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Independent predictors and lymph node metastasis characteristics of multifocal papillary thyroid cancer

Li Genpeng, MD[a], Lei Jianyong, MD[a,b], You Jiaying, BS[b], Jiang Ke, MD[a], Li Zhihui, MD[a,b], Gong Rixiang, MD[a,b], Zhang Lihan, BS[b], Zhu Jingqiang, MD[a,b,*]

Abstract

The multifocal papillary thyroid cancer (PTC), with more aggressive and poorer prognosis, is not rare in papillary histotype. Few studies evaluated risk factors and lymph node metastasis in multifocal PTC. The aim of this present study focusing on risk factors and lymph node metastasis characteristics in multifocal PTC was excepted to assist clinical decisions regarding surgery.

It was a retrospective study. The 1249 consecutive patients with PTC were reviewed. Of these, 570 patients who met the criteria were selected: 285 with solitary papillary thyroid cancer and 285 with multifocal PTC. The risk factors and lymph node metastasis in multifocal PTC were investigated by univariate and multivariate analysis.

Multifocal PTC showed a higher positive rate of capsular invasion, extrathyroidal extension, tumor size >10 mm, pathological T classification, N+ stage, local recurrence, and radioactive iodine ablation (RAI). Capsular invasion (hazard ratio [HR], 1.589; 95% confidence interval [CI],1.352–1.984), advanced pathological T classification (HR, 3.582; 95% CI, 2.184–5.870), and pathological N+ stage (HR, 1.872; 95% CI, 1.278–2.742) were related to increased risk of multifocality and there was a significant increased HR for central neck compartment involvement in male sex (HR, 2.694; 95% CI, 1.740–4.169), advanced pathological T classification (HR, 2.403; 95% CI, 1.479–3.907) and multifocality (HR, 1.988; 95% CI, 1.361–2.906).

There is a significant association between capsular invasion, advanced pathological T classification, N+ stage, and multifocal PTC. Total thyroidectomy plus prophylactic bilateral central lymph node dissection should be recommended during surgery due to a stronger predilection for level VI lymph node metastasis in multifocal PTC.

Abbreviations: BMI = body mass index, C = clinical, LNM = lymph node metastasis, P N+ = pathological positive lymph node metastasis, PTC = papillary thyroid cancer, RIA = radioactive iodine ablation.

Keywords: lymph node metastasis, multifocality, papillary thyroid carcinoma

1. Introduction

The incidence of thyroid carcinoma has been increasing more rapidly than other cancers in recent decades,[1] largely because of the growing use of sensitive diagnostic tools, such as high-resolution ultrasound and fine-needle aspiration biopsy.[2–4] Among thyroid carcinomas, papillary thyroid cancer (PTC), the most common histotype (>85% of all registered cases), is largely responsible for the increased rates of thyroid cancer.[5] Although, it is suggested to be an indolent disease with a favorable prognosis, some tumors with certain clinicopathological features can still show aggressive behavior with poor prognosis.[6,7] Papillary thyroid cancer often presents with multifocal tumors and unilateral or bilateral multifocal PTC is not rare. Clinically, the presence of ≥2 anatomically separated foci in the thyroid gland is defined as multifocal PTC; it most often presents as multiple microcarcinomas (maximum size of tumor ≤10 mm) and occasionally has visible lesions.[8] Multifocality may arise from intrathyroidal metastases from a single malignant clone, as well as multiple independent origins accompanied by intra-thyroidal metastasis.[9] The reported prevalence of multifocal PTC ranges from 18% to 87% depending on epidemiological and methodological factors.[10] It is well-established that PTC has a strong predilection for lymph node metastasis, most commonly to the central neck compartment (level VI) which are bordered by the hyoid bone superiorly, suprasternal notch inferiorly, and the carotid sheaths laterally.[11] Approximately, 30% to 90% of patients with PTC will have clinical or occult cervical lymph node involvement.[12] However, cervical lymph node involvement characteristics and risk factors in multifocal PTC are rarely mentioned. Accordingly, a retrospective analysis was performed to identify risk factors and lymph node metastasis characteristics in multifocal PTC that expect to inform clinical decision-making. This article mainly focuses on the association of multifocal PTC with central lymph node metastasis.

