Article

Discovery Medicine 2024; 36(180): 209–216
https://doi.org/10.24976/Discov.Med.202436180.20

Clinicopathologic Characteristics of Thyroid Microcarcinoma: Findings from a Hospital-Based Study in Vietnam

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Published: 20 January 2024

Background: Thyroid microcarcinoma (TMC) incidence has significantly increased in recent decades. The rates of lymph node metastasis extrathyroidal extension have been significantly different in patients with TMC ≤5 mm versus those with size >5 mm. The current analysis aimed to examine the clinicopathologic features of TMC measuring <5 mm and to compare them with those of TMC ≥5 mm.

Methods: A total of 273 patients with TMC confirmed by histological examination from December 2020 to May 2021 were enrolled in Bach Mai Hospital, Hanoi, Vietnam. Unconditional logistic regression models were used to determine the association between clinicopathological factors and tumor size, central lymph node metastasis and extrathyroidal extension.

Results: We found 212/273 patients (77.7%) were diagnosed incidentally. The majority of patients were female (87.5%) and had a mean age of 44.2 years. The mean tumor size (±standard deviation (SD)) was 5.72 ± 2.33 mm. Most of the patients were also diagnosed with papillary TMC. Multifocal and bilateral lesions accounted for 13.2% and 12.1%, respectively. The extrathyroidal invasion was observed in 14.7% (40 patients), while 24.5% (67 patients) were those with central lymph node metastases. The rate of extrathyroidal extension in patients with tumor size ≥5 mm was significantly higher than in patients with tumor size <5 mm (odds ratio (OR) = 4.98; 95% confidence interval (CI): 1.48–16.70; $p = 0.004$). Patients with body mass index (BMI) <23 kg/m^2 were found to be protected against the odds of extrathyroidal extension (OR = 0.38, 95% CI: 0.19–0.75; $p = 0.004$) compared to those with BMI ≥23 kg/m^2. In univariable mode, central lymph node metastasis was positively associated with the odds of the presence of extrathyroidal extension (OR = 2.70, 95% CI: 1.34–5.45; $p = 0.004$). In the multivariable model, central lymph node metastasis was also associated with the presence of extrathyroidal extension (OR = 2.507, 95% CI: 1.194–5.264; $p = 0.017$). Univariate analysis demonstrated that tumor size ≥5 mm (OR = 2.04; 95% CI: 1.01–4.17; $p = 0.047$) and extrathyroidal extension (OR = 2.71; 95% CI: 1.34–5.45; $p = 0.004$) were risk factors of central cervical lymph node metastasis. In multivariable models, the extrathyroidal extension was associated with central lymph metastasis.

Conclusions: TMC <5 mm tumor size is less likely to have aggressive characteristics, including extrathyroidal extension, than a TMC ≥5 mm. Long-term follow-up studies are thus warranted to investigate the factors in the prognosis of TMC.

Keywords: thyroid microcarcinoma; TMC; differentiated thyroid carcinoma; thyroid cancer

Background

Worldwide, the detectable rate of thyroid cancer has increased during the past decades, owing to the increased identification of small papillary thyroid cancers and widespread adoption of imaging modalities, including ultrasonography (US) and US-guided fine-needle aspiration (FNA) cytology [1–4].

Differentiated thyroid carcinoma (DTC) is the most common histopathological type of thyroid cancer. Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) are the most common pathology of DTC. According to the World Health Organization (WHO), a PTC with a size of less than or equal to 10 mm is defined as papillary microcarcinoma [5]. Several studies show that papillary microcarcinoma accounts for more than 40% of newly diagnosed thyroid cancer [6,7]. In general, thyroid microcarcinoma

has a good prognosis, low mortality rate and long disease-free survival [8,9]. A study from the Mayo Clinic among 900 patients with an average follow-up of 17.2 years found that the 40-year cause-specific mortality was 0.7% [10].

