Oral Oncology 94 (2019) 106–110

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Multifocality of papillary thyroid carcinoma as a risk factor for disease recurrence

Woo Ri Choi[a], Jong-Lyel Roh[a,*], Gyungyup Gong[b], Kyung-Ja Cho[b], Seung-Ho Choi[a], Soon Yuhl Nam[a], Sang Yoon Kim[a]

[a] Departments of Otolaryngology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[b] Departments of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Papillary thyroid carcinoma
Multifocality
Bilaterality
Recurrence
Risk factor

ABSTRACT

Objectives: Tumor multifocality or bilaterality is associated with increased risk of papillary thyroid carcinoma (PTC) recurrence. However, its prognostic value in clinical outcomes remains controversial. This study aimed to evaluate the association of multifocality or bilaterality with recurrence and survival after total thyroidectomy.
Methods: This was a retrospective study of 2390 consecutive patients with pathologically confirmed PTC who underwent total thyroidectomy. Multifocality and bilaterality were decided based on the final pathology results, that is, if there were two or more tumor foci and bilateral location, respectively. Primary outcomes were recurrence-free survival (RFS). Cox proportional hazards regression analyses were used to assess the associations of multifocality, bilaterality, and other clinicopathological factors with RFS.
Results: Multifocal and bilateral PTC were found in 892 (37.3%) and 593 (24.8%) patients, respectively. Multivariate analyses showed that multifocality, lymphovascular invasion, N category, and number of positive lymph node (> 5) were significant independent variables predictive of RFS (all $P < 0.05$). Multifocality was associated with adjusted hazard ratios for RFS of 1.93 (95% confidence interval = 1.33–2.80; $P = 0.001$). In a subset analysis, the prognostic value of multifocality was found to be significant in those patients with PTC > 1 cm, but not in papillary thyroid microcarcinoma.
Conclusions: Tumor multifocality is an independent risk factor of PTC recurrence after total thyroidectomy. This indicate a more progressive state of disease, being included in risk stratification.

Introduction

Papillary thyroid carcinoma (PTC) is the most treatable disease of human malignancy with very low disease-specific mortality [1–3]. PTC is the major subtype of thyroid malignancy with rapidly increasing incidence because of early detection using ultrasonography and surveillance techniques [4,5]. The overall incidence in the US increased by 3% annually, along with increased cancer-specific mortality for advanced-stage PTC [6]. However, PTC is commonly associated with an indolent clinical course of > 90% overall survival rates at 20 years and 30 years after total or near-total thyroidectomy [7]. The overall survival rates of PTC are excellent but differ according to age, tumor size and local invasion, and metastasis [3,8,9]. Despite very low disease-specific mortality, PTC recurrence is relatively common in locoregional and distant sites [3]. Tumor and metastatic disease factors have been included in the risk stratification system of structural disease recurrence recently proposed by the American Thyroid Association (ATA) [10]. In addition, the American Joint Committee on Cancer (AJCC) has recently updated the tumor-node-metastasis (TNM) staging system (8th edition) by significantly changing the age-at-diagnosis cut-off to 55 years, and minor extrathyroidal extension and upper mediastinal lymph node (LN) involvement to downstaging [9].

Tumors with two or more foci (multifocality) and bilateral location (bilaterality) frequently arise in the thyroid gland, with the prevalence of multifocality ranging from 32% to 39% [11–13] and that of bilaterality ranging from 13% to 56% [14–17]. Several studies have shown that multifocality and bilaterality are associated with an increased risk of disease recurrence and overall mortality [12,18–20]. Multifocality or bilaterality may be an aggressive subset of PTC but is not considered as a risk factor in current risk stratification or cancer staging system [9,10]. Patients with multifocal PTC at high risk may be managed with more active treatment planning, such as total thyroidectomy and

* Corresponding author at: Department of Otolaryngology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea.
E-mail address: rohjl@amc.seoul.kr (J.-L. Roh).

https://doi.org/10.1016/j.oraloncology.2019.05.023
Received 11 February 2019; Received in revised form 20 May 2019; Accepted 25 May 2019
Available online 29 May 2019
1368-8375/

subsequent radioactive iodine ablation (RAI) therapy for bilateral multifocal PTC. However, the prognostic value of tumor multifocality or bilaterality is controversial, creating a dilemma in the current management of PTC. Therefore, this study aimed to evaluate the association of multifocality or bilaterality with recurrence and survival after total thyroidectomy in a large cohort of 2390 consecutive PTC patients.

