

SM Otolaryngology Independent Predictors of Malignancy in Patients with Multinodular Goiter

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Abstract

Introduction: Thyroid nodule is a common clinical finding. 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) due to the presence of multinodularity.

Objective: The present study was conducted to detect the independent predictors of malignancy in patients with MNG.

Patients & Methods: Medical records of patients who were admitted for thyroidectomy at Alexandria Main University Hospital and Medical Research Institute Hospital between January 2013 and January 2016 were reviewed. Demographic and clinical data, US reports, FNA reports, and final histopathological results were recorded and analyzed by univariate and multivariate analysis. Patients with a STN, hyper- or hypo-thyroidism, previous history of surgery for thyroid cancer or those with incomplete data were excluded.

Results: Reports of 1014 patients were reviewed, 419 patients with euthyroid MNG were included in the study. Malignancy rate was 19.3% (81/419). Micro-calcification, solid consistency, ill-defined margins, and presence of suspicious cervical lymph nodes by US were statistically significant predictors. Rate of malignancy in Bethesda II was 8.9% (false negative). Malignant rate increased with increasing in Bethesda rating from Bethesda IV (17.4%) to Bethesda V (51.7%), and lastly Bethesda VI (90.9%). Multivariate analysis revealed that micro-calcifications, suspicious cervical lymph nodes and Bethesda VI FNA were the independent predictors of malignancy. Other malignancy predictors that were only significant by univariate analysis were solid component of the nodule, and ill-defined margins.

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

Introduction

Thyroid nodules are a common clinical finding, with an estimated prevalence on the basis of palpation ranging from 3%-7% [1-3]. They are more common in the elderly, in women, in subjects with iodine deficiency, and in those with a history of radiation exposure [1].

The mean incidence of malignancy in thyroid nodules is 14% [4,5], which has been found to increase profoundly due to the wide application of high resolution Ultrasound (US) and Fine-Needle Aspiration (FNA) [6,7]. Patients with Multinodular Goiter (MNG) have been reported to have the same risk of malignancy as those with Solitary Thyroid Nodule (STN) [8-10]. However, one large study reported that STN had a significantly higher likelihood for malignancy than MNG, although the risk of malignancy per patient was the same and independent of the number of nodules [11]. Diagnosis of MNG should rely on US examination since approximately 20%-48% of patients with one palpable thyroid nodule are found to have additional nodules on US [12,13].

The present retrospective study was carried out to detect the independent predictors of malignancy in patients with MNG.

Patients and Methods

Study population

All medical records of 1014 patients who were admitted to Alexandria Main University Hospital and Medical Research Institute Hospital, between January 2013 and January 2016, were retrospectively reviewed. After excluding patients with STN, hyper- or hypothyroidism, patients with incomplete recorded data, and those with a past history of thyroid malignancy (surgical thyroid biopsy for carcinoma), 419 patients who presented with euthyroid MNG (confirmed by US) and underwent thyroidectomy were included in the current study.

Demographic and clinical data

Age, gender, family history of thyroid cancer, previous history of irradiation or thyroid surgery,

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blood group, retrosternal extension, and clinical presentation were all reviewed.

Imaging data

The largest or the most suspicious nodule was evaluated in the reviewed reports regarding the following parameters; echogenicity, calcifications, halo (complete, incomplete), margins, consistency, vascularity, size (size was divided according to maximum diameter/ nodule into < 2 cm, 2- 4 cm, > 4 cm), 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) [4] was used, where BI is non-diagnostic or unsatisfactory, BII is benign, BIII means atypia 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 (BVI) in diagnosing malignancy in MNG. 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, Calif 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 (χ^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. Agreement of the different predictive factors with the outcome was used and was expressed in sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV),

and accuracy. Odd Ratio (OR) and 95% Confidence Interval (CI) were used to calculate the ratio of the odds of an event occurring in one malignant group to the odds of it occurring in the benign group. Univariate and multivariate logistic regression were assessed. Significance of obtained results was judged at the 5% level.

Results

Out of 419 patients with MNG, 81 (19.3%) were confirmed to have malignant disease by final histopathology. Thirteen out of 44 (29.5%) male patients had malignancy, compared to (18.1%, 68/375) female patients ($\chi^2 = 3.289$, p 0.07).