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[a] Thyroid and Parathyroid Surgery Center, West China Hospital, [b] West China School of Medicine, Sichuan University, Sichuan, Chengdu, China.

[*] Correspondence: Zhu Jingqiang, Thyroid and Parathyroid Surgery Center, West China Hospital of Sichuan University, Chengdu 610041, China (e-mail: zhujingqiang@scu.edu.cn).

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2. Patients and methods

We conducted a retrospective analysis. The medical records of PTC patients (N = 1249) who underwent thyroidectomy plus lymph node dissection at the department of Thyroid and Parathyroid Surgery Center, West China Hospital of Sichuan University, between January 1, 2015 and December 31, 2015, were reviewed. Preoperative fine-needle aspiration biopsy and postoperative specimen were reviewed by 2 experienced pathologists in a blind fashion, who confirmed the diagnosis of PTC and the number of tumor foci. Patients who performed total thyroidectomy plus bilateral central neck dissection and identified with multifocal tumors from 18 to 80 years were selected (N = 285). Meanwhile, an equal number of solitary PTC patients were chosen for comparison using a random number table. Those who undergone less-than-total thyroidectomy cases, unilateral central neck dissection and had ever neck surgery, radiation exposure, a definite or suspected family history of PTC, and incomplete medical records were not included.[13] In present study, for multifocal tumors, the tumor with the maximum diameter was considered the primary tumor. Data on the patients' clinical features (sex, age at diagnosis), tumor histological characteristics (maximum size of tumor, solitary or multifocal foci, Hashimoto thyroiditis, capsular invasion, extrathyroidal extension, pathological tumor stage), distant metastasis at diagnosis, radioactive iodine ablation, radioactive iodine ablation dose (mCi), local or distant recurrence, and died of thyroid cancer were extracted from the database. Local or distant recurrence was diagnosed by metastatic lymph node or newly detected tumor >6 months after the initial operation as confirmed by imageological examination (mainly ultrasonography) or fine-needle aspiration biopsy.[14] The follow-up time of study population was 12 to 26 months, and mean time was 18.7 months. The histologic diagnosis was classified according to World Health Organization system. Tumor classification was standardized using the TNM system of the American Joint Committee on cancer (version 7). Univariate and multivariate analyses were performed, concentrating on risk factors and central neck compartment involvement characteristics in multifocal PTC.

Statistical analysis was performed using SAS9.3. (SAS institute Inc, Cary, NC) Continuous variables with normal distribution are expressed as the mean ± standard deviation, and continuous variables without normal distribution are expressed as medians. Categorical variables are presented as numbers. Continuous variables with normal distribution were compared using Student's sample *t* test or analysis of variable. Categorical variables were compared using the chi-square test or Fisher exact chi-square test. A level of 5% was used to identify significant relationships. Independent predictors were determined by multivariable cox's regression model based on the risk factors related to multifocality and central lymph node metastasis. $P < .05$ with a 95% confidence interval indicated statistical significance.

3. Results

3.1. Risk factors and independent predictors associated with multifocality

Clinical and pathological factors that could be associated with multifocality were investigated in this present study, including age, sex, body mass index (BMI), Hashimoto thyroiditis, capsular invasion, extrathyroidal extension, size of the largest focus, pathological T classification, pathological N+ stage, TNM stage, distant metastasis at diagnosis, local or distant recurrence, radioactive iodine ablation (RAI), RAI dose (mCi), died of thyroid cancer. No significant differences were found between the solitary and multifocality group in sex, height (cm), weight (kg), BMI (kg/m^2), distant metastasis or distant recurrence, RAI dose (mCi), died of thyroid cancer, etc. (all $P > .05$; Table 1). Of the patients, however, a statistically differences were showed in the presence of autoimmune thyroid disease (76 vs 51), capsular invasion (226 vs

Table 1

The baseline demographics and tumor characteristics of patients with solitary and multifocal PTC.

