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ORIGINAL ARTICLE

Clinicopathologic characteristics of incidental thyroid carcinoma in euthyroid patients receiving total thyroidectomy for multinodular goiter: A retrospective cohort study

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Abstract

Background: Total thyroidectomy is the treatment of choice for multinodular goiter (MNG). In some of these cases, incidental thyroid cancer (ITC) is detected postoperatively. Papillary thyroid microcarcinoma (PTMC), the most common type of ITC, has clinical factors and pathologic similarities with ITC that have not been well clarified previously. We investigated the incidence and characteristics of ITC and PTMC in euthyroid patients undergoing total thyroidectomy for MNG.

Methods: We retrospectively investigated the data of 151 euthyroid patients who underwent total thyroidectomy for MNG between January 2016 and December 2020. Patients with PTMC were then selected from among those with ITC for further data analysis.

Results: The incidence rates of ITC and PTMC were 31.1% (47/151) and 21.1% (32/151), respectively. The mean age of patients with ITC was 52.8 ± 11.7 years, which was younger than that of patients with benign MNG (57.2 ± 12.5 years, $p < 0.05$). Bilateral cancer was observed in 17 patients with ITC (17/47, 36.2%) and nine with PTMC (9/32, 28.1%). The numbers of patients in the ITC and PTMC groups whose cancer was not on the side comprising the dominant tumor were 15 (15/47, 31.9%) and 13 (13/32, 40.6%), respectively. The multivariate analysis demonstrated that younger age was a clinical factor associated with ITC and PTMC.

Conclusion: Younger age is a clinical factor for ITC and PTMC. We recommend taking considering clinical factors and pathologic characteristics of ITC and PTC when considering total thyroidectomy in euthyroid patients with MNG.

Keywords: Goiter; Incidental thyroid cancer; Papillary thyroid cancer; Papillary thyroid microcarcinoma, Thyroidectomy

1. INTRODUCTION

Multinodular goiter (MNG) is one of the major benign thyroid diseases that may be treated with total thyroidectomy. However, many euthyroid patients with either one or multiple but small nodules contralateral to the lobe with the dominant nodule are reluctant to undergo total thyroidectomy. Postoperative hypothyroidism requiring lifelong thyroxine replacement therapy has been cited as a concern. Furthermore, incidental thyroid cancer (ITC) is sometimes detected in the final pathological examination, which warrants the requirement of completion thyroidectomy if the patients initially underwent only unilateral thyroidectomy.

The most common ITCs are papillary carcinomas, a majority of which occur as papillary thyroid microcarcinoma (PTMC).[1,2] However, the incidence of ITC after surgery varies widely in literature, ranging from 2% to 30%.[1,3–8] Certain risk factors, such as sex, age, history of neck irradiation, family history, calcifications observed during imaging studies, size of the thyroid tumor, and thyroid-stimulating hormone (TSH) levels, may be related to ITC; however, this remains controversial.[1,8–14] Although previous studies have focused on clinical factors related to cancer, the knowledge on pathologic characteristics of ITC is limited. Thus, we investigated ITC while focusing on those of PTMC to clarify the possible clinical risk factors and pathologic characteristics in euthyroid patients who underwent total thyroidectomy for MNG.

2. METHODS

2.1. Study design and patient selection criteria

We retrospectively investigated the data of patients who underwent total thyroidectomy for MNG between January 2016 and December 2020. The exclusion criteria of this study were as follows: (1) patients with MNG only on one side; (2) patients with nodules that were suspected of malignancy or had malignant features on preoperative fine needle aspiration cytology (FNAC) based on the Bethesda System for Reporting Thyroid Cytopathology[15]; (3) patients whose thyroid function tests

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showed hyperthyroidism or hypothyroidism and were under treatment or had received treatment at some time before surgery; (4) patients in whom distant metastases occurred due to thyroid cancer preoperatively but FNAC was negative for malignancy; and (5) and patients with a history of thyroidectomy.

Of the 191 patients underwent total thyroidectomy for MNG, 40 were excluded (19 with hyperthyroidism, four with hypothyroidism undergoing treatment, 15 with a history of thyroidectomies, and two with a preoperative diagnosis of distant metastatic thyroid cancer). Finally, 151 patients were included in this study. Subsequently, we selected patients with PTMC from among those with ITC for further data analysis.

