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Original Article

The risk of thyroid carcinoma in multinodular goiter compared to solitary thyroid nodules: A retrospective analysis of 600 patients

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ABSTRACT

Background: It is generally believed that multinodular goiter (MNG) is associated with a lower risk of malignancy compared to solitary thyroid nodules (STN). This will be the null hypothesis in this retrospective study and we aim to prove or reject it.

Methods: Medical files and histopathology reports of 600 patients who underwent thyroidectomy over 4-year period were reviewed. Data including patient's age, gender, presentation, ultrasonography, FNAC, surgical procedures, final histopathologic diagnosis and stage of malignant tumors were collected and analyzed. The primary end point was assessment of risk of thyroid carcinoma in patients with MNG compared to those with STN. Secondary endpoints included demographic differences and prognosis.

Results: There were 459 females (76.5%). Mean age was 44.3 ± 14.5 years (range 14–85). After exclusion of 33 patients, 224 (39.5%) had STN and 343 (60.5%) had MNG. The prevalence of thyroid cancer was 41.1% (92/224) in STN compared to 29.2% (100/343) in MNG (Chi-Square = 8.593, $p < 0.01$). However, on multiple logistic regression analysis this correlation was found insignificant ($p = 0.640$). Only male gender ($p = <0.000005$) and preoperative impression of malignancy ($p = 0.000082$) were significantly associated with thyroid carcinoma.

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Conclusion: The risk of thyroid carcinoma in STN and MNG was similar. Male gender was identified as a risk factor for thyroid cancer while age, number and size of nodules were not.

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Introduction

Thyroid nodules are common with prevalence of 2–6% for clinically palpable nodules and 19–68% for ultrasonography (US) detected nodules.¹ Most of these are benign with estimated risk of malignancy of 7–15% depending age, sex, radiation exposure, family history and other factors.^{2,3} The incidence of thyroid cancer is increasing worldwide partly due to increased detection by US and other imaging studies but also to true increase in incidence of papillary thyroid carcinoma (PTC).⁴

Up to 40% of patients with clinically solitary thyroid nodule (STN) are found to have multiple nodules on US.⁵ It is generally believed that multinodular goiter (MNG) is associated with lower risk of malignancy compared to STN.^{5–8} This will be the null hypothesis of this retrospective study which was designed to prove or reject it.

Material and methods

The study was conducted at a quaternary referral center serving around 4 million populations. Pathology department database was searched for thyroid biopsies over a period of 4 years (January 2013–December 2016). Medical files and histopathology reports of 600 patients who underwent thyroidectomy were reviewed. Data including patients' age, gender, presentation, preoperative US, fine-needle aspiration cytology (FNAC), indications and types of surgical procedures, final histopathologic diagnoses and stage of malignant tumors were collected and analyzed. The primary end point was assessment of the risk of thyroid carcinoma in patients with MNG compared to those with STN. Secondary endpoints include demographic and prognostic differences between the two groups.

Patients were classified into two groups based on the presence of a single (STN) or multiple nodules (MNG) in their thyroid gland by clinical examination and preoperative ultrasonography.

Preoperative diagnoses were classified as benign, suspicious or malignant based on clinical findings (i.e. cervical lymphadenopathy, hoarseness of voice, presence of metastasis), ultrasonographic features⁹ and FNAC (The Bethesda system for reporting thyroid cytopathology).¹⁰

Histopathological examination revealed more than one finding in 26.3% of specimens.

For statistical analysis, thyroid cancer apart from incidental papillary microcarcinomas (IPMCs) was considered the primary diagnosis when present. Otherwise, the histopathologic diagnosis that relates most to patients' complaint was considered the primary diagnosis.

Each patient with thyroid cancer was assigned a TNM-stage using The American Joint Committee on Cancer (AJCC) staging system, 7th edition.¹¹ When more than one tumor was present (i.e. multifocal or collision tumors), patient was assigned the higher stage.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 21 software. Descriptive statistics are displayed as means, frequencies and percentages. Chi-square test and regression analysis were used when appropriate to identify independent risk factors of malignancy in patients with thyroid nodules. A *p* value less than 0.05 is considered statistically significant. Approval by our institution ethical committee was obtained for study conduction and publication.

