who underwent thyroidectomy with or without CLN dissection, were identified at Sanggye Paik Hospital. Of 434 patients, 135 patients (31%) had multifocal tumors.

Of a total of 381 patients who underwent near-total or total thyroidectomy, 131 patients (34%) had multifocal tumors. Of a total of 53 patients with PTC, who underwent thyroid lobectomy, four patients (7.5%) had multifocal tumors.

Mean age, gender, tumor size, and extrathyroid extension were not significantly different between single and multifocal groups. Compared with patients with single PTC, a multifocal PTC group demonstrated a higher ratio of near-total or total thyroidectomy (P<0.001) and RAI-T (P<0.001), and higher CLN metastasis (P=0.003).

Recurrence, disease-free survival (Figure 1)

Of a total of 434 patients, 36 (8%) had a recurrence. Multifocality was significantly associated with tumor recurrence during the follow-up period (median 122 months): 13% [17 patients; lymph node (LN), 16 patients; contralateral lobe, 1 patient; median 40 months] of the multifocal group compared with 6% (19 patients; LN, 14 patients; contralateral lobe, 5 patients; median 45 months) of the single group (P=0.03 by log-rank test; *Figure 1*). However, this association disappeared on multivariate analysis, adjusting for conventional clinicopathological predictors of recurrence (*Table 2*).

Multivariate analysis of the association of multifocality with various clinicopathological parameters (Table 3)

We analyzed associations between multifocality and clinicopathological parameters used for predicting recurrences, such as age, gender, tumor size, extrathyroid extension, and CLN metastasis using multivariate analysis. The association between multifocality and CLN metastasis remained

Table 1 The clinicopathological characteristics according to presence of multifocality

Characteristics	Solitary (n=299)	Multifocal (n=135)	P value
Age (years)	48±12	49±11	0.17[a]
Gender (M:F)	36:263	18:117	0.75[b]
Near-total or total thyroidectomy, n [%]	250 [84]	131 [97]	<0.001
Post-operative radioiodine therapy, n [%]	155 [52]	97 [72]	<0.001
Size (cm)	1.4±1.0	1.3±0.9	0.13[a]
Extrathyroid extension, n [%]			0.35[b]
No extension	143 [48]	55 [41]	
Minimal extension	146 [49]	76 [56]	
Gross extension	10 [3]	4 [3]	
LNM, n [%]			0.003[b]
No metastasis	142 [47]	47 [35]	
N1a	75 [25]	47 [35]	
N1b	8 [3]	12 [9]	
Nx	74 [25]	29 [21]	

[a], by Student's *t*-test; [b], by Fisher's exact test. LNM, lymph node metastasis.

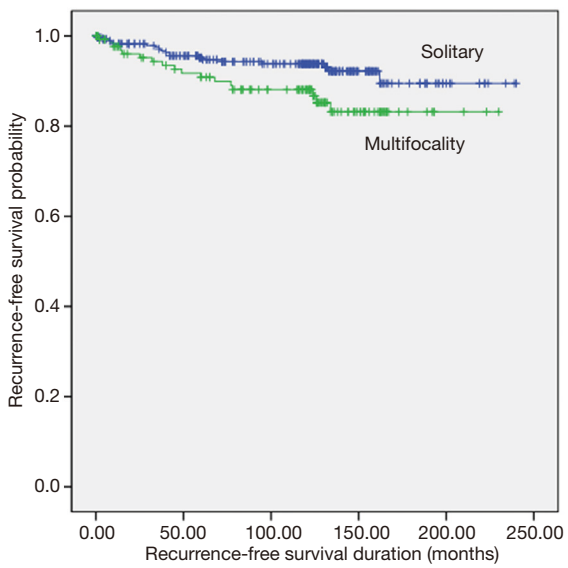

Figure 1 Disease-free survival according to multifocality in 434 patients without distant metastasis at the time of initial diagnosis. The Kaplan-Meier method for recurrence with the log rank test was used for statistical comparisons.

significant with multivariate analysis after adjusting for clinicopathological parameters (P<0.001).

Discussion

In this study, we evaluated if multifocality in PTC is associated with a poor prognostic factor such as CLN metastasis, distant metastasis, or tumor recurrence. This study showed that multifocality was associated with CLN metastasis and tumor recurrence in patients with PTC. However, the association between multifocality and tumor recurrence disappeared on multivariate analysis, adjusting for poor prognostic factors.

Multifocality has a significant association with CLN metastasis after adjusting for poor prognostic factors. In logistic regression analysis, multifocality was associated with central LN (N1a) metastasis (hazard ratio, 2.06) and lateral LN (N1b) metastasis (hazard ratio, 5.11). In other studies, multifocality is associated with central or lateral CLN metastasis (9,10). CLN metastasis is known for poor prognosis,

Table 2 Univariate and multivariate analysis of the association of clinical recurrence with various clinicopathological parameters

Variables	Univariate analysis[a]		Multivariate analysis[b]	
	Log-rank statistics	P value	Hazard ratio (95% CI)	P value
Age (>55 years)	0.028, df =1	0.87		
Gender (male)	10.348, df =1	0.001	3.16 (1.48–6.74)	0.003
Near-total or total thyroidectomy	3.137, df =1	0.08		
Post-operative radioiodine therapy	2.573, df =1	0.11		
Tumor size (>1 cm)	4.892, df =1	0.03	0.50 (0.23–1.08)	0.08
Multifocality	4.650, df =1	0.03	0.53 (0.27–1.06)	0.07
Extrathyroid extension	3.937, df =2	0.14		
Minimal extension				
Gross extension				
LNM	21.812, df =3	<0.001		0.01
N1a			0.27 (0.10–0.74)	0.01
N1b			0.67 (0.29–1.50)	0.32
Nx			1.94 (0.66–5.75)	0.23

[a], by the Kaplan-Meier method for recurrence with the log-rank test; [b], by Cox's proportional hazard model and the forward stepwise method. CI, confidence interval; LNM, lymph node metastasis.