To date, there is an increasing number of patients diagnosed with thyroid cancer when the tumor size is less than 5 mm [11]. The recurrence-free survival rate of patients at a single center 35 years after primary surgery was higher for those with Thyroid microcarcinoma (TMC) ≤5 mm than those with tumors from 6 to 10 mm [11]. The rates of lymph node metastasis, extrathyroidal extension, and capsular invasion have been significantly different in patients with TMC ≤5 mm versus those with size >5 mm. However, differences in the prognosis of these groups after a similar extent of surgery remain undetermined [12–14].

Therefore, the current study's objective was to evaluate the differences in clinical and subclinical characteristics and lymph node metastasis among patients with TMC with a size ≤5 mm compared to patients with a size >5 mm. The treatment regimen of TMC less than 1 cm is still controversial in different countries. Surgery is considered the optimal treatment modality to evaluate whether the tumor is invaded or metastasized [6,9]. Findings from the study thus have great clinical implications for clinicians to choose between surgery or other treatment options, such as radiofrequency ablation as an optimal treatment modality.

Methods

Study Population

This retrospective study included 273 patients with thyroid microcarcinoma treated at Bach Mai Hospital and the National Hospital of Endocrinology from December 2020 to May 2021. Thyroid carcinoma measuring less than or equal to 10 mm was classified as microcarcinoma [5]. Each thyroid surgery case in our institutions was thoroughly taken care of and determined based on the guidelines issued by the American Thyroid Association (ATA). Total thyroidectomy was performed for patients with bilateral tumors, extrathyroidal invasion, and lymph node metastasis (LNM) upon intraoperative findings or a history of head or neck radiotherapy. Hemithyroidectomy was incorporated in the treatment plan for patients with a single intrathyroidal lesion (≤1 cm), no evidence of LNM on staging US, and no personal history of radiation therapy to the head and neck.

Thyroid cancer was considered multifocal when there was a presence of two or more tumor foci. Bilateral thyroid malignancy was defined as cancer diagnosed in both thyroid lobes. The extrathyroidal extension (ETE) was defined as an extension of the primary tumor outside of the thyroid capsule and invasion into the surrounding structures.

The following information was extracted from the medical charts, including age, sex, body mass index (BMI), diagnosis, histopathologic subtype, Thyroid Imaging Reporting and Data Systems (TIRADS) classification, focality, bilaterality, surgical treatment, lymph nodes, metastasis, tumor size, and extrathyroidal extension. Studied patients were further classified into two sub-groups: sub-group I was those with tumor size <5 mm and sub-group II was those with tumor size ≥5 mm. Two investigators abstracted information independently (Vu H. and Nguyen L). In case there was a discrepancy, a senior physician (Nguyen B) came in to resolve the discrepancy. All study participants were asked to provide written informed consent and this study was approved by the Institutional Review Board of Bach Mai Hospital [836/BVBM-HDDD].

Table 1. Distribution of clinicopathologic characteristics of study participants in the current study.

Characteristics	Distribution (n = 273), %
Age, mean (±SD)	44.23 ± 11.28
<55	214 (78.4)
≥55	59 (21.6)
Sex, n (%)	
Male	34 (12.5)
Female	239 (87.5)
Body mass index (kg/m^2), mean (±SD)	22.12 ± 2.69
FT4, mean (±SD)	15.93 ± 2.88
TSH, mean (±SD)	2.42 ± 10.08
TG, mean (±SD)	28.97 ± 40.79
Histopathologic subtype, n (%)	
Papillary	263 (96.3)
Follicular	10 (3.7)
TIRADS classification , n (%)	
TIRADS 4	143 (52.4)
TIRADS 5	130 (47.6)
Focality, n (%)	
Unifocal	237 (86.8)
Multifocal	36 (13.2)
Bilaterality, n (%)	
Yes	33 (12.1)
No	240 (87.9)
Surgical treatment, n (%)	
Total thyroidectomy	190 (69.6)
Lobectomy	83 (30.4)
Central Lymph nodes metastasis, n (%)	
Yes	67 (24.5)
No	206 (75.5)
Extrathyroidal extension, n (%)	
Yes	40 (14.7)
No	233 (85.3)
Tumor size, n (%), min, max	5.72 ± 2.33 (1–10)
<5 mm	70 (25.6%)
≥5 mm	203 (74.4%)

SD, standard deviation; FT4, free thyroxine; TSH, thyroid-stimulating hormon; TG, Thyroglobulin; TIRADS, Thyroid Imaging Reporting and Data Systems.