Methods

Study patients

Electronic records were sort to identify the patients with pathologically confirmed PTC who underwent total thyroidectomy at the Department of Otolaryngology of our hospital between 2006 and 2015. The presence of thyroid tumors and some metastatic nodes were preoperatively diagnosed with high-resolution ultrasonography-guided fine needle aspiration. Pathologic findings from tumor and nodal surgical specimens were thoroughly reported by the board-certified pathologists with > 25 years of clinical experience. Patients who underwent hemithyroidectomy, with previous history of thyroid or neck surgery or previous neck irradiation, with poorly differentiated pathology, with other cancer types at diagnosis, and were lost to follow-up < 2 years were excluded. Finally, a total of 2390 patients were included in this study. This study was approved by the Institutional Review Board of our hospital, which waived the requirement for informed consent.

All study patients with or without cervical metastasis (level VI) underwent total thyroidectomy plus central neck dissection, according to our institutional protocol. The extent of surgery, such as total thyroidectomy or hemithyroidectomy, was decided based on the previous version of the ATA guideline for differentiated thyroid cancer [21]. Patients with clinical metastasis to the lateral neck underwent additional simultaneous LN dissection at neck levels Ib–V or II–IV [22,23]. The tumor and nodal specimens were sent to examine the pathological findings: tumor size, multifocality, bilaterality, extrathyroidal extension, perineural invasion, lymphovascular invasion, LN positivity, and size, number, and extranodal extension of metastatic LN. Postoperative RAI therapy were performed in most patients who underwent total thyroidectomy as indicated in the previous ATA guidelines [21]. Patients were followed up at the outpatient clinic every 3 months during the first year and annually thereafter. Neck ultrasonography, chest radiography, whole-body iodine scanning, and serum thyroid function (free thyroxin, thyroid-stimulating hormone, and thyroglobulin) were also tested during the follow-up period [24,25]. Structural recurrence or new lesions were detected by imaging modalities followed by histological examination of biopsied samples [10,26]. Additional surgery was performed in patients with structural recurrences, while patients with unresectable or distant metastatic diseases received RAI therapy. Those with iodine-refractory diseases were treated with tyrosine kinase inhibitors [21,27].

Variables

Patients' demographic data such as age (< 55/≥55 years) and sex were included as variables. The following tumor findings were included as pathological variables: tumor size, extrathyroidal extension (no/microscopic/macroscopic), perineural invasion, and lymphovascular invasion. The following nodal findings were also included: nodal positivity, number of positive LN (≤5/ > 5), size of positive LN (≤3/ > 3 cm), LN ratio, and extranodal extension. Multifocality and bilaterality were decided based on the final pathology results, that is, if there were two or more tumor foci and bilateral location, respectively. Papillary thyroid microcarcinoma (PTMC) was defined as tumor size of 1 cm or less as determined by pathological examination. LN ratio was defined as the number of positive LNs divided by the number of harvested LNs [22]. Pathological T and N categories using TNM staging system recently proposed by the AJCC (8th ed.) [9] were also included.

Statistical analysis

Continuous variables were expressed as means and standard deviations or medians and ranges, while categorical variables were expressed as numbers and percentages. The variables were compared between groups with unifocal and multifocal PTC using the χ^2 or Fisher's exact test for categorical variables and *t*-test for continuous variables. Multivariate binary logistic regression analysis was used to identify the independent factors associated with pathological multifocality with the entry and backward stepwise selection procedure of all variables that produced $P < 0.05$ on univariate analyses. Recurrence-free survival (RFS) was the primary endpoint because the index cancer-specific and all-causing mortality occurred in < 1% of all study patients. RFS was defined as the period from the start of treatment to the first event of recurrence at any site or last visit.