2.2. Clinical and pathologic characteristics

We studied the clinical and pathological characteristics as well as surgical outcomes of the selected patients. In addition, the possible clinical risk factors for malignancy, such as sex, age, body mass index, duration from diagnosis to operation, family history of thyroid diseases, size of the dominant tumor, medical and surgical histories, history of other cancers, and incidence of gynecologic and breast diseases, were evaluated. Furthermore, clinical symptoms, including palpable tumor, discomfort during breathing, difficulty in swallowing, and voice changes, were analyzed. The size of the dominant tumor and number of bilateral thyroid tumors obtained from ultrasound examinations were also recorded.

Additionally, pathological findings, including FNAC results, tumor characteristics (unilateral or bilateral and unifocal or multifocal), extent of invasion (capsular invasion, angioinvasion, lymphatic invasion, perineural invasion, or extrathyroid extension), association with benign thyroid diseases, and weight and volume of the excised thyroid glands, were evaluated. Finally, the maximum size of the PTMC was recorded in cases of multifocal tumors.

2.3. Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA). Continuous data were reported as mean values and analyzed using the Student *t* test. Univariate analysis of categorical variables was performed using Pearson's χ^2 test (or Fisher exact test for 2×2 tables). Potential clinical factors were included in a multivariable logistic regression model to identify the possible risk factors associated with ITC or PTMC. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed to measure the strength. Statistical significance was set at $p < 0.05$.

This study was conducted in accordance with the Declaration of Helsinki and local laws, and the study protocol was approved by the local ethics committee.

3. RESULTS

3.1. Clinical characteristics of patients

In total, 151 patients (126 females, 25 males; 5:1 female-to-male ratio) were included in this study. There were 104 patients with benign MNG and 47 with ITC (Table 1). The mean age of patients with benign MNG who had undergone total thyroidectomy was 57.2 ± 12.5 years, which was older than that of patients with ITC (52.8 ± 11.7 years; $p < 0.05$). However, the difference in age between patients with benign MNG and those with PTMC was not statistically significant (52.6 ± 12.5; $p = 0.068$). Among the 47 patients with ITC, 32 had only PTMC (32/47, 68.1%). The incidence of ITC was 31.1% (47/151) and that of PTMC was 21.1% (32/151). The percentage of patients who had a history of surgery and gynecologic and breast diseases was higher in the ITC group than in the benign MNG group, whereas that of patients with benign MNG was higher among in the group presenting with palpable neck tumors than both ITC and PTMC groups ($p < 0.05$).

Based on the preoperative FNAC tests with Bethesda category II, the incidence values of ITC and that of PTMC were 26.4% and 18.1%, respectively. In those with Bethesda category III nodules (ie, atypia of undetermined significance [AUS] or follicular lesion of undetermined significance [FLUS]), the incidence of ITC and PTMC were 41.2% and 27.5%, respectively (Table 1). The number of thyroid tumors detected by ultrasound and that of preoperative FNAC procedures among the benign MNG, ITC, and PTMC groups were similar. The dominant tumors were bigger in the benign MNG group than in the ITC group ($p = 0.04$), but there was no statistically significant difference between the benign MNG and PTMC groups (Table 1). The volume and weight of excised thyroid glands in the benign MNG group were larger than that of those in the ITC group ($p < 0.05$), although only the volume of excised thyroid glands showed a statistically significant difference in comparison with that of the PTMC group. Furthermore, postoperative complications were rare in both groups of patients (Table 1).

3.2. Pathologic characteristics of ITC

Although the primary histological type of ITC was papillary microcarcinoma, one patient had minimally invasive follicular carcinoma, and one had metastatic PTMC involving the central lymph nodes. The mean size of the PTMC was 0.48 cm and 25 of 47 PTMCs were less than 0.5 cm (25/47, 53.2%) in size. Bilateral cancer was detected in 17 of the 47 patients with ITC (17/47, 36.2%) and in 9 nine the 32 patients with PTMC (9/32, 28.1%). The numbers of patients in the ITC and PTMC groups who had multifocal carcinomas were 20 (20/47, 42.6%) and 11 (11/32, 34.4%), respectively. The numbers of patients in the ITC and PTMC groups whose unilateral cancer was not on the side comprising the dominant tumor were 15 (15/47, 31.9%) and 13 (13/32, 40.6%), respectively. The pathological findings are summarized in Table 2.

