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Predictors of Malignancy in Patients with Solitary and Multiple Thyroid Nodules

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Abstract

Introduction: Ultrasound (US) and Fine-needle aspiration (FNA) are the main methods used for investigating thyroid nodules, with questionable predictive values in multinodular goiter (MNG) compared to solitary thyroid nodule (STN).

Objective: To detect the independent predictors of malignancy in patients with solitary and multiple nodules.

Patients and methods: Medical records of patients who were admitted for thyroidectomy at Alexandria Main University Hospital and Medical Research Institute Hospital between January 2014 and January 2016 were reviewed. Demographic and clinical data, US reports, FNA reports (Bethesda "B" system), and final histopathological results were recorded and analyzed. Patients with hyper- or hypo-thyroidism, previous history of thyroid cancer or those with incomplete data were excluded.

Results: Collectively, 20% (111/554) of the study population proved to have malignancyon final histopathology, 19.3% (82/422) with MNG and 22% (29/132) with a STN. Combining gender and age showed that significantly more male patients with MNG under the age of 45 years had thyroid cancer (X^2=11.75, p=0.003).Statistically significant US features in the MNG Group included micro-calcifications, solid composition, echogenicity, incomplete halo, ill-defined margins, and suspicious cervical lymph nodes (LNs). In STN, significant US features included complex composition of nodules, peri-nodular vascularity, and also suspicious cervical LNs. The FNA results of BII-V reports showed that 16.9% (69/408) and 17.6% (22/125) of patients with MNG and STN, respectively, had false negative results. The risk of malignancy showed a significant rise from BIV to BVI lesions in both Groups. Multivariate analysis revealed that, in MNG, the highest malignancy predictor was micro calcification, followed by FNA (BVI) and then suspicious cervical LNs. In STN, the features that retained significance in multivariate analysis were suspicious LNs& BVI-FNA.

Conclusion: Based on the data presented, it may be concluded that the independent predictors of malignancy were US findings of micro-calcification in patients with MNG, suspicious cervical LNs and Bethesda VI on FNA in patients with both MNG and STN.

Keywords: Predictors; Malignancy; Multinodular; Goiter; Solitary nodule; Ultrasound; FNA

Introduction

Thyroid nodules are a common clinical finding, with an estimated prevalence of 3% to 7% on the basis of palpation [1-3]. They are more common in the elderly, in women, and in presence of iodine deficiency and history of exposure to radiation [1]. Diagnosis of multinodular goiter (MNG) should rely on ultrasound (US) examination since approximately 20%-50% of patients diagnosed clinically as having a solitary thyroid nodule (STN), are found to have additional nodules on US [1,4,5]. The mean incidence of malignancy in thyroid nodules is 14% [6,7], which increased markedly in recent years due to the wide application of high resolution US and fine-needle aspiration (FNA) [8,9]. While patients with MNG have been reported to have the same risk of malignancy as those with STN [10-12], Other authors reported a higher likelihood of malignancy for STN [10,13]. The present study was conducted to detect the independent predictors of malignancy in patients with MNG as compared to STN.

Patients and Methods

Study population

The medical records of 1217 patients who were admitted to Alexandria Main University Hospital and Medical Research Institute Hospital, between January 2014 and January 2016, were retrospectively reviewed. After excluding patients with hyper- or hypo-thyroidism or history of thyroid cancer, and those with incomplete data, patients who underwent thyroidectomy for euthyroid MNG (Group 1, n=422) or STN (Group 2, n=132) were included in the present study, and constituted the study population (n=554).

Demographic and clinical data

Age, gender, family history of thyroid cancer, previous history of irradiation or thyroid surgery, clinical presentation on admission, and retrosternal extension were all recorded.

Imaging data

The solitary nodule and the largest or most suspicious nodule (in case of MNG) were evaluated in the reviewed reports regarding the

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following parameters; echogenicity, calcifications, halo, margins, composition (solid, cystic, mixed), size (divided according to maximum diameter/nodule into <2 cm, 2-4 cm, >4 cm), vascularity (Doppler examination), and the presence of suspicious cervical lymph nodes (LNs) (rounded, >0.5 cm, lost hilum, peripheral vascularization, cystic changes, and calcification).