Univariate Cox proportional hazards regression analyses were performed to evaluate the prognostic factors associated with RFS. Multivariate Cox proportional hazards regression analyses were conducted using a backward stepwise selection procedure with all clinically relevant variables. The odds ratio (OR), hazard ratio (HR) and 95% confidence interval (CI) were estimated. Univariate and multivariate analyses of factors related to RFS were conducted in all PTC patients and the subgroups of PTMC and PTC of > 1 cm tumor size (non-PTMC). The Kaplan-Meier and log-rank tests were used to determine survival and statistical significance, respectively. A *P*-value less than 0.05 was considered significant, and all statistical tests were two tailed. All statistical analyses were performed using the IBM SPSS software, version 24.0 (Chicago, IL, USA).

Results

Patient characteristics

This study included 2390 patients, of which 516 were men (21.6%) and 1874 were women (78.4%), with a median age of 52 years (range: 12–88 years). Multifocal and bilateral PTC were found in 892 (37.3%) and 593 (24.8%) patients, respectively. The median tumor size was 1.3 cm (interquartile range [IQR] = 0.8–1.8 cm), and PTMC was found in 1307 (54.7%) patients. Perineural invasion and lymphovascular invasion were found in 28 (1.2%) and 211 (8.8%) patients, respectively. Pathological nodal positivity was found 1,452 patients (60.8%): N1a in 1007 patients (42.1%) and N1b in 445 patients (18.6%). The median number of positive LN was 1 (IQR = 0–4) and the LN ratio was 0.11 (0–0.30). LNs of > 5, positive LN of > 3 cm, and LN ratio of > 0.3 were found in 469 (19.6%), 26 (1.1%), and 588 (24.6%) patients, respectively. Advanced T3 and T4 categories were found in 540 (22.6%) and 83 (3.5%), respectively. The patients were followed for a median of 92 months (range: 24–143 months). During follow-up, a total of 118 patients (4.9%) had recurrence at the following sites: 13 (0.5%) patients in the thyroidectomy bed, 95 (4.0%) patients in the regional site, and 25 (1.0%) patients in distant site, with overlapping in recurrence site in some patients. At the last follow-up, 29 patients died of PTC or other causes. The 5-year and 10-year RFS rates were 98.9% (98.7–99.1%) and 91.1% (90.0%–92.2%), respectively; the 5-year and 10-year overall survival rates were 99.2% (99.0–99.4%) and 98.4% (98.1%–98.7%), respectively.

Comparison between unifocal and multifocal PTC

When compared between unifocal and multifocal PTC, several tumor and nodal findings differed significantly: macroscopic extrathyroidal extension, pathological LN positivity, N1b category, number of positive LN > 5, and LN ratio > 0.3, extranodal extension, and T4 category (all $P < 0.05$) (Table 1). Multifocal PTC had more positive

Table 1
Comparison of patient characteristics between unifocal and multifocal PTC ($N = 2390$).

	Unifocal PTC	Multifocal PTC	P[a]
No. of patients (%)	1498 (62.7)	892 (37.3)	
Age (years)			
Mean ± SD	51.4 ± 12.3	51.4 ± 12.1	0.931
≥55	616 (41.1)	359 (40.2)	0.674
Gender, men	319 (21.3)	197 (22.1)	0.650
Tumor size (cm), mean ± SD	1.3 ± 3.6	1.3 ± 1.0	0.791
Tumor size, > 1 cm	666 (44.5)	417 (46.7)	0.277
Extrathyroidal extension			
Microscopic	696 (46.5)	441 (49.4)	0.159
Macroscopic	200 (13.4)	177 (19.8)	< 0.001
Perineural invasion	15 (1.0)	13 (1.5)	0.538
Lymphovascular invasion	120 (8.0)	91 (10.2)	0.068
Nodal status			
Pathological positivity	846 (56.5)	606 (67.9)	< 0.001
N1a	615 (41.1)	392 (43.9)	0.166
N1b	231 (15.4)	214 (24.0)	< 0.001
No of positive LN, mean ± SD	2.7 ± 4.6	4.5 ± 7.0	< 0.001
No of positive LN > 5	226 (15.1)	243 (27.2)	< 0.001
Size of metastatic foci (mm), mean ± SD	2.3 ± 5.5	3.5 ± 7.6	< 0.001
Size of positive LN, > 3 cm	12 (0.8%)	14 (1.6%)	0.080
LN ratio, > 0.3	347 (23.2)	241 (27.0)	0.034
Extranodal extension	207 (13.8)	195 (21.9)	< 0.001
T category (AJCC 8th ed.)			
T1	1050 (70.1)	564 (63.2)	0.001
T2	93 (6.2)	60 (6.7)	0.617
T3	320 (21.4)	220 (24.7)	0.062
T4	35 (2.3)	48 (5.4)	< 0.001
Postoperative RAI	1347 (89.9)	833 (93.4)	0.004
Follow-up, median (range), months	93 (24–143)	90 (24–143)	0.167
Recurrence, any site[b]	53 (3.5)	65 (7.3)	< 0.001
Local	6 (0.4)	7 (0.8)	0.217
Regional	42 (2.8)	53 (5.9)	< 0.001
Distant	15 (1.0)	10 (1.1)	0.781
Death from PTC	1 (0.1)	7 (0.8)	0.003
Death from other causes	13 (0.9)	8 (0.9)	0.941