Table 2. Distribution and the association between selected clinicopathologic characteristics with tumor size in the current study.

Characteristics	Tumor size <5 mm	Tumor size ≥5 mm	OR	95% CI	*p*-value
Age, mean (SD)	44.70 ± 10.70	44.06 ± 11.50			
<55	52	162	1.37	0.72–2.58	0.333
≥55	18	41			
Sex, n (%)					
Male	8	26	0.88	0.38–2.04	0.763
Female	62	177			
Body mass index (kg/m^2), mean (SD)	22.00 ± 2.96	22.17 ± 2.60			
<23	53	136	0.65	0.35–1.21	0.173
≥23	17	67			
Hisopathologic subtype, n (%)					
Papillary	68	195	0.72	0.15–3.46	0.677
Follicular	2	8			
TIRADS classification, n (%)					
TIRADS 4	44	99	0.56	0.32–0.98	0.042
TIRADS 5	26	104			
Focality, n (%)					
Unifocal	63	174	1.50	0.63–3.60	0.361
Multifocal	7	29			
Bilaterality, n (%)					
Yes	6	27	1.63	0.65–4.15	0.295
No	64	176			
Surgical treatment, n (%)					
Lobectomy	30	53	0.47	0.27–0.83	0.009
Total thyroidectomy	40	150			
Central Lymph nodes metastasis, n (%)					
No	59	147	2.04	1.01–4.17	0.047
Yes	11	56			
Extrathyroidal extension, n (%)					
No	67	166	4.98	1.48–16.70	0.004
Yes	3	37			

SD, standard deviation; OR, odds ratio; CI, confidence interval.

Table 3. Multivariate analysis of risk factors of tumor size.

Factors	OR	95% CI	*p*-value
TIRADS classification	0.633	0.357–1.123	0.115
Surgical treatment	1.487	0.793–2.788	0.215
Central lymph nodes metastasis	1.402	0.638–3.077	0.394
Extrathyroidal extension	0.259	0.075–0.895	0.014

Statistical Analysis

Means and standard deviation (SD) were calculated for continuous variables, while counts and proportions were computed for categorical variables. Continuous variables were categorized into two sub-groups. Unconditional logistic regression models were used to evaluate the association between age (<55 vs. ≥55), sex (male vs. female), BMI (<23 vs. ≥23 kg/m^2), diagnosis (incidental vs non-incidental), histopathologic subtype (papillary vs. follicular), TIRAD classification (TIRAD 4 vs. TIRAD 5), focality (unifocal vs. multifocal), bilaterality (yes vs. no), surgical treatment (lobectomy vs. total thyroidectomy), lymph nodes (yes vs. no), and metastasis (yes vs. no) with tumor size and extrathyroidal extension, using both univariable and multivariable models. Independent variables in each logistic regression model were the binarized values, including tumor size (<5 mm or ≥5 mm) or extrathyroidal extension status (presence or absence). The univariable models independently tested for association of each categorical variable (exposure) with the response, where one category of this variable was assigned as the baseline exposure (with logistic regression coefficient set to 0 and OR = 1). The purposeful selection process begins with a univariate analysis of each variable. Any variable having a significant univariate test at some arbitrary level is selected as a candidate for the multivariate analysis. Statistical analysis was conducted using SPSS 20.0 software (IBM Corp., Chicago, IL, USA). All *p* values were two-sided, and *p* values less than or equal to 0.05 were considered to be statistically significant.

Table 4. Distribution and the association between selected clinicopathologic characteristics with extracapsular invasion status in the current study.