The mean age of the study population was 43.73±11.93 years, with no statistically significant difference between the malignant and benign groups (43 years and 44 years, respectively). Likewise, when the population of study was divided into ≥ 45 years and < 45 years, no significant difference between both groups was found ($\chi^2 = 0.040$, p 0.842).

Data of previous thyroid surgery were available in 95.2% (399/419) of patients, and showed that 8.6% of patients (3/35) with history of thyroid surgery had malignancy on final histopathology. Data of family history of thyroid cancer and previous radiation exposure were available in 94% of patients (394/419), and showed that all 11 patients with family history of thyroid malignancy were found to have benign disease on final pathologic results, and that the two patients who had history of radiation exposure turned out also to have benign disease.

The majority of patients (95.2%) 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. Blood grouping results were available in 65.9% of patients (276/419). The highest malignancy prevalence was seen in A- patients (25%), followed by O+ patients (18.9%) and A+ patients (17.3%). However, the difference was not statistically significance ($\chi^2=4.99$, P 0.599).

Table 1: Relation between US findings and thyroid malignancy (n = 387).

	Pathology				Sensitivity	Specificity	PPV	NPV	Accuracy
	Benign (n = 320)		Malignant (n = 67)						
	n	%	n	%					
Hypoechoic(n=111)									
-ve (n=277)	234	84.5	43	15.5	35.82	73.13	21.82	84.48	66.67
+ve (n=111)	87	78.2	24	21.8					
X² (p)	2.179 (0.140)								
Microcalcifications (n=29)									
-ve (n=358)	304	84.9	54	15.1	19.40	95.0	44.83	84.92	81.91
+ve (n=29)	16	55.2	13	44.8					
X² (p)	16.579 (<0.001)								
Solid (n=28)									
-ve (n=359)	302	84.1	57	15.9	14.93	94.38	35.7	81.12	80.62
+ve (n=28)	18	64.3	10	35.7					
X² (FEp)	7.140 (0.016)								
Incomplete halo (n=2)									
-ve (n=385)	320	83.1	65	16.9	2.99	100.0	100.0	83.12	83.20
+ve (n=2)	0	0.0	2	100.0					
X² (FEp)	9.602 (0.030)								
Ill-defined margin (n=372)									
-ve (n=372)	311	83.6	61	16.4	8.96	97.19	40.0	83.60	81.9
+ve (n=15)	9	60.0	6	40.0					
X² (FEp)	5.611 (0.030)								
Intra-nodular vascularity (n=13)									
-ve (n=374)	312	83.4	62	16.6	7.46	97.50	38.5	83.42	81.9
+ve (n=13)	8	61.5	5	38.5					
X² (FEp)	4.203 (0.056)								

χ^2 : Chi square test

FE: Fisher Exact test*: Statistically significant at p ≤ 0.05

Table 2: Fine-Needle Aspiration (FNA) Biopsy as a diagnostic test for thyroid malignancy (n=361).

FNA (n=361)	Pathology				Odds Ratio (95%LL-UL)	Sensitivity	Specificity	PPV	NPV	Accuracy
	Benign		Malignant							
	n	%	n	%						
Bethesda Classification										
-ve (II-V) (n=350)	292	83.4	58	16.6	50.345 (6.322-400.91)	14.7	99.7	90.9	83.4	83.7
+ve (VI) (n=11)	1	9.1	10	90.9						
Total (n=361)	293	81.2	68	18.8						
χ^2 (p)	38.549 (<0.001*)									

χ^2 : Chi square test *: Statistically significant at p ≤ 0.05.

Table 3: Multivariate analysis logistic regression of predictors of thyroid malignancy.

	B	SE	P value	Odds Ratio	95.0% CI	
					Lower	Upper
- Microcalcification	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 (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

Ultrasound reports were available in 92.4% of the reviewed records (387/419); of those, 67 patients (17.3%) were found to have malignancy. Ultrasound features were summarized in Table 1. As may be seen, statistically significant US features included microcalcifications, solid nodules, echogenicity, incomplete halo, and ill-defined margins. Ultrasonographic reports regarding Cervical Lymph Nodes (LNs) were available in 92.4% of patients (387/419). Eleven (52.4%) patients out of 21 with suspicious cervical LNs proved to be malignant ($\chi^2=19.09$, p < 0.001).

