Cancer Management and Research

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Multifocality is associated with central neck lymph node metastases in papillary thyroid microcarcinoma

This article was published in the following Dove Press journal:
Cancer Management and Research

Weihui Zheng[1]
Kejing Wang[1]
Junzhou Wu[2]
Wendong Wang[1]
Jinbiao Shang[1]

[1]Department of Head & Neck Surgery Zhejiang Cancer Hospital and Key Laboratory of Head & Neck Cancer Translational Research of Zhejiang Province, Hangzhou, People's Republic of China; [2]Department of Cancer Research, Zhejiang Cancer Hospital, Hangzhou, People's Republic of China

Background: This study aimed to assess the predictive factor of multifocality to identify patients at high risk of central lymph node metastasis (CLNM).

Patients and methods: Papillary thyroid microcarcinoma patients who underwent total or hemi-thyroidectomy with effective unilateral or bilateral central lymph node dissection were enrolled.

Results: Multifocality, age, sex, tumor size, extrathyroidal extension, and nodular goiter were significantly associated with CLNM. Multifocality was an independent predictor for CLNM in multivariate analysis. Compared with unifocal disease, the odds ratio for CLNM was 1.447 for patients with ≥2 tumor foci (P<0.001) and 2.978 for patients with ≥3 tumor foci (P<0.001). The significant association is at ≥3 foci diseases.

Conclusion: Multifocality with ≥3 tumor foci was an independent predictive factor for CLNM in papillary thyroid microcarcinoma. Multifocality should be assessed when selecting patients for prophylactic central neck lymph node dissection, and we speculate that patients with multifocality should undergo more radical treatment.

Keywords: papillary thyroid microcarcinoma, central compartment lymph node, multifocal, metastases, predictor

Introduction

The incidence of papillary thyroid cancer (PTC) has increased significantly worldwide in the past few decades.[1–3] Papillary thyroid microcarcinoma (PTMC), a subset of PTCs, is defined as a thyroid carcinoma sized ≤1.0 cm along its greatest diameter.[4] PTMC accounts for about 35%–70% of all PTC cases,[5–7] and its incidence has dramatically increased in both males and females.[8] PTMC in most cases is slow growing, and the majority of patients have a long survival time, although locoregional lymph node recurrence is common. The surgical treatment of PTMC remains controversial, especially in patients with multifocal disease.

Tumor multifocality is observed in approximately 20%–40% of patients with PTMC[5,9–12] and can be bilateral or unilateral. However, most staging systems do not include the tumor multifocality. While some studies fail to show a significant association between multifocality and recurrent disease,[5,13] multifocality is generally regarded as a risk factor of lymph node metastasis and disease recurrence in PTMC.[9–12,14]

Despite much attention having been paid to the increasing incidence of PTMC, there is still no consensus on the value of prophylactic central lymph node neck dissection (CLND) in PTMC. According to the 2015 ATA guidelines, thyroidectomy

Correspondence: Jinbiao Shang; Wendong Wang
Department of Head & Neck Surgery Zhejiang Cancer Hospital and Key Laboratory of Head & Neck Cancer Translational Research of Zhejiang Province, 1 East Banshan Road, Hangzhou, Zhejiang 310022, People's Republic of China
Tel +86 571 8812 8222
Fax +86 571 8812 2508
Email shangjinbiaodoc@163.com; wangwd@zjcc.org.cn

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/CMAR.S163263

without CLND may be appropriate for small (T1 or T2), noninvasive, clinically node-negative PTC (cN0), but this does not address the issue of whether CLND is of value in PTMC.[15] Despite having small tumors, patients with PTMC have high incidence of lymph node metastasis and extrathyroidal extension (ETE); the incidence of central lymph node metastasis (CLNM) ranges from 30% to 60% in these patients.[5,16–21] Unfortunately, no preoperative clinical features can reliably identify CLNM, and preoperative sonography has an extremely low sensitivity for CLNM.[22] Therefore, it is imperative to develop a suitable approach to identify PTMC patients with a high risk for CLNM who may benefit from CLND.