Histopathological data

The Bethesda system for reporting thyroid cytopathology (BI-BVI) was adopted in this study, where BI is non-diagnostic or unsatisfactory, BII is benign, BIII means atypical or follicular lesion with undetermined significance, BIV is follicular neoplasm, BV is suspicious of malignancy and BVI is malignant. Predictive indices of FNA were calculated to detect the utility of (B-VI) in diagnosing malignancy. All of the available data for each patient were compared to final histopathology.

Statistical analysis

Data were analyzed using IBM SPSS software package version 20.0 (Belmont, Calf 2013). Qualitative data were described using number and percent. Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square (X^2) was conducted using Fisher's exact test or Monte Carlo correction. Quantitative variables were presented as mean and standard deviation of the mean and were compared using the Student t test. Univariate and multivariate logistic regression were used. A p-value of <0.05 was considered to be statistically significant.

Results

Collectively, 20% (111/554) of the study population proved to have malignant disease on final histopathology (Table 1), 82 patients (19.3%, 82/422) belonged to the MNG Group and 29 (22%, 29/132) belonged to the STN Group, with no significant differences between both (X^2=0.404, p=0.525). Table 2 shows the demographic and clinical data of patients with thyroid cancer in both Groups. Male patients with MNG had insignificantly more cancer than female patients (29.5% versus 18.3%, respectively). In the STN Group, female patients had insignificantly more cancer as compared to male patients (23% versus 13.3%, respectively). Family history of thyroid cancer was significantly more in patients with STN (X^2=4.156, p=0.042).Combining gender and age with a cut-off point at 45 years (Table 3) showed significant differences in MNG only, where more male patients under the age of 45 years (47.1%) had cancer as compared not only to female patients in the same age group (14.8%) (X^2=11.75, p=0.003), but also to male patients above the age of 45 years (18.5%) (X^2=4.08, p=0.043). On the other hand, thyroid cancer was encountered more in female patients above the age of 45 years (24.4%) as compared to those below 45 years (14.8%) (X^2=5.39, p=0.020). The majority of patients (95.1%) presented with a slowly progressive neck swelling with or without dyspnea and/or dysphagia not related to any other systemic disease. None of the patients presented with hoarseness of voice. There was no statistically significant difference in malignancy occurrence between patients with retrosternal extension (RSE) (9.7%) and those without (17.5%) (χ^2=1.237, p 0.266) in the MNG Group. Only two patients with STN had RSE, and they proved to have benign thyroid pathology (χ^2=0.530, p=1.000).Table 4 summarizes the US features in both Groups. As may be seen, statistically significant features predictive of cancer in the MNG Group included micro calcification, solid composition, echogenicity, incomplete halo, and ill-defined margins. In addition, 11patients out of 21 (52.4%) with suspicious cervical LNs had malignant disease (χ^2=19.09, p <0.001). Statistically significant US features in the STN Group included complex composition of nodules and peri-nodular vascularity. Moreover, all 5 patients with suspicious cervical LNs in this Group proved to have malignant thyroid disease (χ^2=20.229, p<0.001). Although, largest nodules (> 4 cm) in patients with MNG or STN had the highest rate of malignancy (22.4% and 31.8%, respectively), yet, there was no statistically significant difference regarding nodule size and occurrence of malignancy. The collective reports of BII–BV FNA results (non-malignant) revealed that 17.4% (91/523) turned out to be malignant on final histopathology. Accordingly, 16.9% (69/408) and 17.6% (22/125) of patients with MNG and STN, respectively, had false negative results. On the other hand, BVI FNA (malignant), showed one false positive case (1/14, 8.3%) in patients with MNG as compared to none in those with STN (Table 5). The risk of malignancy showed a significant rise from BIV to BVI lesions in both Groups as shown in Figure 1. Multivariate analysis of predictors of malignancy in MNG revealed that the highest predictor was micro-calcification, followed by FNA (BVI) and then the presence of suspicious cervical LNs (Table 6). In STN, predictors that retained significance in multivariate analysis were the presence of suspicious cervical LNs and BVI FNA.