Table 1 – Distribution of patients by the final histopathological diagnosis.

Diagnosis	Number	%
Nodular hyperplasia	241	40.17
Simple MNG	150	25.00
Toxic MNG	7	1.17
Colloid nodule	30	5.00
Hyperplastic nodule	45	7.50
Adenomatous goiter	7	1.17
Cyst	1	0.17
Pendred disease ^a	1	0.17
Chronic thyroiditis	30	5.00
Hashimoto thyroiditis	18	3.00
Nodular Hashimoto	11	1.83
Fibrosing Hashimoto	1	0.17
Graves' disease	28	4.67
Benign neoplastic	103	17.17
Follicular adenoma	86	14.34
Hurthle-cell adenoma	16	2.67
Toxic follicular adenoma	1	0.17
Malignant	197	32.83
Papillary thyroid carcinoma (PTC)	111	18.50
Papillary microcarcinoma (PTMC)	23	3.83
Occult PTC ^b	2	0.33
Follicular thyroid carcinoma (FTC)	31	5.17
Hurthle cell carcinoma (HCC)	12	2.00
Medullary thyroid carcinoma (MTC)	7	1.17
Anaplastic carcinoma	5	0.83
Lymphoma	3	0.50
Collision tumors ^c	3	0.50
Thyroid dysmorphogenesis	1	0.17

^a Pendred disease is a genetic disorder leading to congenital bilateral sensorineural hearing loss and goiter with euthyroid or mild hypothyroidism.

^b Metastatic PTC in cervical lymph nodes in the absence of detectable thyroid tumor.

^c The coexistence of two adjacent but histologically distinct tumor components.

Results

Over a period of 4 years, 600 patients who underwent thyroid surgery were included in this study. There were 459 females (76.5%) and 141 males (23.5%) with a mean age of 44.3 ± 14.5 years (range 14–85). Final histopathological diagnoses in these patients are detailed in Table 1. Patients with diffuse hyperplasia or Graves' disease (28 patients), lymphoma (3 patients) and occult papillary thyroid carcinoma (2 patients) were excluded from analysis (total 33 patients). None of patients with Graves' disease had thyroid carcinoma.

Of the remaining 567 patients, 370 patients presented with clinically solitary nodule. After sonography, 146 (39.46%) patients were found to have MNG. Therefore, 224 (39.5%) had STN while the remaining 343 (60.5%) had MNG. Patients with STN were significantly younger than patients with MNG (mean age of 41.2 versus 46.8 years, $p < 0.01$). However, there was no gender difference between the two groups (76.3%

versus 78.7% females in STN and MNG respectively, p value = 0.51).

Indications and type of surgery performed are detailed in Table 2. The most common indication was diagnosis of malignant disease when preoperative FNAC and US were inconclusive (46.4%).

Three hundred seventy-five patients (66.1%) had benign thyroid disease and the remaining 192 (33.9%) had thyroid cancer. There were no age difference between patients with benign thyroid diseases and those with thyroid cancer (mean age was 44.5 vs. 44.7 respectively, $p = 0.88$). However, male gender was identified as a risk factor for malignant tumors (Odd ratio 2.318, 95% Confidence-interval 1.546–3.474, $p < 0.01$). As shown in Table 3; the chance of having malignancy in STN was 62.3% in males compared to 33.3% in females (OR 3.1322, 95% CI: 1.6538–5.9323, $p < 0.01$). The risk although lower in MNG was still considerable (OR 1.8473, 95% CI: 1.0749–3.1747, $p = 0.03$).

Prevalence of thyroid cancer was 41.1% (92/224) in STN compared to 29.2% (100/343) in MNG (Chi-Square = 8.593,

Table 2 – Indications and type of surgery.

Indication	No (%)	Procedure	No (%)
Diagnostic ^a	263 (46.38)	Hemithyroidectomy	279 (49.21)
Therapeutic for thyroid cancer	179 (31.75)	Total thyroidectomy	185 (32.63)
Compressive Symptoms	94 (16.58)	2-Stages total thyroidectomy ^b	56 (9.88)
Cosmeses	20 (3.53)	Subtotal thyroidectomy	25 (4.41)
Thyrotoxicosis	8 (1.41)	Completion ^c	16 (2.82)
Pain	3 (0.5)	Enucleation or Biopsy	6 (1.06)

^a To rule out malignancy when FNAC is not conclusive (Bethesda categories III–V).