Note: Variables were expressed as numbers (percentages) unless otherwise indicated.
Abbreviations: LN, lymph node; PTC, papillary thyroid carcinoma; RAI, radioactive iodine ablation therapy; SD, standard deviation.
[a] The χ^2 or Fisher's exact test for categorical variables and the *t*-test for continuous variables.
[b] Overlapping in recurrent sites in some patients.

LNs and larger tumor size than unifocal PTC (both $P < 0.001$). Multivariate logistic regression analysis using backward stepwise elimination showed that T4 category (OR = 2.02, 95% CI = 1.28–3.17) and number of positive LN > 5 (OR = 2.04, 95% CI = 1.66–2.50) remained the independent factors associated with pathological multifocality (all $P < 0.005$) (Supplementary Table S1).

Risk factors for recurrence following thyroidectomy

Univariate analyses showed that multifocality, lymphovascular invasion, LN positivity, number of positive LNs (> 5), size of positive LNs (> 3 cm), LN ratio > 0.3, extranodal extension, and N category were significantly associated with unfavorable RFS outcomes in all PTC patients and both PTMC and non-PTMC subgroups (all $P < 0.05$) (Table 2). Sex (men) and tumor findings of microscopic or macroscopic extrathyroidal extension, tumor size, and T3 or T4 category were significantly associated with poor RFS outcomes in all PTC patients and the non-PTMC subgroup (all $P < 0.05$).

With regard to recurrence, multivariate analyses showed that multifocality, lymphovascular invasion, N category, and number of positive LNs remained the independent variables predictive of RFS in all PTC patients and the non-PTMC subgroup (all $P < 0.05$) (Table 3). N category was the only independent factor predictive of RFS in the PTMC group ($P = 0.001$). Multifocality was associated with a 1.93-fold increased risk (95% CI = 1.33–2.80; $P = 0.001$) of recurrence in all PTC patients. The 5-year and 10-year RFS rates were 99.4% and 93.4% in unifocal PTC, and 97.7% and 86.8% in multifocal PTC, respectively. However, no significant differences were found in the RFS rates between unilateral and bilateral subgroups of multifocal PTC ($P > 0.01$). Fig. 1 represents the Kaplan-Meier curves estimating the recurrence and survival according to the multifocality of PTC.

Discussion

The present study showed the prognostic values of tumor multifocality or bilaterality in a large cohort of 2390 consecutive PTC patients who underwent total thyroidectomy. Multifocal and bilateral PTC were frequently observed in 37.3% and 24.8% of study patients, respectively. Multifocality and was significantly associated with unfavorable RFS outcomes. Multifocality was the independent risk factor predictive of RFS in addition to lymphovascular invasion, N category, and number of positive LNs. The prognostic value of multifocality was more significant in the non-PTMC subgroup than in the PTMC subgroup, showing an approximately twofold increased risk of recurrence. Therefore, this study has identified that tumor multifocality is a predictive risk factor for recurrence after total thyroidectomy in PTC patients.