3.3. Analyses for clinical factors related to ITC

All the parameters that demonstrated $p < 0.100$ in the univariate analysis were included in the logistic regression analysis to identify possible risk factors associated with ITC or PTMC. Although gynecologic and breast diseases, thyroid volume and weight, number of thyroid tumors, and size of the dominant tumor determined by ultrasound were identified as significant risk factors for ITC or PTMC in the univariate analysis (Table 1), these factors did not exhibit statistical significance in the multivariate regression analysis (Table 3).

The logistic regression model was statistically significant for patients with ITC ($\chi^2 = 33.83$; $p < 0.000$). Increasing age was associated with a reduction in the likelihood of exhibiting thyroid cancer, with the odds decreasing by a factor of 1.05 (95% CI for OR is 1.09–1.12). The logistic regression model was statistically significant for patients with PTMC ($\chi^2 = 16.44$, $p = 0.036$). Similar to the patients with ITC, increasing age was associated with a reduction in the likelihood of exhibiting PTMC; the odds of having thyroid cancer decreased by a factor of 1.05 (95% CI for OR is 1.09–1.01). However, patients who could not feel the tumor(s) by touch had 4.08 times higher odds of exhibiting PTMC than those who could (Table 3).

3.4. Patient outcome

The study and follow-up period ended in December 2021. In the benign MNG group, one patient died of pancreatic cancer in the same year that the operation was conducted, while the others lived without local recurrence. In the ITC group, one patient

Table 1

Clinical characteristics of all patients

	All (n = 151)	MNG (n = 104)	ITC (n = 47)	PTMC (n = 32)	p^a MNG × ITC	p^a MNG × PTMC
Gender					0.816	1.000
Female	126	86	40	27		
Male	25	18	7	5		
Age (y)[b]	55.85 ± 12.41 (58 [18–81)	57.22 ± 12.53 (58.5 [18–81])	52.81 ± 11.70 (57 [25–76])	52.56 ± 12.45 (55 [25–76])	0.043[c]	0.068[c]
BMI[b]	25.30 ± 3.94 (24.6 [16.9–41.6])	25.30 ± 4.10 (24.3 [16.9–41.6])	25.29 ± 3.61 (25.6 [18.8–35.1])	25.37 ± 3.69 (25.7 [18.8–35.1])	0.980[c]	0.938[c]
Duration of diagnosis to operation (mo)[b]	50.28 ± 73.95 (23.5 [1–360)	56.14 ± 78.23 (24 [1–360])	37.40 ± 62.41 (12 [1–360])	37.30 ± 44.65 (12 [2–156])	0.159[c]	0.211[c]
Family history of thyroid diseases	19	15	4	3	0.432	0.764
Gynecologic and breast diseases	28	14	14	9	0.023	0.063
Medical history	80	54	26	18	0.728	0.691
Surgical history	89	55	34	22	0.032	0.153
History of another cancer	10	5	5	4	0.287	0.214
Clinical symptoms						
Palpable tumor	127	95	32	20	0.001	0.001
Breath discomfort	34	24	10	7	1.000	1.000
Difficulty in swallowing	29	23	6	3	0.264	0.129
Voice change	6	4	2	2	n.a.	n.a.
FNAC number[b]	2.04 ± 2.00 (1 [1–10])	2.20 ± 1.99 (1 [1–10])	1.89 ± 1.65 (1 [1–10])	2.16 ± 1.89 (2 [1–10])	0.321[c]	0.909[c]
FNAC (unilateral/bilateral)					0.117	0.635
Unilateral	79	39	30	19		
Bilateral	64	48	16	13		
Preoperative FNAC Bethesda category					n.a.[d]	n.a.[d]
Nondiagnostic or unsatisfactory	24	19	5	3		
Benign	72	53	19	13		
Atypia of undetermined significance or follicular lesion of undetermined significance	51	30	21	14		
Follicular neoplasm or suspicious for a follicular neoplasm	4	2	2	2		
Computed tomography scan	38	26	12	9	1.000	0.818
Operation modality					0.176	0.289
Minimally invasive video-assisted thyroidectomy	28	16	12	8		
Conventional	122	87	35	24		
Number of thyroid tumors[b]	4.07 ± 1.92 (4 [1–13])	4.27 ± 2.03 (4 [2–13])	3.64 ± 1.61 (3 [1–9])	3.81 ± 1.55 (3 [2–9])	0.064[c]	0.247[c]
Size of dominant tumor (cm)[b]	3.45 ± 1.64 (3.2 [0.7–8.22])	3.63 ± 1.65 (3.4 [0.9–8.22])	3.04 ± 1.54 (3 [0.7–7.9])	3.07 ± 1.74 (2.925 [0.7–7.9])	0.040[c]	0.097[c]
Thyroid volume (cc)[b]	76.37 ± 55.43 (59.1 [7.5–282.8])	85.85 ± 58.54 (67.45 [16.4–282.8])	55.40 ± 41.13 (50.3 [7.5–211])	58.89 ± 44.49 (49.5 [11.6–211])	0.000[c]	0.007[c]
Thyroid weight (g)[b]	78.09 ± 61.79 (56.65 [5–335.5])	88.01 ± 65.05 (67.5 [20–335.5])	54.41 ± 45.86 (43.95 [5–208.8])	60.00 ± 50.48 (45 [5–208.8])	0.002[c]	0.054[c]
Complications	55	35	20	13	0.573	0.673
Transient recurrent laryngeal nerve palsy	6	4	2	1		
Permanent recurrent laryngeal nerve palsy	1	0	1	0		
Transient hypocalcemia	45	30	15	11		
Permanent hypocalcemia	3	1	2	2		