Nodule size was reported sonographically for 325 out of 387 nodules (84%). Although, largest nodules (> 4 cm) had the highest rate of malignancy (21.3%), yet, there was no statistically significant difference regarding nodule size and occurrence of malignancy ($\chi^2=0.894$, p=0.599). There was no statistically significant difference in

malignancy occurrence between patients with retrosternal extension as detected by CT scan (20%) and those without (16.4%) ($\chi^2=0.30$, p=0.58).

Reports of FNA were found in the reviewed records of 370 (88.3%) patients, of whom 71 (19.2%) lesions were found to be malignant on final histopathological examination. As seen in Table 2, the collective reports of BII-BV (non-malignant) revealed that 16.6% turned out to be malignant on final histopathology. Regarding patients who were BII (benign), 8.9% were false negative. On the other hand, BVI (malignant), showed one false positive case (1/11, 9.1%), and a PPV of 90.9%. The correlation between Bethesda Classification and thyroid malignancy is shown in Figure 1. As may be seen, the difference between the benign and malignant thyroid disease was highly significant for BV and BVI, and was highly protective against cancer for BII.

Multivariate analysis of predictors of malignancy is summarized in Table 3. The highest predictor was microcalcifications, followed by FNA (BVI), presence of suspicious cervical LNs, and lastly echogenicity.

Discussion

The clinical importance of thyroid nodules rests with the need to exclude thyroid cancer, which occurs in 5-15% of cases depending on age, sex, radiation exposure, family history of thyroid malignancy, other associated syndromes, and other factors [2,8,14-16].

In the current retrospective study, 19.3% of patients (81/419) with MNG were found to have malignant disease on final histopathology. Similar results were reported by other authors, with a malignancy rate ranging from 5.7% to 31%, and an average of 1%-14% [2,11,15,17-22]. On the other hand, malignancy rate of STN was reported by McCall *et al.* [23] to be 17% (i.e. close to that of MNG). The difference in

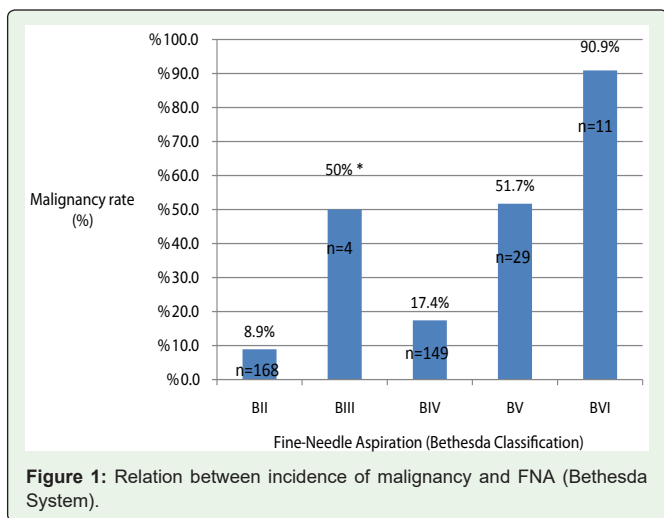


Figure 1: Relation between incidence of malignancy and FNA (Bethesda System).

the reported rates of malignancy among patients with MNG in the above studies undoubtedly reflects difference in the selection criteria used for analysis, as well as geographic differences in the population studied [19].

In the present study, no significant difference in age was found between patients with benign disease and those with malignant disease. The median age was 44 years and 43 years, respectively. Men had a higher malignancy rate (29.5%) than women (18.1%), but the difference was not statistically significant. 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 an independent risk factor for malignancy and will likely not be helpful in predicting the risk of malignancy in a given patient. In 2008, Salmaslioglu *et al.* [20], reported that detection of malignancy did not correlate with patient's age or gender, which is in accordance with the current findings. Other studies however, showed that the rates of thyroid carcinoma on final pathologic evaluation were statistically higher in older male patients [11,24]. It is conceivable that correlating age and gender, and the incidence of malignancy in MNG patients, is widely contradicting; probably due to difference in patients selection and numbers of the study population [1,8,11,25].