Discussion

The clinical importance of thyroid nodules rests with the need to exclude thyroid cancer [2,10,14-16]. In the current study, 19.4% of MNG patients and 22% of STN patients had malignant disease on final histopathology. Similar results were reported by other authors, with a malignancy rate of 5.7%-31% in MNG [2,13,15,17-31] and 17% in STN [32] with no significant difference between both [13,19,32-38]. Thus, the likelihood of thyroid cancer seems to be independent from the number of nodules [13-39]. The difference in the reported rates of malignancy among patients with MNG and STN in the above studies undoubtedly reflects differences in the selection criteria used for analysis, as well as geographic differences in the population studied [19]. Several authors reported that detection of malignancy did not correlate with patient's gender, which is in accordance with the current findings [12,20,40,41]. Other studies however, reported higher rates of thyroid carcinoma in male patients [13,31] especially in patients with follicular neoplasm (BIII, BIV) [13,15,27,31,42-47]. While some authors reported that older age is an independent risk factor of malignancy [29,31,45,46,48-51], others, in accordance with our findings, found no correlation with age in patients with solitary or multiple nodules [12,13,15,18,20,40,41]. In a study by Luo et al. [15], age lost its significance as an independent risk factor for thyroid malignancy when included in a multivariate analysis, suggesting that age is not a very strong independent risk factor for malignancy and will likely not be helpful in predicting the risk of malignancy in a given patient. On the other hand, some investigators found that older age is significantly correlated with the presence of benign neoplasms in thyroid nodules [42,52]. This wide contradiction is probably due to differences in patients selection and numbers of the study population [1,10,13,53]. It is conceivable that both gender and age are weak independent risk factors, but perhaps they add value when combined together as a single index of risk prediction, as shown in the present study that showed a higher risk in male patients with MNG less than 45 years. Combining high resolution US with FNA in evaluating thyroid nodules is considered the modality of choice in investigating nodular

Table I: Final histopathology of malignant tumors in patients with MNG and STN

US Features	MNG (N=422)		STN (N=132)		
Final Histopathology	N	%	N	%	X^2 (p)
Papillary thyroid carcinoma (PTC)	70	85	21	72.5	2.43 (0.118)
Follicular thyroid carcinoma (FTC)	8	9.8	5	17.2	0.76 (0.382)
Medullary thyroid carcinoma (MTC)	2	2.4	2	6.9	1.23 (0.268)
Hurthle cell carcinoma (HCC)	1	1.2	0	0	0.36 (0.55)
Anaplastic thyroid carcinoma +PTC	1	1.2	0	0	0.36 (0.55)
Anaplastic thyroid carcinoma (ATC)	0	0	1	3.4	2.85 (0.091)
Total	82	100	29	100	0.404 (0.525)

Table II: Demographic and clinical data of patients with malignant disease in both Groups (MNG and STN)

Demographic and clinical data		MNG (82/422)	STN (29/132)	X^2 (p)
Gender	Male	13/44 (29.5%)	2/15 (13.3%)	1.55 (0.213)
	Female	69/378 (18.3%)	27/117 (23%)	1.3 (0.249)
X^2 (p)		3.210 (0.073)	0.736 (0.391)	
Age (years)	< 45	44/260 (16.9%)	15/80 (18.8%)	0.142 (0.706)
	> 45	38/162 (23.5%)	14/52 (26.9%)	0.257 (0.612)
X^2 (p)		2.722 (0.099)	1.228 (0.268)	
Previous surgery		12/58 (20.7%)	1/2 (50%)	0.979 (0.322)
Family history of thyroid cancer		0/11	2/6 (33.3%)	4.156 (0.042*)
Radiation history		0/2	0/0	-

* P<0.05

Table III: Incidence of malignancy in patients with MNG and STN in relation to gender and age combined together