The relationship between multifocality and CLNM in PTMC remains unclear. Few studies have assessed the association between the number of foci and the demographic characteristics of PTMC. This study aimed to assess the predictive factor of multifocality for CLNM in PTMC, which may improve our ability to identify patients who may benefit from CLND.

Patients and methods

Patient identification

From January 2007 to December 2015, a total of 12,530 patients underwent thyroidectomy at Zhejiang Cancer Hospital. Of them, 6,826 patients were pathologically diagnosed with PTC (PTC >1 cm in diameter was noted in 2,238 patients) and 4,588 with PTMC. Patients who underwent thyroidectomy without effective central lymph node dissection (dissection of at least 1 lymph node) or lateral lymph node dissection with or without central lymph node dissection were excluded. Patients with PTMC and other types of thyroid cancer such as medullary carcinoma or anaplastic thyroid cancer were also excluded. Eventually, 3,543 patients with PTMC who underwent effective central lymph node dissection (dissection of ≥1 lymph nodes) were enrolled in this study. The 3,543 patients were divided into 2 groups: 2,458 patients with 1 lesion and 1,085 patients with ≥2 foci (Figure 1).

All 3,543 patients in this cohort underwent total or hemithyroidectomy with effective unilateral or bilateral central lymph node dissection. If unilateral malignant lesion was present, ipsilateral central neck dissection of lymph nodes was employed; if bilateral malignant lesions were observed, bilateral central neck dissection of lymph nodes was done. The CLND was performed superior to the hyoid bone, inferior to the suprasternal notch, and lateral to the carotid sheaths. This study was approved by the Ethics Committee of Zhejiang Cancer Hospital. Written informed consent was obtained from all patients before surgery, and all operations were performed by experienced surgeons at the same cancer hospital. All patients gave a written informed consent to have their medical records reviewed for this study.

Data collection

Demographic characteristics, including age, sex, tumor size, multifocality, and tumor laterality (unilateral/bilateral), were collected from electronic medical records. According to the TNM staging system, age was dichotomized at 45 years. Tumor size was classified as <5 or ≥5 mm using the largest diameter. Multifocality was defined as ≥2 tumor foci in the same lobe or different lobes including the thyroid isthmus. The presence of ETE, lymphovascular invasion (LVI), lymphocytic thyroiditis, and nodular hyperplasia was recorded according to the pathological findings. In addition, the postoperative complications and prognosis were also

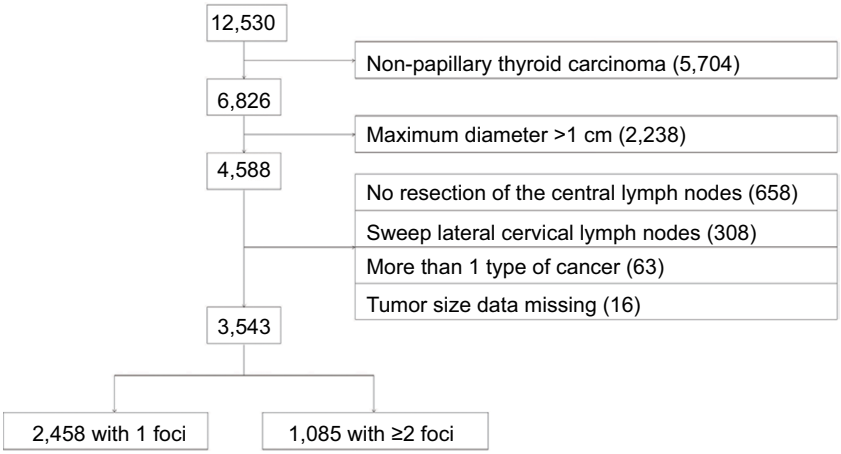

Figure 1 Flowchart of patients' recruitment.

evaluated in these patients. The postoperative complications' information and prognosis were recorded through review of the medical records.