n.a.: with two expected cells (50%) count less than five.

BMI = body mass index; FNAC = fine needle aspiration cytology; ITC = incidental thyroid cancer; MNG = multinodular goiter; PTMC = papillary thyroid microcarcinoma.

[a]Fisher exact test for 2 × 2 tables, except.

[b]Mean (standard deviation), with median and range (in square brackets) in parentheses.

[c]*t* test for continuous variables.

[d]With four expected cell (50%) count less than five.

Table 2

Pathologic characteristics of ITC and PTMC

	ITC (n = 47)	PTMC (n = 32)
Mean size of cancer (mm)	11.4 ± 11.78 (6.0 [1–48])	4.8 ± 2.86 (4.0 [1–10])
Multifocal	20	11
Bilateral	17	9
Cancer not in the same side of dominant tumor	15	13
Capsular invasion	6	3
Angioinvasion	3	1
Lymphatic invasion	3	0
Perineural invasion	3	1
Extrathyroidal extension	7	2
Associated benign diseases		
Nodular goiter	28	23
Lymphocytic thyroiditis	12	7
Adenomatous goiter	10	6
Follicular adenoma	3	3
Hürthle adenoma	2	2
Hürthle cell change	2	2
Lymphoepithelial nodule	1	1
Nodular hyperplasia	1	0

ITC = incidental thyroid cancer; PTMC = papillary thyroid microcarcinoma.

with PTMC died of pancreatic cancer 1 year after the operation, and another with bilateral cancer exhibited unilateral metastases to the neck lymph nodes 6 months after surgery. A patient with bilateral cancer developed unilateral metastases to the level VI lymph node 5 months after surgery and subsequently exhibited unilateral metastases to the lateral neck lymph node 12 months after surgery. Another patient with left thyroid cancer had ipsilateral level VI lymph node metastases 3 years after surgery.