Characteristics	Presence of extrathyroidal extension (n =) %	Absence of extrathyroidal extension (n =), %	OR	95% CI	*p*-value
Age, mean (SD)	45.9 ± 11.74	43.94 ± 11.21			
≥55	8	51	1.12	0.49–2.58	0.789
<55	32	182			
Sex, n (%)					
Male	8	26	1.99	0.83–4.77	0.118
Female	32	207			
Body mass index (kg/m^2)					
≥23	20	64	0.38	0.19–0.75	0.004
<23	20	169			
Histopathologic subtype, n (%)					
Papillary	40	223	0.85	0.81–0.89	0.182
Follicular	0	10			
TIRADS classification, n (%)					
TIRADS 4	17	126	0.63	0.32–1.24	0.176
TIRADS 5	23	107			
Focality, n (%)					
Unifocal	30	207	2.65	1.17–6.05	0.017
Multifocal	10	26			
Bilaterality, n (%)					
No	31	209	2.53	1.08–5.94	0.029
Yes	9	24			
Central Lymph nodes metastasis, n (%)					
No	23	183	2.70	1.34–5.45	0.004
Yes	17	50			
Tumor size, n (%)					
<5 mm	3	67	4.98	1.48–16.70	0.004
≥5 mm	37	166			

SD, standard deviation.

Table 5. Multivariate analysis of risk factors of extrathyroidal extension.

Factors	OR	95% CI	*p*-value
Body mass index	0.426	0.207–0.877	0.022
Focality	0.320	0.024–4.219	0.414
Bilaterality	0.760	0.052–11.001	0.842
Central lymph nodes metastasis	2.507	1.194–5.264	0.017
Tumor size	4.141	1.206–14.217	0.008

Results

The mean age (±SD) was 44.23 ± 11.28 years old in the current cohort of patients. The majority of patients were under 55 years old (78.4%). Females accounted for 87.5% of the total studied population. The majority of patients were with papillary subtype (96.3%). Also, the majority of patients (86.8%) had unifocal tumors, while unilateral carcinoma accounted for 88% of the entire cohort. TIRADS 4 classification was found in 52.4% of patients, while TIRADS 5 was among 47.6% of patients. In addition, tumors limited to the thyroid without extrathyroidal extension invading strap muscles accounted for 85.3%, whereas approximately 69.6% (or 190 patients) with thyroid microcarcinoma underwent total thyroidectomy and thyroid lobectomy with isthmusectomy accounted for 30.4% (or 83 patients) (Table 1).

The mean tumor size was 5.72 ± 2.33 mm. There were 203 patients with tumor size ≥5 mm (74.4%), only 70 patients had tumor size <5 mm (25.6%) (Table 1). In the univariable model, TIRADS classification, surgical treatment, central lymph node metastasis and extrathyroidal extension were associated with tumor size ≥5 mm (Table 2). However, in multivariate analysis, only extrathyroidal extension was associated with tumor size ≥5 mm (Table 3).

Table 4 presented the association analysis results between selected clinicopathologic characteristics with odds of the presence of extrathyroidal extension invading strap muscles. In the univariable models, those with BMI <23 kg/m^2 were found to be protective against the odds of extrathyroidal extension (OR = 0.38, 95% CI: 0.19–0.75), and this pattern remained in the multivariate analysis ($p = 0.022$) (Table 5). Also, in univariable mode, both focality, bilaterality, central lymph node metastasis, and tumor size

Table 6. Distribution and the association between selected clinicopathologic characteristics with central lympho node metastasis status in the current study.

Characteristics	Presence of Metastasis (n =) %	Absence of Metastasis (n =), %	OR	95% CI	*p*-value
Age, mean (SD)	42.55 ± 10.69	44.77 ± 11.44			
≥55	11	48	1.55	0.75–3.19	0.234
<55	56	158			
Sex, n (%)					
Male	9	25	0.89	0.39–2.02	0.780
Female	58	181			
Body mass index (kg/m^2)					
≥23	21	63	0.97	0.53–1.75	0.907
<23	46	143			
Hisopathologic subtype, n (%)					
Papillary	65	198	0.73	0.27–6.34	0.734
Follicular	2	8			
TIRADS classification , n (%)					
TIRADS 5	41	89	0.48	0.28–0.85	0.010
TIRADS 4	26	117			
Focality, n (%)					
Unifocal	59	178	0.86	0.37–2.00	0.728
Multifocal	8	28			
Bilaterality, n (%)					
No	59	181	0.98	0.42–2.29	0.966
Yes	8	25			
Extrathyroidal extension, n (%)					
No	50	183	2.71	1.34–5.45	0.004
Yes	17	23			
Tumor size, n (%)					
<5 mm	11	59	2.04	1.01–4.17	0.047
≥5 mm	56	147			