	Solitary group 285	Multifocality group 285	*P* value
Age at diagnosis (mean ± SD, y)	43.3 ± 11.5	45.3 ± 10.5	.376
>45/≤45	120/165	135/150	.204
Sex (male/female)	77/208	83/202	.576
Height, cm	163.5 ± 5.8	162.4 ± 6.2	.687
Weight, kg	60.5 ± 11.3	61.1 ± 11.7	.782
BMI (>24/≤24 kg/m^2)	62/223	74/211	.238
Hashimoto thyroiditis (yes/no)	51/234	76/209	.012*
Capsule invasion (yes/no)	140/145	226/59	<.0001*
Extrathyroid extension (yes/no)	31/254	65/220	.0001*
Maximum diameter (mean ± SD, mm)	12.1 ± 5.5	13.9 ± 5.4	.651
>10/≤10 mm	113/172	153/132	.0008*
p T classification (T1/T2–T4)	147/138	233/52	<.0001*
P N+ stage (N0/N1a/N1b)	141/104/40	84/131/70	<.0001*
p TNM stage (I/II/III/IV)	208/32/24/21	199/34/23/23	.613
Distant metastasis at diagnosis	2/283	5/280	.45
Recurrence			
Local recurrence	10/275	21/264	.042*
Distant recurrence	0/285	0/285	
RAI	110/175	214/71	<.0001*
RAI dose (median, mCi)	100	100	.478
Died of thyroid cancer	0/285	0/285	

BMI = body mass index, C = clinical, P = pathological, P N+ = pathological positive lymph node metastasis, RAI = radioactive iodine ablation.
* Statistically significantly differences.

Table 2

The multivariable Cox's proportional hazards regression model of multifocal PTC.

Variables	Hazard ratio	95% CI	*P* value
Hashimoto thyroiditis	1.078	0.762–1.589	.432
Capsule invasion	1.589	1.352–1.984	.043*
Extrathyroid extension	1.367	0.826–2.263	.224
Maximum diameter (>10 mm)	1.174	0.808–1.707	.399
p T classification (T2–T4)	3.580	2.184–5.870	<.0001*
P N+ stage	1.872	1.278–2.742	.002*

P N+ = pathological positive lymph node metastasis, P = pathological.
* Statistically significantly differences.

140), extrathyroidal extension (65 vs 31), maximum diameter >10 mm (153 vs 113), pathological T classification (233 vs 147), pathological N+ stage (201 vs 144), local recurrence (21 vs 10), and RAI (214 vs 110) (all $P < .05$; Table 1). Multifocality is associated with more aggressive and poorer prognosis compared with unifocal disease in this present analysis.

As identified in the univariate analysis, 6 significant factors: Hashimoto thyroiditis, capsular invasion, extrathyroidal extension, size of the largest focus >10 mm, advanced pathological T classification, and N+ stage presented a higher positive rate in multifocal PTC. To determine how strongly those factors were associated with multifocality, the multivariable Cox regression model was performed for these 6 factors, which further showed that not autoimmune thyroid disease (HR, 1.078; 95% CI, 0.762–1.589), extrathyroidal extension (HR, 1.367; 95% CI, 0.826–2.263), and size of the largest focus >10 mm (HR, 1.174; 95% CI, 0.808–1.707) but capsular invasion (HR, 1.589; 95% CI, 1.352–1.984), advanced pathological T classification (HR, 3.582; 95% CI, 2.184–5.870), and pathological N+ stage (HR, 1.872; 95% CI, 1.278–2.742) were related to increased risk of multifocality ($P < .05$; Table 2).