Statistical analysis

Descriptive statistics were employed to summarize study data. Continuous data are expressed as mean ± standard deviation. Statistical analyses were performed using SPSS version 23.0 for Mac (IBM Corporation, Armonk, NY, USA). χ^2 test was used to assess the differences between groups in univariate analysis. Logistic regression analysis was applied in multivariate analysis to calculate the odds ratios (ORs) for the associations between CLNM and various clinicopathologic factors. A value of 2-tailed $P<0.05$ was considered statistically significant. Software Prism 6.0c (Graph Pad Software, Inc., La Jolla, CA, USA) was used to generate figures.

Results

Patients' characteristics

A total of 3,543 patients with PTMC were enrolled (Figure 1). There were 2,867 females (80.92%) and 676 males (19.08%) with an average age of 45.70±10.48 years (range, 12–81 years). The average size of the largest focus was 5.97±2.30 mm (range, 0.5–10 mm; median, 6 mm). Multifocality was suspected on ultrasonography in 806 patients, postoperative microscopy indicated multifocality in 1,085 patients, and the consistency rate of multifocality between ultrasonography and microscopy was 74.29% (806/1,085). Overall, from microscopic foci, 2,458/3,543 patients (69.38%) had unifocal PTMC and 1,085 (30.62%) had multifocal PTMC; 767/1,085 patients (70.69%) had 2 foci, 219 (20.18%) had 3 foci, and 99 (9.13%) had ≥4 foci.

The average number of central neck lymph nodes dissected was 4.29±3.23 (range, 1–29). CLNM was found in 1,057/3,543 patients (29.83%), of whom 781/1,057 (73.89%) had 1–2 CLNM, 238 (22.52%) had 3–5 CLNM, and 38 (3.59%) had ≥6 CLNM. ETE was present in 1,487/3,543 (41.97%) patients, LVI in 25/3,543 (0.71%) patients, lymphocytic thyroiditis in 337/3,543 (9.51%) patients, and nodular hyperplasia in 1,163/3,543 (32.83%) patients (Table 1).

Table 1 Demographic characteristics of the cohort of patients with PTMC (n=3,543)

Variable	Mean + SD (median: range) or value (%)
Age (years)	45.70±10.48 (46: 12–81)
<45	1,616/3,543 (45.61%)
≥45	1,927/3,543 (54.39%)
Sex	
Male	676/3,543 (19.08%)
Female	2,867/3,543 (80.92%)
Size of largest focus (mm)	5.97±2.30 (6: 0.5–10)
<5	994/3,543 (28.06%)
≥5	2,549/3,543 (71.94%)
Focality	1.45±0.88 (1: 1–13)
Unifocal	2,458/3,543 (69.38%)
Multifocal	1,085/3,543 (30.62%)
2 foci	767/1,085 (70.69%)
3 foci	219/1,085 (20.18%)
≥4 foci	99/1,085 (9.13%)
Bilateral tumors	1,670/3,543 (47.14%)
Number of central neck lymph nodes dissected	4.29±3.23 (3: 1–29)
Central neck lymph node metastasis	
Negative	2,486/3,543 (70.17%)
Positive	1,057/3,543 (29.83%)
1–2 nodes	781/1,057 (73.89%)
3–5 nodes	238/1,057 (22.52%)
≥6 nodes	38/1,057 (3.59%)
ETE	1,487/3,543 (41.97%)
LVI	25/3,543 (0.71%)
Lymphocytic thyroiditis	337/3,543 (9.51%)
Nodular hyperplasia	1,163/3,543 (32.83%)

Abbreviations: ETE, extrathyroidal extension; LVI, lymphovascular invasion; PTMC, papillary thyroid microcarcinoma.

Postoperative complications and prognosis

Hypocalcemia was found in 9.23% (327/3,543) of patients, hoarseness in 1.72% (61/3,543) of patients, and bleeding in 0.11% (4/3,543) of patients. Among these patients, 344 were lost to follow-up, recurrence was observed in 51 patients, and 5 patients died (1 died of cerebral hemorrhage).