Additional tumor foci can be preoperatively diagnosed along with increased radiological screening tests for thyroid nodules [17]. Occult PTC unrecognized preoperatively can be identified in the bilateral or contralateral lobe in more than 15% of total thyroidectomy specimens, even in patients with PTMC [16,28–30]. In the present study, multifocality and bilaterality were found in 37.3% and 24.8% of study patients, with no significant difference between the PTMC subgroup and non-PTMC subgroup. The prevalence of additional occult PTC foci was not calculated because the preoperative ultrasonography findings were not included in our study. Even in the era of imaging and screening advancement, the presence of occult multifocal tumor and nodal diseases might be underdiagnosed because of the recent recommendations of less surgical extent for low-risk PTC. A recent ATA guideline recommended that lobectomy can be applied to PTC up to 4 cm in size, without extrathyroidal extension or clinical LN metastasis [10]. High thresholds are increasingly incorporated into the guidelines for thyroid cancer surgery, particularly for low-risk disease [31]. However, increasing evidence showed that multifocality or bilaterality is associated with more advanced disease status, resulting in an increased risk of disease recurrence and overall mortality [12,18–20].

Early studies indicated that tumor multifocality increases the risk of recurrence and cancer mortality [12,18]. The single center study including 1682 Taiwanese patients showed that the 10-year RFS rates of patients with multifocal PTC (20.0%) were lower than those with unifocal PTC (71.9% vs. 85.0%, $P < 0.05$); the 10-year OS rates in patients with multifocal PTC were also lower than those with unifocal PTC (94.4% vs. 95.3%, $P < 0.05$) [18]. Another single-center study involving 2095 patients who underwent total thyroidectomy for PTC showed the role of multifocality (32.1% prevalence) as an independent predictor of disease recurrence/persistence with a 1.45-fold increased risk [12]. However, tumor bilaterality (22.9% prevalence) was not associated with increased risk of PTC recurrence/persistence. Recent studies have also shown the prognostic value of tumor multifocality or bilaterality in PTC patients [19,20]. Meanwhile, a multicenter study was conducted in 2638 PTC patients in six countries from Western and East Asia who underwent total or near total thyroidectomy and followed for a median of 58 months [20]. Multifocality was an independent risk factor associated with increased risk of recurrence (HR = 1.55, 95% CI = 1.28–1.88; $P < 0.001$) but it has no association with mortality ($P = 0.892$). There was no significant difference between unifocal and

Table 2
Univariate analyses of factors associated with recurrence-free survival.

	All PTC		PTMC		Non-PTMC	
	HR (95% CI)	P^a	HR (95% CI)	P^a	HR (95% CI)	P^a
Age, ≥55 years	0.79 (0.55–1.13)	0.198	0.33 (0.15–0.71)	0.005	125 (0.82–1.92)	0.300
Gender, men	2.01 (1.37–2.95)	< 0.001	3.20 (1.58–6.49)	0.001	1.56 (0.98–2.48)	0.059
Multifocality	2.59 (1.80–3.72)	< 0.001	2.51 (1.24–5.05)	0.010	2.74 (1.78–4.22)	< 0.001
Bilaterality	1.40 (0.94–2.10)	0.099	1.21 (0.54–2.71)	0.637	1.48 (0.92–2.36)	0.106
Tumor size, > 1 cm	2.73 (1.82–4.12)	< 0.001				
Extrathyroidal extension						
Microscopic	2.36 (1.38–4.03)	0.002	1.16 (0.56–2.39)	0.687	4.11 (1.48–11.43)	0.007
Macroscopic	5.76 (3.22–10.28)	< 0.001	1.76 (0.39–7.86)	0.459	8.18 (2.90–23.04)	< 0.001
Perineural invasion	2.25 (0.69–7.30)	0.177	1.76 (0.24–13.12)	0.580	3.28 (0.73–14.28)	0.124
Lymphovascular invasion	4.39 (2.87–6.73)	< 0.001	4.80 (1.67–13.77)	0.004	3.32 (2.07–5.34)	< 0.001
Nodal status						
Pathological positivity	7.85 (4.00–15.50)	< 0.001	8.32 (2.92–23.73)	< 0.001	5.15 (2.08–12.71)	< 0.001
N1a	4.43 (2.16–9.20)	< 0.001	5.41 (1.79–16.32)	0.003	2.89 (1.11–7.51)	0.029
N1b	15.46 (7.70–31.06)	< 0.001	22.11 (7.19–68.01)	< 0.001	8.55 (3.41–21.40)	< 0.001
No of positive LN > 5	6.48 (4.46–9.42)	< 0.001	6.89 (3.42–13.90)	< 0.001	5.06 (3.19–8.04)	< 0.001
Size of LN, > 3 cm	3.08 (1.52–6.26)	0.002	10.17 (1.37–75.56)	0.023	2.03 (0.95–4.37)	0.069
LN ratio, > 0.3	2.39 (1.67–5.44)	< 0.001	3.65 (1.82–7.33)	< 0.001	1.73 (1.13–2.66)	0.012
Extranodal extension	5.88 (4.09–8.46)	< 0.001	9.44 (4.64–19.20)	< 0.001	3.92 (2.55–6.04)	< 0.001
T category (AJCC 8th ed.)						
T1	Reference		Reference		Reference	
T2	2.15 (1.23–3.72)	0.007	–		1.53 (0.84–2.81)	0.165
T3	2.54 (1.60–4.02)	< 0.001	1.11 (0.33–3.81)	0.863	2.21 (1.29–3.80)	0.004
T4	4.76 (2.68–8.44)	< 0.001	4.67 (0.63–34.80)	0.133	3.49 (1.84–6.60)	< 0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; LN, lymph node; PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma.
[a] Univariate Cox proportional hazard regression models, $P < 0.05$.