	MNG (N=82)			STN (N=29)		
Age Sex	< 45 y N = 260	> 45 y N=162	X^2 (p)	< 45 y N = 80	> 45 y N=52	X^2 (p)
Male	8/17 (47.1%)	5/27 (18.5%)	4.082 (0.043*)	1/8 (12.5%)	1/7 (14.3%)	0.01 (0.920)
Female	36/243 (14.8%)	33/135 (24.4%)	5.39 (0.020*)	14/72 (19.4%)	13/45 (28.9%)	1.391 (0.238)
X^2 (p)	11.750 (0.003)*	0.440 (0.623)		0.228 (1.000)	0.657 (0.659)	
Total	44/260 (16.9%)	38/162 (23.4%)		15/80 (18.8)	14/52 (26.9%)	

Table IV: Ultrasound (US) features in patients with MNG and STN

	N		%		N	%		(p)		N
	N	%	N	%	(p)	N	%	N	%	(p)
Hypoechoic	87	78.4	24	21.6	2.109 (0.155)	16	73	6	27.3	0.757 (0.390)
Micro-calcification	16	53.3	14	46.7	19.575 (<0.001)*	6	60	4	40	2.544 (0.121)
Solid	18	64.3	10	35.7	7.140 (0.016)*	13	68	6	31.6	1.698 (0.219)
Complex	139	81.3	32	18.7	0.420 (0.517)	46	90	5	9.8	6.144 (0.013)*
Incomplete halo	0	0	2	100	9.602 (0.03)*	0	0	1	100	3.912 (0.205)
Ill-defined margins	10	62.5	6	37.5	4.751 (0.029)*	5	63	3	37.5	1.520 (0.359)
Peri-nodular vascularity	17	77.3	5	22.7	0.478 (0.489)	7	50	7	50	8.452 (0.009)*
Intra-nodular vascularity	9	64.3	5	35.7	3.436 (0.064)	9	60	6	40	3.995 (0.080)
Cervical LNs	10	47.6	11	52.4	19.075 (<0.001)*	0	0	5	100	20.229 (<0.001)*

χ2: Chi square test

*: Statistically significant at p ≤ 0.05

Table V: FNA (Bethesda System) [6] results as diagnostic test for malignancy

Bethesda System	MNG (N=417**)				STN (N=129**)			
	Benign (N=340)		Malignant (N=82)		Benign (N=103)		Malignant (N=29)	
	N	%	N	%	N	%	N	%
B (II-V)	337	83.6	66	16.4	100	82.0	22	18.0
BVI	1	7.1	13	92.9	0	0	7	100.0
X^2 test	33.232 (p<0.001)*				9.075 (p=0.003)*			

χ^2: Chi square test

*: Statistically significant at p ≤ 0.05

**: Patients with BI-FNA were not included (MNG Group, n=5 – STN Group, n=3)

thyroid gland [1,26]. Out of the analyzed US features in this study, micro calcification, solid composition, incomplete halo, and ill-defined margins were significant risk factors in patients with MNG, in addition to suspicious cervical lymph nodes in both Groups. Similar results were reported by other studies that investigated the risk of malignancy in MNG alone [20,54-57], or in both MNG and STN [51,54,58-61]. Ultrasound features cannot accurately distinguish between benign and malignant thyroid disease. Although certain sonographic features are associated with increased risk of malignancy, the predictive value of these criteria are not sufficiently high or low to preclude the missing of FNA, and it is recommended that US features are used in combination with FNA and clinical presentation to reach the proper management [12,13,51,58,62,63]. Cytopathological examination is the corner stone in appraising the malignant potential of a given thyroid nodule. A meta-analysis study reported non-diagnostic incidence rate (BI) between 1.8% and 23.6%, with a collectively reported malignancy rate of 16.8% [8]. In the current study, three of 9 patients (33.3%) who were classified as BI had cancer. This high rate could be attributed to several factors; not all FNA in the present study were obtained under US guidance, no on-site smear adequacy assessment was adopted, not all reviewed FNA reports were performed by same pathologist, and most of biopsied nodules were large in size (≥ 4 cm), which may be associated with a high malignancy rate, reaching 27% as reported by Pinchot et al. [31] and Gharib et al. [1]. In this study, 8.4% of BII patients had false negative results (i.e. malignant disease). The false negative rate of 0-8% was reported by several authors [8,10,17,64,65], with the rate being higher in large nodules (≥ 4 cm) [10,31,66]. In this study, the rate of malignancy increased with increasing in Bethesda rating from BIV to BVI. Similar findings were reported in the literature with an average rate of malignancy of 1.2%-25.3% in BIV [6,8,17,46,67,68] 60%-75%