Univariate analysis

The associations between CLNM and several demographic factors were further investigated. In univariate analysis, CLNM was significantly associated with patients younger than 45 years, males, and patients with a largest focus of ≥5 mm, multifocality, ETE, or nodular hyperplasia (all $P<0.001$). There were no significant associations of CLNM with bilateral tumors ($P=0.813$), LVI ($P=0.120$), and lymphocytic thyroiditis ($P=0.187$; Table 2).

Multivariate analysis

Binary logistic regression was employed for multivariate analysis to calculate the ORs for CLNM (Tables 3 and 4). Age, sex, size of largest focus, ETE, nodular hyperplasia, and multifocality (≥2 foci) were controlled in 3,543 patients.

Table 2 Factors associated with CLNM in PTMC (n=3,543) in univariate analysis using the χ^2 test

Variable	Central lymph node metastasis		*P*-value
	Positive (n=1,057) n (%)	Negative (n=2,486) n (%)	
Age (years)			<0.001
<45	554 (52.41)	1,062 (42.72)	
≥45	503 (47.59)	1,424 (57.28)	
Sex			<0.001
Male	252 (23.84)	424 (17.06)	
Female	805 (76.16)	2,076 (82.94)	
Size of largest focus (mm)			<0.001
<5	183 (17.31)	811 (32.62)	
≥5	874 (82.69)	1,675 (67.38)	
Focality			<0.001
Unifocal	658 (62.25)	1,800 (72.41)	
Multifocal	399 (37.75)	686 (27.59)	
2 foci	223 (55.89)	544 (79.30)	
3 foci	105 (26.32)	114 (16.62)	
≥4 foci	71 (17.79)	28 (4.08)	
Bilateral tumors	495 (46.83)	1,175 (47.26)	0.813
ETE	557 (52.70)	918 (36.93)	<0.001
LVI	11 (1.04)	14 (0.56)	0.120
Lymphocytic thyroiditis	90 (8.51)	247 (9.94)	0.187
Nodular hyperplasia	292 (27.63)	871 (35.04)	<0.001

Abbreviations: CLNM, central lymph node metastasis; ETE, extrathyroidal extension; LVI, lymphovascular invasion; PTMC, papillary thyroid microcarcinoma.

Table 3 Factors associated with CLNM in PTMC (n=3,543) in multivariate logistic regression analysis

Variable	Central lymph node metastasis		95% CI	
	OR	*P*-value	Lower	Upper
Multifocality (≥2 foci)	1.447	<0.001	1.236	1.693
Age (<45 years)	1.462	<0.001	1.258	1.699
Sex (female)	0.682	<0.001	0.569	0.817
Size of largest focus (≥5 mm)	1.854	<0.001	1.532	2.243
ETE	1.552	<0.001	1.328	1.814
Nodular hyperplasia	0.826	0.023	0.701	0.974

Abbreviations: CI, confidence interval; CLNM, central lymph node metastasis; ETE, extrathyroidal extension; OR, odds ratio; PTMC, papillary thyroid microcarcinoma.

Table 4 Factors associated with CLNM in multifocal PTMC (n=1,085) in multivariate logistic regression analysis

Variable	Central lymph node metastasis		95% CI	
	OR	*P*-value	Lower	Upper
Multifocality (≥3 foci)	2.978	<0.001	2.256	3.932
Sex (female)	1.500	0.020	1.065	2.112
Size of largest focus (≥5 mm)	2.432	<0.001	1.678	3.525
ETE	1.474	0.005	1.127	1.928

Abbreviations: CI, confidence interval; CLNM, central lymph node metastasis; ETE, extrathyroidal extension; OR, odds ratio; PTMC, papillary thyroid microcarcinoma.

Multifocality (≥2 foci) was significantly associated with CLNM (OR =1.447, 95% confidence interval [CI] =1.236–1.693; *P*<0.001). Five other factors were also independent predictors for CLNM (Table 3): age (OR =1.462; *P*<0.001), female sex (OR =0.682; *P*<0.001), the largest focus ≥5 mm (OR =1.854; *P*<0.001), ETE (OR =1.552; *P*<0.001), and nodular hyperplasia (OR =0.826; *P*=0.023).