Table 3
Multivariate analyses for recurrence-free survival.

	All PTC		PTMC		Non-PTMC	
	HR (95% CI)	P^a	HR (95% CI)	P^a	HR (95% CI)	P^a
Multifocality	1.93 (1.33–2.80)	0.001			2.05 (1.32–3.18)	0.002
Lymphovascular invasion	2.04 (1.31–3.19)	0.002			1.95 (1.19–3.20)	0.008
Nodal status						
N1a	2.75 (1.30–5.81)	0.008	4.10 (1.32–12.73)	0.015	2.47 (0.88–6.96)	0.086
N1b	4.12 (1.76–9.66)	0.001	11.25 (3.24–39.03)	< 0.001	3.64 (1.25–10.57)	0.018
No of positive LN > 5	1.81 (1.09–2.99)	0.021			2.40 (1.39–4.16)	0.002

Abbreviations: CI, confidence interval; HR, hazard ratio; LN, lymph node; PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma.
[a] The multivariate models were performed using a backward stepwise selection procedure with all clinically relevant variables on univariate results (Table 2).

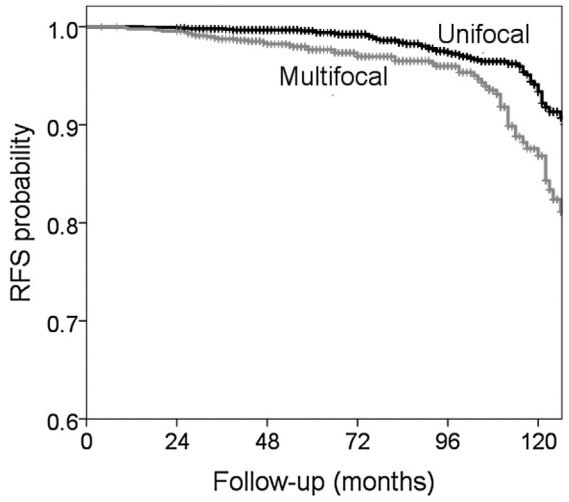

Fig. 1. Kaplan-Meier curves estimating recurrence-free survival (RFS) according to the multifocality of PTC. Log-rank test, $P < 0.005$.

multifocal PTC in terms of OS, as validated from the analyses of Surveillance, Epidemiology, and End Results database including a total of 89,680 patients from SEER database from 2004 to 2013 [20]. Furthermore, a recent study involving 2211 Chinese PTC patients who underwent total/near-total thyroidectomy showed that the predictive role of tumor bilaterality was associated with higher incidence of LN metastasis and BRAF mutation, and shorter disease-free survival [19].