History of previous radiation exposure and presence of family history of thyroid cancer are well established risk factors that even affect the decision for FNA biopsy of thyroid nodule more than the nodule size itself [1,8,10,26, 27]. Significant difference could not be detected in the present study regarding family history of thyroid cancer, previous radiation exposure, or even history of previous thyroid surgery. This may be attributed to incomplete or inaccurate data of patients' records in the present retrospective study.

Combining high resolution US with FNA in evaluating thyroid nodules is considered the modality of choice in investigating nodular thyroid gland [1,28]. Out of the analyzed US features in this study, microcalcification was an independent risk factor with the highest Odds ratio, followed by ill-defined margins and then solid consistency of thyroid nodules. In the current study, microcalcification had high specificity of 95%. Similar results were reported by other studies that investigated the risk of malignancy in MNG alone [20,29-32], or in both MNG and STN [29, 33-37].

Ill-defined irregular margins on US had a high specificity of 97.19%, albeit with a very low sensitivity of 8.9%. Other studies reported a wide range of sensitivity (7%-97%) [20,38] and a variable specificity, with 15%-59% of benign nodules having poorly defined margins [10,20,39]. The AACE (American Association of Clinical Endocrinology) Guidelines reported specificity of ill-defined irregular margins to range from 48% - 91.8% [1]. In the present study, the rate of ill-defined margins was greater in malignant nodules than in benign ones (8.95% - 2.81%, respectively).

Similar to our findings, Salmaslioglu *et al.* [20] reported that nodules with solid component were significantly associated with malignancy in patients with MNG. However, intra-nodular hypervascularity, contrary to the reports of other studies [8,35,36] was not statistically significant in patients with malignancy as compared to those with benign disease.

Hypo-echogenicity was the most presenting US feature in the present study (n=111), being non-significantly higher in malignant

nodules. More than three quarters (78%) of hypoechoic nodules were found to be benign. Similarly, Panini *et al.* [10] reported that 55% of benign nodules were hypoechoic. Moreover, most non-palpable thyroid nodules were reported to be hypoechoic and benign [20,33]. Thus, hypo-echogenicity seems to have a very poor predictive value when interpreted alone to predict malignancy [33]. On the other hand, another study showed significant difference in hypoechoic appearance between benign and malignant nodules [20].

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 between 1.8% and 23.6%, with a collectively reported malignancy rate of 16.8% [6]. In the current study, 9 (2.3%) patients were classified as Bethesda I with a malignancy rate of 33% (3/9). 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 is associated with a high malignancy rate, reaching 27% as reported by Pinchot *et al.* [24] and Gharib *et al.* [1]. In this study, 8.4% of Bethesda II patients had false negative results (i.e. malignant disease). The false negative rate of 0-8% were reported by several authors [6,8,17,40,41], with the rate being higher in large nodules (≥ 4 cm) [8,24,42].

The rate of malignancy increases with increasing in Bethesda rating from Bethesda IV (17.4%) to Bethesda V (51.7%), and lastly, Bethesda VI (90.9%). The average of reported rate of malignancy in the literature ranged from 1.2%-25.3% for Bethesda IV [4,6,17,43-45], from 60%-75% for Bethesda V [4,6,46,47], and from 97%-99% for Bethesda VI [4,8]. Ideally, false positive cases in Bethesda VI reports should be less than 1%, ranging from 0.5%-10% [17,48-50]. Similar to the presented results, the PPV of Bethesda VI in MNG ranged between 50% and 96% [17].

Based on the data presented, it may be concluded that [1] the most significant independent predictors of malignancy in patients with MNG are microcalcifications, suspicious cervical LNs by US, and FNA (Bethesda VI), and [2] other malignant predictors include solid component of the nodule, and ill-defined margins but are only significant on univariate analysis. Comparison between the predictors of malignancy between MNG and STN merits further studies and is currently being investigated.

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