Table VI: Multivariate analysis logistic regression of predictors of thyroid malignancy in patients with MNG

Predictors of Malignancy	B	SE	P value	Odds Ratio	95.0% CI	
					Lower	Upper
Microcalcification (US)	1.452	0.453	0.001*	4.270	1.758	10.374
FNA (B VI)	3.079	1.189	0.010*	21.736	2.114	223.491
Suspicious cervical LN (US)	1.538	0.599	0.010*	4.655	1.438	15.072
Ill-defined margin (US)	1.056	0.64	0.099	2.876	0.82	10.088
Solid composition (US)	0.794	0.495	0.108	2.212	0.839	5.832
Intra-nodular vascularity (US)	0.909	0.713	0.202	2.481	0.613	10.035

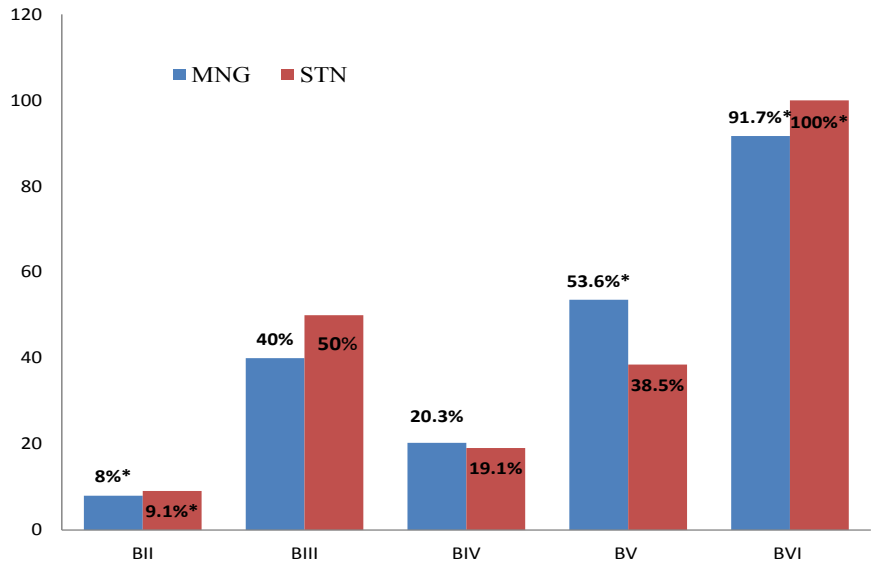

Figure 1: Relation between the incidence of malignancy and FNA (Bethesda system) in patient with MNG and STN

in BV [6,8,39,69], and 97%-99% in BVI [6,70]. Ideally, false positive cases in BVI reports should be less than 1%, ranging from 0.5%-10% [17,71,72].

Conclusion

Based on the data presented, it may be concluded that (1) thyroid nodules in MNG may harbor malignancy similar to those of STN,(2) the most significant independent predictor of malignancy is the presence of micro-calcifications (by US)in MNG in addition to suspicious cervical LNs by US, and FNA (Bethesda VI) in both MNG and STN, and (3) other predictors of malignancy include solid composition of the nodule, incomplete halo and ill-defined margins in MNG, as well complex composition and peri-nodular vascularity in STN; however, these are only significant on univariate analysis.

Conflict of Interest

Authors have no conflict of interest to disclose.

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