In subsequent analysis, the association between CLNM and multifocality was evaluated with the same model; patients with ≥3 foci had a significantly higher OR for CLNM than patients with ≤2 foci (multifocal; OR =2.978, 95% CI =2.256–3.932; *P*<0.001; n=1,085). Similarly, among patients with multifocality, having the largest focus of ≥5 mm (OR =2.432; *P*<0.001) and ETE (OR =1.474; *P*=0.005) were significantly associated with CLNM. Being female was also a risk factor for CLNM in multifocal PTMC (OR =1.500; *P*=0.020). Age (*P*=0.897) and nodular hyperplasia (*P*=0.678) were not associated with CLNM in multifocal PTMC (Table 4; data not shown).

The association between the number of the foci and CLNM was also assessed. The incidence of CLNM was 26.77% in unifocal disease patients, 29.07% in patients with 2 foci, 47.95% in patients with 3 foci, and 71.72% in patients with ≥4 foci. A significant association existed between multifocality and CLNM in PTMC (*P*<0.001; Figure 2).

Multifocality was observed in 30.62% of patients with PTMC, and the incidence of CLNM was 36.77% (399/1,085) in multifocal PTMC compared to 26.77% (658/2,458) in patients with unifocal disease. The incidence of CLNM increased with the number of PTMC foci. There was no significant difference in CLNM between unifocal PTMC (26.77%) and PTMC with 2 foci (29.07%). However, the incidence of CLNM was 1.79-fold higher for PTMC with 3

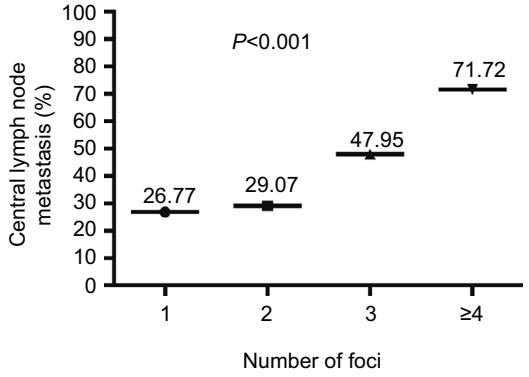

Figure 2 Association between CLNM and the number of foci in PTMC (n=3,543).
Abbreviations: CLNM, central lymph node metastasis; PTMC, papillary thyroid microcarcinoma.

foci (47.95%) and 2.68-fold higher for PTMC with ≥4 foci (71.72%), compared to unifocal disease. Multivariate analysis confirmed that multifocality (≥2 foci) was significantly associated with CLNM (OR =1.447). Furthermore, patients with ≥3 foci had a higher risk of CLNM than patients with 2 foci (OR =2.978; $P<0.001$).

Discussion

This study investigated the relationship between multifocality and CLNM in PTMC. This study reveals that multifocality is significantly associated with CLNM in PTMC. The high incidence of CLNM for patients with multifocal PTMC may indicate higher tumor aggressiveness and a higher risk of regional recurrence.

Consensus regarding the association between multifocality and CLNM has not yet been reached. Similar to our study, Afif et al[23] reported an association between the number of foci in PTC and CLNM ($P<0.001$; OR =2.355 for ≥3 tumor foci; $P=0.026$), although PTMC was not analyzed as a separate subgroup. A meta-analysis by Qu et al[24] revealed that CLNM was associated with multifocality in PTMC (relative risk =1.40, $P=0.001$). Guo et al[17] reported the presence of 2, 3, or ≥4 foci was associated with a significantly higher risk of CLNM in PTMC (OR =1.675, 2.360, and 2.703, respectively) compared to unifocal PTMC. Similar findings have been reported by other studies.[19,20] In contrast, multifocality was significantly related to CLNM in univariate analysis ($P=0.020$) but not in multivariate analysis ($P=0.138$) in the study by Zhou et al,[21] and Lee et al[18] suggested multifocality was not associated with CLNM and did not significantly influence the predictive factor of CLNM. It is possible that the differences in sample size and selection criteria among studies may explain the discrepancies. Our study indicates that multifocality is significantly associated with CLNM in PTMC.