The present study supported the findings of previous studies indicating that PTC multifocality is associated with advanced disease status in terms of macroscopic extranodal extension, tumor and nodal stage, and number and size of positive LNs. Multifocality has been suggested as a factor predictive of neck LN metastasis in PTC [32]. Multifocality might be present along with an aggressive type of PTC and more metastatic potential. From our subgroup analyses, multifocality or bilaterality was not an important prognostic factor in the PTMC subgroup but in the non-PTMC subgroup. This finding might imply that tumor multifocality is associated with increased disease recurrence in the non-PTMC and has little or no significance for PTMC [13]. A recent study also showed the increased risk of recurrence (HR = 4.05, 95% CI = 2.07–7.93) and mortality (HR = 7.25, 95% CI = 2.19–24.03) in bilateral PTC patients [33]. However, the prognostic role of

multifocality or bilaterality for disease-specific or OS remains controversial [20], which needs further multi-institutional studies with long-term follow-up. The other risk factors of recurrence identified in our study are already well known and incorporated into the management guideline and staging system [9,10], which may prevent further description of these factors in detail.

Our study has several limitations. This study is retrospective in nature and has high proportional inclusion of PTMC. Small tumors might only require observational trial or active surveillance without surgical treatment [34]. However, higher rates of extrathyroidal extension, LN metastasis, and extranodal extension were found in our cohort. Additionally, routine prophylactic central neck dissection is not advocated by the ATA guidelines, which might be a weak point of our cohort [10]. However, it would be an advantage that our analyses were also based on thoroughly examined pathological tumors and nodal findings, with clear clinical and follow-up information accumulated over a median of 92 months.

Conclusions

The present study has shown that tumor multifocality is an independent risk factor of PTC recurrence after total thyroidectomy. The prognostic value of multifocality is particularly significant in PTC patients with tumor size > 1 cm. Thus, multifocality may indicate a more progressive state of disease, being included in risk stratification, management guidelines, and post-treatment surveillance of patients with PTC.