3.2. Central neck compartment metastasis characteristics of multifocal papillary thyroid cancer

Pathologically positive lymph node metastasis was significantly much more common in the multifocal PTC group than in the solitary group (201; 70.5% vs 144; 50.5%; Table 1). In previous studies, lymph node metastasis characteristics in multifocal PTC were rare mentioned. Therefore, the effect of the multifocal PTC on level VI lymph node metastasis was further examined. The association was investigated between several relevant clinical and pathological factors pertaining to the patient and disease, with level VI lymph node metastasis in this present study by univariate analysis. Certain baseline demographics and tumor characteristics, such as increasing age, BMI, Hashimoto thyroiditis, size of the largest focus >10 mm, and clinical T classification were not significantly associated with central lymph node positivity in the study population ($P > .05$; Table 3). However, according to the pathological evaluation, significant differences of central neck compartment involvement were observed on male sex, multifocality, capsular invasion, extrathyroidal extension, and advanced pathological T classification (all $P < .05$; Table 3).

The hazard ratio (HR) for VI lymph node metastasis was identified by Cox proportional hazards regression model based on the above mentioned factors. Controlling for male sex, multifocality, capsular invasion, extrathyroidal extension, and advanced T classification, the HR with capsular invasion and extrathyroidal extension were 1.309 and 1.247, respectively, and this discrepancy did not reach a statistically significant difference ($P > .05$; Table 3). However, there was a significant increased HR for central neck compartment involvement in male sex (HR, 2.694; 95% CI, 1.740–4.169), advanced pathological T classification (HR, 2.403; 95% CI, 1.479–3.907), and multifocality (HR, 1.988; 95% CI, 1.361–2.906) (all $P < .05$; Table 3).

4. Discussion

Papillary thyroid cancer (PTC) is the most common histotype of thyroid malignancy, with a strong predilection for lymph node metastasis, most commonly to the central neck compartment (level VI).[11] In previous study, few studies assessed lymph node metastasis in multifocal PTC. It is generally believed that PTC is an indolent cancer with an excellent prognosis and a low mortality rate. It should not be overtreated. Indeed, the current 30-year overall survival rates of total/near-total thyroidectomy PTC patients with or without radioiodine ablation therapy are >90%,[15] but there is still a report of patient with lethal case fulminant mPTC.[16] In present study, multifocality was associated with higher rates of disease recurrence and poorer prognosis compared with unifocal disease, in accordance with previous studies.[6,17] Multifocality has been reported in 18% to 87% of patients with PTC[10] and was observed in 22.8% of the patients in our center in 2015. The incidence of lymph node involvement solitary PTC is approximately 50%. Because of its higher propensity for lymph node metastasis, multifocal PTC

Table 3

Univariate and multivariate analysis of the clinical and pathological factors that could be associated with central lymph node metastasis.

	Univariate analysis			Multivariate analysis	
Variables	P N+	*P* value	Hazard ratio	95% CI	*P* value
Age at diagnosis (>45/≤45)	162/189	.389			
Sex (male/female)	126/225	.0006*	2.694	1.740–4.169	<.0001*
BMI (>24/≤24 kg/m^2)	84/267	.959			
Tumor size (>10/≤10 mm)	172/179	.157			
Focality (multifocal/unifocal)	207/144	<.0001*	1.988	1.361–2.906	.0004*
Hashimoto thyroiditis (yes/no)	72/279	.300			
Capsule invasion (yes/no)	278/73	<.0001*	1.309	0.807–2.124	.276
Extrathyroid extension (yes/no)	68/283	.041*	1.247	0.568–2.723	.586
c T classification (T1/T2–4)	287/64	.584			
P T classification (T1/T2–4)	53/298	<.0001*	2.403	1.479–3.907	.0004*

BMI = body mass index, C = clinical, P N+ = pathological positive lymph node metastasis.
* Statistically significantly differences.