Prophylactic CLND in the management of PTC remains controversial, especially in PTMC.[25] Chang et al[16] reported 39% (239/613) of patients with PTMC had CLNM, and they recommended prophylactic CLND for all patients. In contrast, Wada et al[26] stated only patients with palpable lymph nodes should undergo prophylactic CLND. In the last decade, patients with PTMC in our hospital have routinely undergone prophylactic CLND, regardless of the presence of palpable lymph nodes. However, it would be desirable to identify subgroups of patients with less aggressive PTMC at low risk of CLNM who could avoid prophylactic CLND.

The reported incidence of CLNM in PTMC ranges from 30% to 60%.[5,16–21] In this study, 29.83% of patients had CLNM, which is lower than previously reported. This could be attributed to the fact that most patients had earlier stage disease and because patients who underwent lateral lymph node dissection were excluded from this study. Several studies have identified lymph node metastasis, including lateral lymph node metastasis, as a prognostic factor for poor outcome in PTMC.[9–12,14,27] Mercante et al[14] found that lymph node metastasis was an independent risk factor for recurrence or distant metastasis ($P<0.05$). Usluogullari et al[12] reported that lymph node metastasis was an independent predictor of recurrence in multivariate analysis (OR =51.4; $P=0.003$). Agarwal et al[27] stated that lymph node metastasis was associated with more aggressive disease, recurrence, and poorer prognosis. Multifocality has also been associated with aggressive disease and poor prognosis in PTMC. Chow et al[9] found the risk of cervical lymph node recurrence was 6.2-fold ($P<0.01$) and 5.6-fold ($P<0.02$) higher if lymph node metastasis and multifocal disease were present at diagnosis. Qu et al[11] reported that the presence of >3 tumor foci was an independent predictor of recurrence in multivariate analysis (HR =2.60, $P=0.001$). However, Mehanna et al[13] failed to find that tumor multifocality and lymph node involvement were significantly associated with recurrence in PTMC. Kim et al[5] found that multifocality was an independent risk factor for disease recurrence in PTC but not in PTMC. Further studies are required to define the prognostic value of CLNM in PTMC in the absence of lateral lymph node metastasis as a confounding factor. Moreover, large, multicentered studies with longer follow-up period are warranted to draw definitive conclusions.

In this study, CLNM was significantly associated with age, sex, tumor size, multifocality, ETE, and nodular hyperplasia in univariate analysis. Multivariate analysis confirmed that all these factors are independent predictive factors for CLNM in PTMC, in agreement with previous findings.[20,28–30] Moreover, bilateral tumors, LVI, and lymphocytic thyroiditis were not significantly associated with CLNM in this study, consistent with previously reported studies.[31,32] Otherwise, coexistence of thyroiditis was previously identified as a negative independent predictor for CLNM.[33,34] However, in the analysis of patients with multifocal PTMC, age and nodular hyperplasia were not found to be independent predictors for CLNM. It is difficult to explain the role of sex as a predictor for CLNM. In the entire cohort, being female (OR =0.682, $P<0.001$) was associated with reduced risk of CLNM, whereas being female was a risk factor for CLNM in multifocal PTMC (OR =1.500, $P=0.020$). Similar reports have not been published on the effect of sex on the risk of CLNM, and the predictive factor of sex for CLNM in multifocal PTMC still needs to be further elucidated in future studies.

Although a large number of patients were included, there were still limitations in this study. First, the retrospective nature precluded the identification of the mechanistic relationships between prognosis and multifocality or CLNM. Second, all patients were treated at a single hospital. Third, a number of patients did not undergo CLND due to the low rate of ultrasonography-guided preoperative fine-needle aspiration in PTMC; these patients were diagnosed using the final pathology as having incidental PTMC and excluded from this study. In general, incidental PTMC has features suggestive of less aggressive disease and a lower incidence of CLNM. Although this bias does not affect the association between multifocality and CLNM, the incidence of CLNM reported in this study may be lower than that in other studies of PTMC. Moreover, the relationship between lateral lymph node metastasis and multifocality was not assessed in this study. Lastly, the impact of molecular marker such as a determinant of sensitivity to proteasome inhibitors (BRAFV600E) on multifocality and CLNM requires further research.