Table 3 Multivariate analysis of the association of multifocality with various clinicopathological parameters

Clinicopathological parameters	Multifocality		
	Hazard ratio	95% CI	P value
Age (>55 years)	1.30	0.81–2.11	0.28
Gender (male)	0.95	0.50–1.80	0.95
Tumor size (>1 cm)	0.65	0.42–1.03	0.06
Extrathyroid extension			0.40
Minimal extension	0.24	0.84–2.04	0.24
Gross extension	0.72	0.22–2.86	0.72
LNM			0.002
N1a	2.06	1.23–3.46	0.006
N1b	5.11	1.89–13.81	0.001
Nx	1.15	0.67–1.99	0.614

Statistical analysis performed by binary logistic regression analysis. CI, confidence interval; LNM, lymph node metastasis.

mostly lateral CLN metastasis, more aggressive (11). However, pre-operative neck ultrasonotraphy was reported to have low sensitivity for central lymph node metastasis (LNM) (12) and lateral LNM (13). If multifocalicy of PTC is present, close monitoring of CLN metastasis is needed.

Multifocality has a significant association with CLN metastasis, why cannot it affect recurrence?

First, the degree of multifocality might be different. Although it is defined as multifocality when there are two or more PTCs, the number of tumors was very variable in this study, such as 2, 3, 4, 5, 7, and many multiple tumors. Kim *et al.* reported that multifocality and the number of tumor lesions were an independent risk factor for recurrence (5). In this study, however, there were rarely many multiple tumors, so the analysis of tumor recurrence based on the number of tumors did not produce significant results (data not shown). The concept of total tumor diameter (TTM) may also be used to overcome this limit. In papillary thyroid microcarcinoma (PTMC), Zhao *et al.* reported multifocal PTMC with TTM as the sum of the maximal diameter of each tumor >1 cm had a similar risk of LNM, so, they recommended routine central neck dissection in this subgroup (14). But this study did not analyze TTM.

Second, multifocality might be mixed with intraglandular metastases and multicentricity. Either intraglandular metastases from a single PTC or independent neoplastic

clones are proven as to how multifocal PTC form (1,2). A lymphatic drainage system can cause intra-thyroidal metastatic spreading. It contains a communicating network of intralobular lymphatic vessels in both lobes and the isthmus enclosed in a capsule (2). A study in the Korean population showed at least 39.5% of the multifocal PTC could be caused to independently arising PTCs rather than to intra-thyroidal spread of single PTC (15). That is, in about 40% of multifocal PTC, multifocality could not be a worse prognostic factor. However, we did not study the origin of multifocal PTC (intrathyroidal spread of single PTC *vs.* multicentricity).

Third, it may be because almost all patients with multifocal PTCs underwent total thyroidectomy and/or RAI-T. In this study, 97% of total patients with multifocal PTCs underwent more than subtotal thyroidectomy compared to 84% of those with solitary PTCs. Only 3% of total patients with multifocal PTCs underwent lobectomy, and only one patient developed recurrence in the contralateral lobe. However, Harries *et al.* showed that unifocal PTC and multifocal PTC patients had similar rates of recurrence of the contralateral lobe, regional recurrence, and overall survival with a median follow-up of 58 months (16). RAI-T also did not decrease the risk of recurrence in PTC (17).

Fourth, multifocality may be a factor that has nothing to do with a worse prognosis. Poor prognosis may be more strictly related to other carcinogenic genes involved and underlying molecular mechanisms of tumor development and progression. Or it may take too much time to find out the risk of multifocality because PTC has an excellent prognosis. However, this also means that if it occurs at a very young age, it may be a factor that may affect relapse after decades.

This study has some limitations. First, the subject of this study is the heterogeneous population. We analyzed patients with near-total or total thyroidectomy or lobectomy. However, there was no different recurrent rate between a total thyroidectomy group and a lobectomy group (data not sown). Second, Nx accounted for a considerable percentage. LN dissection was performed if macroscopic CLN metastasis was present on the pre-operative imaging such as neck ultrasonography or neck computed tomography or during surgery. LN dissection only based on a macroscopic involvement can be an important bias. However, microscopic subclinical CLN metastases have a much smaller risk of recurrence than clinical macroscopic CLN metastases (18). Even if Nx is a high percentage, it is considered that the likelihood of having an overall prognosis is minimal.

However, this study has some strengths. First, this study is suitable to see the prognosis of PTC progressing slowly by following up for more than 10 years. Second, this data represents the real world by reflecting realistic surgery such as lobectomy, total thyroidectomy, and/or Nx.

Conclusions

In conclusion, multifocality could be associated with poor prognoses such as CLN metastasis and tumor recurrence. However, this association with multifocality and tumor recurrence disappeared on multivariate analysis. Therefore, we suggest that multifocality could belong to the low risk factor of PTC, but CLN metastasis should be closely monitored.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Inje University Sanggye Paik Hospital (No. SGPAIK 2020-09-019) and individual consent for this retrospective analysis was waived.

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