4. DISCUSSION

The incidence values of ITC and incidental PTMC in our study were 31.1% and 21.1%, respectively. In previous studies, the incidence of ITC among patients with MNG varied due to different inclusion criteria, such as surgical extent, lobectomy or total thyroidectomy, preoperative FNAC categories, thyroid functional status, and history of thyroidectomies.[1, 3–8] Miccoli et al[1] reported that ITC occurs more frequently in euthyroid patients than in thyrotoxic patients. In our study, we included only euthyroid patients with MNG who had undergone total thyroidectomy to simplify the study variables because the cancer incidence among patients with MNG varies depending on the functional status.[8,14]

Cancer distribution varies depending on the preoperative FNAC grading based on the Bethesda System for Reporting Thyroid Cytopathology.[15] We enrolled patients with preoperative FNAC category indicating advanced atypia of AUS or FLUS other than those whose results indicated benign, nondiagnostic, and unsatisfactory categories. We believe that this study reflects scenarios closer to clinical practice, wherein patients usually hesitate to undergo surgery when FNAC reports show no malignancy. We found that the incidence of ITC was higher in patients with FNAC category showing atypia of AUS or FLUS than in those with benign thyroid disease. The incidence values of ITC and PTMC were 26.4% and 18.1%, respectively, in patients whose preoperative FNAC results demonstrated benign nodules, and 41.2% and 27.5%, respectively, in those who demonstrated FNAC category depicting atypia of AUS or FLUS. Campbell et al[12] reported that euthyroid patients with MNG and benign nodules based on FNAC results showed a thyroid cancer incidence of 23.1% and a PTMC incidence of 15.7%. Another large database study by Paparodis et al[14] demonstrated a PTMC incidence of 13.3% in euthyroid patients with MNG and benign nodules based on FNAC results. These findings were similar with our study. Although Mulita et al[16] reported that 18.42% of patients with MNG and AUS/FLUS according to preoperative FNAC results had ITC, cancer distribution based on surgical extent and cancer size were not specified in this study. If surgery is avoided for patients showing nodules belonging to the benign FNAC category preoperatively, 12.6% of ITC cases (19/151) and 8.6% of incidental PTMC cases (13/151) would go undetected (Table 1).

In our study, 17 patients with ITC (17/47, 36.2%) and nine with PTMC (9/32, 28.1%) had bilateral cancer. The rates of multifocality were 42.6% and 34.4% in the ITC and PTMC groups, respectively. Lin et al[17] reported that patients with MNG who developed papillary carcinoma were at an increased risk of multifocality than those with a single nodule. Their study depicted a 23.4% multifocal rate and 19.4% bilateral rate, and total thyroidectomy for MNG was suggested to avoid reoperation and the associated complications.[17] In three previous studies, the multifocality rates of ITC ranged between 61.3% and 76.1%,[11,18,19] which were much higher than those we observed. However, the multifocality rate of ITC in patients with MNG (13.8%) was lower than ours in one study.[1] Considering a high incidence of ITC, total thyroidectomy for MNG could prevent a second operation or completion thyroidectomy and its associated complications.[5,7,20] Considering published data in relation to our study findings regarding the rates of bilateral and multifocal ITC and PTMC, our results are worthy of preoperative consideration in cases of total thyroidectomy.

Table 3

Multivariable logistic regression analysis of potential risk factors of ITC and PTMC

	ITC				PTMC			
		95% CI for odds ratio				95% CI for odds ratio		
	Odds ratio	Lower	Upper	*p*	Odds ratio	Lower	Upper	*p*
Age	0.953	0.917	0.989	0.012[a]	0.955	0.918	0.994	0.024[a]
Gynecologic and breast diseases	0.437	0.137	1.398	0.163	0.668	0.192	2.317	0.525
Palpable tumor	3.653	0.986	13.532	0.052	4.087	1.169	14.29	0.027[a]
Number of thyroid tumors	0.811	0.605	1.088	0.163	0.983	0.729	1.327	0.913
Size of dominant tumor	0.746	0.528	1.054	0.096	0.841	0.589	1.201	0.340
Thyroid volume	0.999	0.976	1.022	0.933	0.995	0.971	1.019	0.675
Thyroid weight	0.993	0.972	1.014	0.494	1.001	0.98	1.021	0.962
Constant	171.292			0.001	10.701			0.130

[a]The significance level is set at $p < 0.05$.

CI = confidence interval; ITC = incidental thyroid cancer; PTMC = papillary thyroid microcarcinoma.