Conclusion

This study indicates that multifocality is associated with an increased risk of CLNM in PTMC. Multifocality with ≥3 tumor foci was an independent predictor for CLNM. In addition to the size of the largest focus and ETE, multifocality should be considered when selecting subgroups of patients with PTMC for prophylactic CLND. We recommend that patients with multifocality should receive more radical treatment.

Acknowledgment

We thank all the patients who participated in this study. This work was supported by the Zhejiang Provincial Natural Science Foundation of China (LQ14H160002, LY15H160008).

Author contributions

WHZ and JBS conceived and designed the experiments; WHZ performed the experiments; WHZ analyzed the data; KJW, JZW, WDW, and JBS contributed reagents, materials, and analysis tools; and WHZ wrote the paper. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. McNally RJ, Blakey K, James PW, Gomez Pozo B, Basta NO, Hale J. Increasing incidence of thyroid cancer in Great Britain, 1976–2005: age-period-cohort analysis. *Eur J Epidemiol*. 2012;27(8):615–622.
2. Morris LG, Sikora AG, Tosteson TD, Davies L. The increasing incidence of thyroid cancer: the influence of access to care. *Thyroid*. 2013;23(7):885–891.
3. Wang Y, Wang W. Increasing incidence of thyroid cancer in Shanghai, China, 1983-2007. *Asia Pac J Public Health*. 2015;27(2):NP223–NP229.
4. Sobin LH. Histological typing of thyroid tumours. *Histopathology*. 1990;16(5):513.
5. Kim KJ, Kim SM, Lee YS, Chung WY, Chang HS, Park CS. Prognostic significance of tumor multifocality in papillary thyroid carcinoma and its relationship with primary tumor size: a retrospective study of 2,309 consecutive patients. *Ann Surg Oncol*. 2015;22(1):125–131.
6. Kutler DI, Crummey AD, Kuhel WI. Routine central compartment lymph node dissection for patients with papillary thyroid carcinoma. *Head Neck*. 2012;34(2):260–263.
7. Leboulleux S, Tuttle RM, Pacini F, Schlumberger M. Papillary thyroid microcarcinoma: time to shift from surgery to active surveillance? *Lancet Diabetes Endocrinol*. 2016;4(11):933–942.
8. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87–108.
9. Chow SM, Law SC, Chan JK, Au SK, Yau S, Lau WH. Papillary microcarcinoma of the thyroid-Prognostic significance of lymph node metastasis and multifocality. *Cancer*. 2003;98(1):31–40.
10. Lombardi CP, Bellantone R, De Crea C, et al. Papillary thyroid microcarcinoma: extrathyroidal extension, lymph node metastases, and risk factors for recurrence in a high prevalence of goiter area. *World J Surg*. 2010;34(6):1214–1221.
11. Qu N, Zhang L, Ji QH, et al. Number of tumor foci predicts prognosis in papillary thyroid cancer. *BMC Cancer*. 2014;14:914.
12. Usluogullari CA, Onal ED, Ozdemir E, et al. A retrospective analysis of prognostic factors predictive of lymph-node metastasis and recurrence in thyroid papillary microcarcinoma. *Minerva Endocrinol*. 2015;40(1):15–22.
13. Mehanna H, Al-Maqbili T, Carter B, et al. Differences in the recurrence and mortality outcomes rates of incidental and nonincidental papillary thyroid microcarcinoma: a systematic review and meta-analysis of 21 329 person-years of follow-up. *J Clin Endocrinol Metab*. 2014;99(8):2834–2843.
14. Mercante G, Frasoldati A, Pedroni C, et al. Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients. *Thyroid*. 2009;19(7):707–716.
15. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;26(1):1–133.
16. Chang YW, Kim HS, Kim HY, Lee JB, Bae JW, Son GS. Should central lymph node dissection be considered for all papillary thyroid microcarcinoma? *Asian J Surg*. 2016;39(4):197–201.
17. Guo Y, Liu Z, Yu P, et al. Using foci number to predict central lymph node metastases of papillary thyroid microcarcinomas with multifocality. *Int J Clin Exp Med*. 2015;8(6):9925–9930.
18. Lee SH, Lee SS, Jin SM, Kim JH, Rho YS. Predictive factors for central compartment lymph node metastasis in thyroid papillary microcarcinoma. *Laryngoscope*. 2008;118(4):659–662.
19. Lim YC, Choi EC, Yoon YH, Kim EH, Koo BS. Central lymph node metastases in unilateral papillary thyroid microcarcinoma. *Br J Surg*. 2009;96(3):253–257.
20. Wang WH, Xu SY, Zhan WW. Clinicopathologic factors and thyroid nodule sonographic features for predicting central lymph node metastasis in papillary thyroid microcarcinoma: a retrospective study of 1,204 patients. *J Ultrasound Med*. 2016;35(11):2475–2481.