^b Hemithyroidectomy followed by completion.

^c Hemithyroidectomy for one lobe when the other lobe has been removed outside our hospital or many years ago.

Table 3 – Chance of thyroid cancer by gender and number of thyroid nodules.

Gender	Solitary thyroid nodule			Multinodular goiter		
	Benign	Malignant	%Malignant	Benign	Malignant	%Malignant
Female	112	59	34.5%	199	71	26.3%
Male	20	33	62.3%	44	29	39.7%
Total	132	92	41.1%	243	100	29.2%

Table 4 – Types of thyroid carcinoma in STN compared to MNG ($p = 0.353$).

Type	MNG				STN (%) ^a
	Unifocal	Multifocal ipsilateral	Multifocal bilateral	Total (%) ^a	
PTC	24	9	22	55 (55.0)	57 (62.0)
PTMC	7	2	7	16 (16.0)	8 (8.7)
FTC	14	1	–	15 (15.0)	16 (17.4)
HCC	8	–	1	9 (9.0)	3 (3.3)
MTC	2	–	1	3 (3.0)	5 (5.4)
Anaplastic	2	–	–	2 (2.0)	3 (3.3)
IPMC ^b	19	1	5	25/243 (10.3)	10/132 (7.6)

^a Percentage of each thyroid cancer type out of total number of cancers in the group.

^b Number of IPMCs divided by total number of patients with benign thyroid disease.

PTC: papillary thyroid carcinoma, PTMC: papillary thyroid microcarcinoma, FTC: follicular thyroid carcinoma, HCC: Hurthle-cell carcinoma, MTC: medullary thyroid carcinoma, IPMC: incidental papillary microcarcinoma.

Table 5 – Accuracy of preoperative assessment.

Preoperative assessment	STN	MNG	p-Value
True positive	56	60	
False positive	1	3	
True negative	24	105	
False negative	4	12	
Inconclusive	139	163	
Sensitivity	93.33%, 95CI (0.8407–0.9738)	83.33% (0.7309–0.9020)	0.08
Specificity	96.00%, 95CI (0.8046–0.9929)	97.20% (0.9208–0.9904)	0.75
Positive Likelihood Ratio	23.33, 95CI (3.42–159.41)	29.7222 (9.78–92.00)	
Negative Likelihood Ratio	0.07, 95CI (0.3–0.18)	0.17, 95CI (0.10–0.29)	
Accuracy	94.12%	91.67%	0.21

Table 6 – Stage distribution in STN and MNG. Although patients with MNG had significantly more advanced stage, this was related to younger age of patients with STN and not to T or N status.

Criterion	STN	MTN	p-Value
Stage distribution (%)			<0.001
I	73.9%	48.0%	
II	6.5%	16.0%	
III	10.9%	29.0%	
IV	8.7%	7.0%	
T status (%)			0.88
T1	32.6%	29.0%	
T2	27.2%	31.0%	
T3	33.7%	35.0%	
T4	6.5%	5.0%	
N status (%)			0.26
N0	72.8%	81.0%	
N1a	16.3%	14.0%	
N1b	10.9%	5.0%	
Age			
Mean $\pm$ SD	40.78 $\pm$ 14.62	48.31 $\pm$ 14.95	<0.001
% less than 45years	62.0%	41.0%	<0.001

$p < 0.01$). However, on logistic regression analysis this correlation was found to be insignificant ($p = 0.18$).

The most common tumor was PTC diagnosed in 134 patients in addition to 2 patients who had collision tumors (70.8%) followed remotely by follicular carcinoma (FTC) in 16.1%, Hurthle-cell carcinoma (HCC) in 6.3%, medullary carcinoma (MTC) in 3.6% and anaplastic carcinoma in 2.6%. Three patients had collision tumors (macroscopic PTC in all with FTC in 2, and MTC in the third). Types of thyroid carcinoma in both groups were similarly distributed ($p = 0.35$) as shown in Table 4. Multifocal tumors occurred in 46% of patients with MNG particularly in PTC with 31% of these being bilateral and 3% collision tumors. In addition, 35 patients with benign thyroid disease (9.3%) were found to have IPTMCs. Of these, 25 occurred in MNG.