The mean size of PTMC in our study was 0.48 cm, which was similar to that found in a previous study[2,18]; such small tumors are usually ignored during ultrasound examination of MNG. FNAC may also yield false-negative results for nodules less than 1 cm.[21] Furthermore, when FNAC results are not reviewed by an experienced cytopathologist, there is an increased risk for undetected thyroid cancer.[12] Small tumors not suspected for malignancy are not analyzed using FNAC. In cases of MNG, multifocal microcarcinomas with no malignant ultrasonographic signs may occur.[17] Nevertheless, it is impractical to perform FNAC for every thyroid tumor when no signs of malignancy are detected during imaging. In cases where only one nodule is found in patients who have received a clinical diagnosis of MNG, it would be worth performing FNAC because of the higher risk of malignancy.[22] Our study showed similar numbers of preoperative FNAC procedures in both the benign MNG and ITC groups. According to previously published reports and our study findings, increasing the number of FNAC procedures or performing bilateral FNAC in cases of MNG would not increase the rate at which preoperative PTMCs are diagnosed.

Our study showed that there were 15 patients with ITC (15/47, 31.9%) and 13 with PTMC (13/32, 40.6%) who had no cancer ipsilateral to the dominant tumor. Patients with MNG often hesitate when making decisions regarding surgical extent owing to postoperative hypothyroidism and long-term thyroxine replacement therapy, especially in cases of only one or multiple small nodules on the nondominant side. When only the lobe with the dominant tumor is operated on to preserve thyroid function, there is a chance of missing 9.9% (15/151) of ITC cases. These patients may have to undergo a second thyroidectomy.

It is challenging to diagnose PTMC preoperatively. The correlation of clinical factors, such as sex, age, neck irradiation, family history, calcifications on imaging, TSH level, and thyroid gland size, with ITC or PTMC has been investigated but remain controversial.[1,8–14,23] The results of the univariate analysis in our study showed that patients with ITC tend to be younger than those with benign MNG. In multivariate analysis, younger age appeared to be an independent risk factor for ITC and PTMC, which concur with those of a study by Apostolou et al.[8] Since both small and large series study revealed the same trend that younger age is a potential risk factor for thyroid cancer. Hence, the mechanism of genetic alterations related to thyroid cancer is worthy for further study.

We noted no difference in incidence based on sex between the benign MNG and ITC or PTMC groups. While some previous studies have also reported that sex is not related to the incidence of ITC in patients undergoing surgery for benign thyroid disease or MNG,[1,9] two other studies have shown that male sex is a predictive factor for thyroid cancer in cases of MNG.[8,10] Campbell et al[12] also reported that men may be at an increased risk for undetected thyroid cancer. These varied findings may be because of different numbers of patients and selection criteria in these studies.

The size of dominant tumor and volume and weight of the excised thyroid were higher in the benign MNG group than in the ITC group; however, only the volume of the resected thyroid showed a statistically significant difference when compared with that of the PTMC group. Our results are identical to those of a previous study, which showed that the size of smaller thyroid nodules is closely associated with higher thyroid cancer rates.[8] Large nodule size has long been considered a risk factor for thyroid tumor malignancy; however, this has not been conclusively established.[24,25] For example, both our study and the one by McHenry et al[26] did not reveal this correlation. Thus, the occurrence of thyroid cancer and progressive enlargement of MNG may have another unknown mechanism for tumor development.

Our study revealed differences in gynecologic and breast diseases between the benign MNG and ITC groups but no statistically significant difference between the benign MNG and PTMC groups. In the logistic regression analysis for the evaluation of possible clinical risk factors, there was no statistically significant difference. This may be because of the limited number of patients. Estrogen and its receptors may contribute to the pathogenesis and progression of thyroid cancer in women that may explain the difference related to sex.[27]

Despite the detailed analysis of risk factors, our study has some limitations because the results were based on the experiences of a single center with a limited number of patients. Studies from multicenter or national data banks would provide stronger and more complete evidence.

In conclusion, multivariate analysis showed that younger age was a risk factor associated with ITC and PTMC. When discussing the need for total thyroidectomy in euthyroid patients with MNG, surgeons should consider clinical factors and pathologic characteristics of ITC and PTMC, such as cancer incidence, multifocality, chance of bilateral cancer, and inconsistency in the rate of dominant tumor.

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