may have a higher lymph nodes metastasis rate of >50%. In our study population, 285 patients had multifocality, and 201 of these patients identified lymph node metastasis. The incidence of central lymph node involvement reached 70.5%. Due to the indolent nature of PTC, whether lymph node metastasis is a poor prognostic factor remains controversial. Several studies have treated lymph node metastasis as a sign of poor prognosis.[18–21] Other reports, however, suggest that lymph nodes positivity has no long-term influence on patient prognosis.[22,23] One factor that is well-established and widely adopted is that lymph node metastasis has a strong association with recurrence.[24] Therefore, risk factors and tumor metastasis to the neck compartment in multifocal PTC were investigated.

In this present study, multifocality showed a higher positive rate of Hashimoto thyroiditis, capsular invasion, extrathyroidal extension, tumor size >10 mm, advanced p T classification, p N+ stage, local recurrence, RAI. There is a significant association between capsular invasion, advanced pathological T classification, N+ stage, and multifocal PTC by multivariable Cox regression model. Meanwhile, univariate and multivariate analysis of the clinical and pathological factors associated with central lymph node metastasis showed that multifocality was one of independent risk factors for level VI lymph node metastasis. Multifocality increases the risk of metastasis to the central neck compartment in PTC.

The 2009 Revised American Thyroid Association (ATA) recommends therapeutic level VI dissections in patients with clinical evidence of lymph node involvement.[25] However, the role for prophylactic level VI lymph node dissection remains largely controversial.[26] Approximately, 30% to 90% of patients with PTC will have clinical or occult cervical lymph node involvement.[12] Prophylactic central neck dissection increase the risk of postoperative complications, mainly hypoparathyroidism and laryngeal nerve injury.[27] Therefore, some studies have recommended that prophylactic central neck dissection should only be considered in patients with high risk factors, such as male patients, younger patients, and those with larger tumor sizes and extrathyroidal extensions.[28] However, prophylactic central neck dissection makes it possible for us to accurately assess the stage of tumors postoperation for evaluating the necessity of radioactive iodine therapy[28]; there is an increased risk of complications in second operation when the tumor recurs in the central compartment.[29] Importantly, prophylactic central neck dissection actually is relatively safe in the hands of an experienced surgeon and it can prevents recurrence and improves tumor-free or overall survival effectively due to removal of microscopic metastases in the central compartment lymph node.[30]

Like any other, this study has its limitations. Because this was a retrospective review, the data were retrospectively collected and analyzed. The selection of single patients may generate a selection bias. Furthermore, the sample size was not sufficiently large as only 570 patients were ultimately identified. Studies with larger sample sizes are needed to further confirm our predictive model. In addition, in Wang et als' study,[26] the insular histotype identified more poor prognosis and in Wang et als' study,[31] patients with tall cell variant of PTC is more aggression than classic PTC, being associated with increased incidence of multifocality, extrathyroidal extension, lymph node involvement, distant metastasis, and recurrence. The association of the subtype of PTC, such as follicular variant, diffuse sclerosing, insular, tall cell variant, columnar, etc., with multifocality and central lymph node metastasis did not conduct further exploration because of lacking a further subdivision of PTC in our institution. Lalmi et al[32] suggest that the promising perspective applied to diagnosis and prediction of thyroid cancer lies in molecular biology test, however, gene mutation (BRAF, RAS, RET, TERT), gene rearrangements (RET/PTC), and immuno- histochemical markers were considered only the FNAB cannot give definite diagnosis at our center, the predictors of molecular biology also need further delineation.

Taken together, multifocality was associated with more aggressive and poorer prognosis. Capsular invasion, advanced pathological T classification and N+ stage were independent predictors of multifocal PTC. Total thyroidectomy with prophylactic bilateral central lymph node dissection should be recommended during surgery in multifocal PTC due to a higher propensity for level VI lymph node metastasis.

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