Malignant STNs were significantly smaller in size compared to benign STNs (31.1 mm vs. 35.6 mm, $p = 0.03$). However, malignant tumors in the STN and MNG group were not significantly different in size (31.1 mm vs. 28.9 mm respectively, $p = 0.42$). In patients with MNG, carcinoma was found in the largest nodule in 77% of cases and elsewhere in the remaining 23%.

Hashimoto (autoimmune) thyroiditis (HT) was the primary histopathologic diagnosis in 30 patients and an additional diagnosis in 78 patients (overall prevalence 18.0%).

Thyroiditis was present around 20.3% of PTCs and 13.95% of FTCs including HCCs.

The correlation between presence of thyroiditis and thyroid cancer was insignificant (Odds Ratio 1.006, 95% CI: 0.641–1.580, $p = 0.98$).

The accuracy of preoperative diagnosis in both groups was similar as shown in Table 5 ($p = 0.97$). Still, patients with thyroid carcinoma in MNG group had significantly more advanced stage compared to patients with STN as shown in Table 6 ($p < 0.01$). On multiple regressions analysis the difference in TNM stage was related to age of patients ($p < 0.01$) and not to multiplicity of nodules ($p = 0.62$).

Finally, multiple regressions analysis was used to identify important predictors of thyroid carcinoma in this study. Table 7 summarizes overall results. Only male gender ($p = 0.0003$) and preoperative impression of malignancy ($p < 0.00005$) were significantly associated with thyroid carcinoma.

Table 7 – Predictors of thyroid cancer. Results of multiple logistic regression analysis.

Parameter	Number of cases	Univariate		Multivariate	
		OR (95%CI)	p-value	OR (95%CI)	p-value
Number of nodules (reference MNG)					
MNG	343	1.0		1.0	
STN	224	1.694 (1.189–2.412)	0.004	1.453 (0.842–2.507)	0.18
Gender (reference female)					
Female	441	1.0		1.0	
Male	126	2.318 (1.546–3.474)	<0.01	2.792 (1.600–4.874)	<0.01
Preoperative diagnosis (reference benign)					
Benign	144	1.0		1.0	
Suspicious	303	1.975 (1.093–3.569)	0.02	1.979 (1.043–3.756)	0.04
Malignant	120	232.0 (75.4–713.96)	<0.01	244.5 (77.6–770.5)	<0.01
Thyroiditis (reference absent)					
Absent	464	1.0		1.0	
Present	103	1.006 (0.641–1.580)	0.98	1.461 (0.788–2.709)	0.23
Age group (reference > 80 years)				Not performed ^a	
≤20	16	1.364 (0.112–16.577)	0.81		
21–30	86	1.778 (0.177–17.821)	0.63		
31–40	137	1.419 (0.144–14.036)	0.77		
41–50	151	1.356 (0.137–13.378)	0.79		
51–60	91	1.789 (0.179–17.896)	0.62		
61–70	59	1.214 (0.118–12.508)	0.87		
71–80	23	3.273 (0.295–36.311)	0.33		
>80	4	1.0			
Size (mm, reference > 61)				Not performed ^a	
≤10	107	0.366 (0.089–1.505)	0.16		
11–20	126	0.571 (0.149–2.197)	0.42		
21–30	134	0.910 (0.241–3.431)	0.89		
31–40	84	0.869 (0.218–3.461)	0.84		
41–50	60	0.555 (0.134–2.298)	0.42		
51–60	21	0.798 (0.131–4.880)	0.81		
>61	35	1.0			
OR: odds ratio, 95%CI: 95% confidence interval.					
^a Multivariate regression analysis was not performed as there was no significant correlation on univariate analysis.					

OR: odds ratio, 95%CI: 95% confidence interval.

^a Multivariate regression analysis was not performed as there was no significant correlation on univariate analysis.