SD, standard deviation.

were positively associated with the odds of the presence of extrathyroidal extension. The respective ORs and 95% CIs were 2.65 (1.17–6.05), 2.53 (1.08–5.94), 2.70 (1.34–5.45), and 4.98 (1.48–16.70). However, in the multivariable model, central lymph node metastasis, and tumor size were associated with the presence of extrathyroidal extension (Table 5).

Similarly, Table 6 shows the associations between selected characteristics and odds of metastasis status. In the univariable model, TIRADS 4 was inversely associated with odds of central lymph node metastasis, compared with TIRAD 5 (OR = 0.48, 95% CI: 0.28–0.85). Also, both extrathyroidal extension (OR = 2.71, 95% CI: 1.34–5.45) and tumor size (OR = 2.04, 95% CI: 1.01–4.17) were associated with odds of metastasis status in the univariable model. In the multivariable model, extrathyroidal extension was associated with the central lymph metastasis (Table 7).

Table 7. Multivariate analysis of risk factors of central lymph metastasis.

Factors	OR	95% CI	*p*-value
TIRADS classification	1.723	0.295–3.930	0.126
Extrathyroidal extension	2.345	1.143–4.813	0.022
Tumor size	1.661	0.797–3.462	0.164

Discussion

In this hospital-based retrospective study of 273 patients with thyroid microcarcinoma at a single hospital in Hanoi, Vietnam, we found that extrathyroidal extension was associated with the odds of tumor size ≥5 mm and the central lymph node metastasis was also positively correlated to extrathyroidal extension in multivariate analysis.

Prior studies have shown that large tumor size is associated with a worse prognosis; microcarcinomas with tumor size >5 mm have a higher rate of lymph node metastasis, extrathyroidal extension, and multifocality compared with tumor <5 mm in size [15,16]. In our study, most of tumor size was from 5 mm to 10 mm (74.4%). We did not find a difference in age, gender, BMI, multifocal cancer, and bilateral cancer between the two groups with tumor sizes ≥5 mm and <5 mm. Our findings were consistent with the study on 396 patients with papillary microcarcinoma conducted by Lee *et al*. [17]. The authors indicated that age, gender, and multifocal cancer were not associated with tu-

mor size [17]. Similarly, a study by Kim *et al*. [18] found that there was no difference between age, sex, and bilaterality between those with tumor size ≥5 mm and <5 mm. In addition, in multivariate analysis we found that extrathyroidal extension remained to be associated with the odds of tumor size, which is consistent with prior studies [17,18].

In our study, extrathyroidal extension was observed in 40 patients (14.7%). In univariable mode, both focality, bilaterality, central lymph node metastasis, and tumor size were positively associated with the odds of the presence of extrathyroidal extension. However, in the multivariable model, only central lymph node metastasis, and tumor size were associated with the presence of extrathyroidal extension. Extrathyroidal extension invading strap muscles was also an independent predictor of central cervical lymph node metastasis in the univariable model (OR = 2.71, 95% CI: 1.34–5.45) and the multivariable model (OR = 2.35, 95% CI: 1.14–4.81). Patients with extrathyroidal extension had significantly higher central cervical lymph node metastasis proportion than those with tumors limited to the thyroid (42.5% vs. 21.5%).