21. Zhou YL, Gao EL, Zhang W, et al. Factors predictive of papillary thyroid micro-carcinoma with bilateral involvement and central lymph node metastasis: a retrospective study. *World J Surg Oncol*. 2012;10:67.
22. Khokhar MT, Day KM, Sangal RB, et al. Preoperative high-resolution ultrasound for the assessment of malignant central compartment lymph nodes in papillary thyroid cancer. *Thyroid*. 2015;25(12):1351–1354.
23. Al Afif A, Williams BA, Rigby MH, et al. Multifocal papillary thyroid cancer increases the risk of central lymph node metastasis. *Thyroid*. 2015;25(9):1008–1012.
24. Qu N, Zhang L, Ji QH, et al. Risk factors for central compartment lymph node metastasis in papillary thyroid microcarcinoma: a meta-analysis. *World J Surg*. 2015;39(10):2459–2470.
25. Wong KP, Lang BH. The role of prophylactic central neck dissection in differentiated thyroid carcinoma: issues and controversies. *J Oncol*. 2011;2011:127929.
26. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. *Ann Surg*. 2003;237(3):399–407.
27. Agarwal S, Agarwal A, Chand G. Incidental papillary microcarcinoma of the thyroid – further evidence of a very low malignant potential: a retrospective clinicopathologic study with up to 30 years of follow-up. *Ann Surg Oncol*. 2011;18(Suppl 3):S306.
28. Ahn BH, Kim JR, Jeong HC, Lee JS, Chang ES, Kim YH. Predictive factors of central lymph node metastasis in papillary thyroid carcinoma. *Ann Surg Treat Res*. 2015;88(2):63–68.
29. Siddiqui S, White MG, Antic T, et al. Clinical and pathologic predictors of lymph node metastasis and recurrence in papillary thyroid microcarcinoma. *Thyroid*. 2016;26(6):807–815.
30. So YK, Son YI, Hong SD, et al. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. *Surgery*. 2010;148(3):526–531.
31. Qu N, Zhang L, Lin DZ, Ji QH, Zhu YX, Wang Y. The impact of coexistent Hashimoto's thyroiditis on lymph node metastasis and prognosis in papillary thyroid microcarcinoma. *Tumour Biol*. 2016;37(6):7685–7692.
32. Wreesmann VB, Nixon IJ, Rivera M, et al. Prognostic value of vascular invasion in well-differentiated papillary thyroid carcinoma. *Thyroid*. 2015;25(5):503–508.
33. Kim SS, Lee BJ, Lee JC, et al. Coexistence of Hashimoto's thyroiditis with papillary thyroid carcinoma: the influence of lymph node metastasis. *Head Neck*. 2011;33(9):1272–1277.
34. Paulson LM, Shindo ML, Schuff KG. Role of chronic lymphocytic thyroiditis in central node metastasis of papillary thyroid carcinoma. *Otolaryngol Head Neck Surg*. 2012;147(3):444–449.