Discussion

Appropriate management of thyroid nodule whether solitary or multiple relies on proper clinical assessment, TSH level, ultrasonography and FNAC.^{12,13} When the patient is thyrotoxic or has pressure symptoms the decision to do surgery is generally straightforward. However, in asymptomatic euthyroid patients the decision is more difficult and knowing the risk of malignancy is critical for patient counseling and decision making (whether to observe or perform surgery).

Overall occurrence of thyroid cancer in this study group was high (33.9%) compared to similar studies on the subject.^{6–8} This partly relates to pooling of suspicious and malignant thyroid lesions in our referral center but also to low incidence of endemic goiter in our country as a result of use of iodized salt.¹⁴

Male gender was identified as a risk factor for thyroid cancer. Almost 2 out of 3 males with STN will prove to harbor malignancy. However, age was not found to affect the risk of malignancy. Our results contrast with that of Smith et al.¹⁵ and Rago et al.¹⁶ who found male gender and young age to be independent risk factors for thyroid carcinoma but

in concordance with Luo et al.¹⁷ who reported age as a very weak independent predictor of malignancy (OR 0.97, 95%CI 0.960–0.987, $p < 0.001$). Thyroid cancer can occur at any age, but the risk peaks earlier for women (who are most often in their 40 s or 50 s when diagnosed) than for men (who are usually in their 60 s or 70 s). Mean age of males in this study was 46.2 ± 15.6 and this may have contributed to our findings.

On univariate analysis, the incidence of thyroid cancer was significantly higher in STN compared to MNG (41.1 vs. 29.2% respectively, OR = 1.694, 95%CI 1.189–2.412, $p < 0.01$). However, on multiple logistic regression analysis MNG had the same risk of malignancy as STN when gender and preoperative diagnosis were included in the analysis (OR 1.453, 95%CI 0.842–2.507, $p = 0.18$). Our results are in concordance with those of several similar studies.^{18–20}

Some studies found association between increasing nodule size and risk of malignancy.^{21,22} Others claim that size > 40 mm may lead to false negative FNAC.²³ In this study malignant nodules were smaller than benign nodules. There were 16 false negative FNACs and the average size in these nodules was 26.05 ± 16.94 mm. Our findings are similar to those reported by Megwalu²⁴ and Kamran et al.²⁵

Some studies suggest an association between Hashimoto thyroiditis and PTC as well as lymphoma.^{26,27} This may partly relate to continuous stimulation by follicular cells by elevated TSH-levels commonly found in autoimmune thyroiditis. In this study, although HT was more commonly found around PTC compared to FTC, the difference did not reach statistically significant level (20.3% vs. 13.95%, $p = 0.634$).

At our institution, FNAC is performed routinely by pathologist, endocrinologist and by radiologist under US-guidance. This study proved that aspiration of largest nodules could lead to missing sampling of a quarter of malignant tumors. This is in concordance with results of Mihailescu et al.,²⁸ Paksoy et al.²⁹ and Arsoy et al.³⁰ who reported in different studies that aspirating only the largest nodule will miss 1/3–2/3 of cancers and aspirating the two largest nodules would miss 17% of cases. As such, aspiration under US-guidance which takes nodule features into consideration is strongly recommended in patients with MNG.

Patients with tumors arising in MNG had more advanced stages mainly stage II&III. On multiple logistic regression analysis the distribution of the T and N status between STN and MNG were similar and the main difference was in age. Advanced age was significantly associated with advanced TNM stage ($p < 0.00005$). This was partly related to current TNM-staging 7th system for thyroid cancers which incorporates age in staging. Patients who are <45 years (62.0% in STN vs. 41.0% in MNG in this study) are assigned stage I in absence of distant metastases and stage II in presence of distant metastasis irrespective of T and N status.

In conclusion, risk of thyroid carcinoma in STN and MNG is similar. Male gender and preoperative impression of malignancy by clinical findings, US or FNAC are the main predictors of thyroid carcinoma. Furthermore, US should be routinely employed for assessment of thyroid nodule whether single or multiple. Each nodule in MNG should be managed independently based on US-characteristics.

Conflicts of interest

The authors have none to declare.

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