Funding

No funding was received in support of this work.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.05.023.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
[2] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018.
[3] Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418–28.
[4] Wiltshire JJ, Drake TM, Uttley L, Balasubramanian SP. Systematic review of trends in the incidence rates of thyroid cancer. Thyroid 2016;26:1541–52.
[5] Simard EP, Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. CA Cancer J Clin 2012;62:118–28.
[6] Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. JAMA 2017;317:1338–48.
[7] Markovina S, Grigsby PW, Schwarz JK, DeWees T, Moley JF, Siegel BA, et al. Treatment approach, surveillance, and outcome of well-differentiated thyroid cancer in childhood and adolescence. Thyroid 2014;24:1121–6.
[8] Edge SBBD, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC cancer staging manual. 7th ed.New York, NY: Springer; 2010. p. 29–40.
[9] Amin MBES, Greene FL, Byrd DR, Brookland RK, Washington MK, editors. AJCC cancer staging manual. 8th ed.New York, NY: Springer; 2017. p. 873–90.
[10] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, 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;26:1–133.
[11] Shi X, Liu R, Basolo F, Giannini R, Shen X, Teng D, et al. Differential clinicopathological risk and prognosis of major papillary thyroid cancer variants. J Clin Endocrinol Metab 2016;101:264–74.
[12] Kim HJ, Sohn SY, Jang HW, Kim SW, Chung JH. Multifocality, but not bilaterality, is a predictor of disease recurrence/persistence of papillary thyroid carcinoma. World J Surg 2013;37:376–84.
[13] 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;22:125–31.
[14] Pitt SC, Sippel RS, Chen H. Contralateral papillary thyroid cancer: does size matter? Am J Surg 2009;197:342–7.
[15] Pasieka JL, Thompson NW, McLeod MK, Burney RE, Macha M. The incidence of bilateral well-differentiated thyroid cancer found at completion thyroidectomy. World J Surg 1992;16. 711–6; discussion 6–7.
[16] Koo BS, Lim HS, Lim YC, Yoon YH, Kim YM, Park YH, et al. Occult contralateral carcinoma in patients with unilateral papillary thyroid microcarcinoma. Ann Surg Oncol 2010;17:1101–5.
[17] So YK, Kim MW, Son YI. Multifocality and bilaterality of papillary thyroid microcarcinoma. Clin Exp Otorhinolaryngol 2015;8:174–8.
[18] Lin JD, Chao TC, Hsueh C, Kuo SF. High recurrent rate of multicentric papillary thyroid carcinoma. Ann Surg Oncol. 2009;16:2609–16.
[19] Wang W, Su X, He K, Wang Y, Wang H, Wang H, et al. Comparison of the clinicopathologic features and prognosis of bilateral versus unilateral multifocal papillary thyroid cancer: An updated study with more than 2000 consecutive patients. Cancer 2016;122:198–206.
[20] Wang F, Yu X, Shen X, Zhu G, Huang Y, Liu R, et al. The prognostic value of tumor multifocality in clinical outcomes of papillary thyroid cancer. J Clin Endocrinol Metab 2017;102:3241–50.
[21] Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American thyroid association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–214.
[22] Zheng CM, Ji YB, Song CM, Ge MH, Tae K. Number of metastatic lymph nodes and ratio of metastatic lymph nodes to total number of retrieved lymph nodes are risk factors for recurrence in patients with clinically node negative papillary thyroid carcinoma. Clin Exp Otorhinolaryngol 2018;11:58–64.
[23] Lee DY, Hwang SM, An JH, Son KR, Baek SK, Kim SG, et al. Predicting extrathyroidal extension in patients with papillary thyroid microcarcinoma according to a BRAF mutation. Clin Exp Otorhinolaryngol 2017;10:174–80.
[24] Denaro N, Merlano MC, Russi EG. Follow-up in head and neck cancer: do more does it mean do better? A systematic review and our proposal based on our experience. Clin Exp Otorhinolaryngol 2016;9:287–97.
[25] Chong A, Ha JM, Han YH, Kong E, Choi Y, Hong KH, et al. Preoperative lymph node staging by FDG PET/CT with contrast enhancement for thyroid cancer: a multicenter study and comparison with neck CT. Clin Exp Otorhinolaryngol 2017;10:121–8.
[26] Kruijff S, Aniss AM, Chen P, Sidhu SB, Delbridge LW, Robinson B, et al. Decreasing the dose of radioiodine for remnant ablation does not increase structural recurrence rates in papillary thyroid carcinoma. Surgery 2013;1337–44:154. discussion 44–5.
[27] Laursen R, Wehland M, Kopp S, Pietsch J, Infanger M, Grosse J, et al. Effects and role of multikinase inhibitors in thyroid cancer. Curr Pharm Des 2016;22:5915–26.
[28] Lee YC, Eun YG, Sohn YM, Rhee SY, Hong IK, Chon S, et al. Predictive factors for occult contralateral carcinoma in patients with unilateral papillary thyroid microcarcinoma by preoperative ultrasonographic and pathological features. World J Surg 2015;39:1736–41.
[29] Lee KJ, Cho YJ, Kim JG, Lee DH. How many contralateral papillary thyroid carcinomas can be missed? World J Surg 2013;37:780–5.
[30] Wu ZG, Yan XQ, Su RS, Ma ZS, Xie BJ, Cao FL. How many contralateral carcinomas in patients with unilateral papillary thyroid microcarcinoma are preoperatively misdiagnosed as benign? World J Surg 2017;41:129–35.
[31] Kovatch KJ, Hoban CW, Shuman AG. Thyroid cancer surgery guidelines in an era of de-escalation. Eur J Surg Oncol. 2018;44:297–306.
[32] Zhao Q, Ming J, Liu C, Shi L, Xu X, Nie X, et al. Multifocality and total tumor diameter predict central neck lymph node metastases in papillary thyroid microcarcinoma. Ann Surg Oncol 2013;20:746–52.
[33] Qu N, Zhang L, Wu WL, Ji QH, Lu ZW, Zhu YX, et al. Bilaterality weighs more than unilateral multifocality in predicting prognosis in papillary thyroid cancer. Tumour Biol 2016;37:8783–9.
[34] Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. World J Surg 2010;34:28–35.