Extrathyroidal extension is a valuable prognostic factor which can be used for recurrence risk stratification and directly affects surgical planning. Prior studies showed that the proportion of extrathyroidal extension ranged from 2% to 53% [10,19]. According to a study conducted by Korean investigators, this incidence was considerable, up to 53% [19]. One possible explanation for the difference between our findings and prior studies is that in these studies, microscopic extrathyroidal extension was taken into consideration [19]. Our finding was higher than the percentage found in the study by Arora *et al*. [20], which reported this rate was only 4.5% [20]. Noted that in this study, only cases with clearly gross extrathyroidal extension were considered as extrathyroidal extension invading surrounding structures [20]. Currently, the definition used in the study conducted by Kim *et al*. [21] has been widely accepted as the definition of extrathyroidal extension invading surrounding structures.

Cervical lymph node metastasis is a common feature of papillary thyroid carcinoma. Although papillary thyroid carcinoma has a good prognosis with a 10-year survival rate of 99%, cervical lymph node metastasis is associated with an increase in the incidence of recurrence [22,23]. Our central cervical lymph node metastasis rate was 24.5%. Different studies have shown that tumor size is related to cervical lymph node metastasis, especially central cervical lymph node [24,25]. In our study, the univariable model showed that tumor size was associated with increased odds of metastasis status; however, this association became insignificant in the multivariable model, which is not in line with prior studies [24,25]. Regarding the cut-off of tumor size, some authors found that tumor size (>6.7 mm) was related to central cervical lymph node metastasis [26,27].

Tumor size is a prognostic factor in papillary thyroid carcinoma according to different classification systems such as the American Join Committee on Cancer (AJCC), and the metastases, age at diagnosis, completeness of resection, invasion and size of the tumor (MACIS) scoring system [28,29]. However, it remains controversial in papillary microcarcinoma, even though tumor size is associated with cervical lymph node metastasis [30]. For instance, in a Japanese study on 2070 patients with papillary microcarcinoma with 40 years of follow-up, the recurrence rate at 35 years in the group of tumor size >5 mm was higher than that of the group of tumor size <5 mm (14% vs 3.3%, $p < 0.001$) [11]. In contrast, some authors reported that there was no difference in the mortality and recurrence rates between these two groups [22,25,31]. These results suggested that tumor size may play a less important prognostic role in papillary microcarcinoma in comparison with conventional papillary carcinoma. It should be noted that the previous evidence was all retrospective design. Further studies are, therefore warranted to reinforce the notion that tumor size can be a prognostic factor for recurrence and mortality in patients with papillary microcarcinoma.

This study is not without limitations. First, since this is a retrospective study design, several characteristics, such as clinical features or laboratory results, could not be retrieved. Second, the prognostic significance of tumor size in relation to tumor recurrence could also not be fully investigated. Such investigation requires a prospective cohort design with sufficient sample size and follow-up time.

Conclusions

Our findings suggest that papillary thyroid microcarcinoma measuring more than 5 mm often extends beyond the thyroid capsule than tumors less than 5 mm in size. Besides, central lymph node metastasis is associated with extrathyroidal extension. Further studies in a longitudinal fashion should therefore be conducted to confirm the prognostic role of tumor size in papillary microcarcinoma. Because the treatment of TMC less than 1 cm is currently in debate and surgery, in some countries, is considered an optimal option to evaluate the invasion of the tumor, findings from this study might shed light on choosing surgery over other treatment modalities in monitoring TMC patient less than 1 cm.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

HTV, LMTN, BQN, PP, HNL and QHN contributed to the study conception and design. Material preparation, data

collection and analysis were performed by HTV, LMTN, BQN and QHN. The first draft of the manuscript was written by LMTN and BQN. HNL, PP and BQN revised the article, and all authors commented on previous versions of the manuscript. All authors have read and agreed to the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study and the analysis plan were approved by the Research Ethics Committees of Bach Mai Hospital, Hanoi, Vietnam [836/BVBM-HDDD]. All study participants were asked to provide written informed consent. The study adhered to the Declaration of Helsinki.

Acknowledgment

Not applicable.

Funding

Hung N. Luu is partially funded by the University of Pittsburgh Medical Center (UPMC) Start-up grant.

Conflict of Interest

The authors declare no conflict of interest.

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