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Preoperatively Undiagnosed Thyroid Cancer in Patients Undergoing Surgery for Benign Multinodular Goiter

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ABSTRACT

Background and Objective: Multinodular goiter (MNG) is the most common systemic endocrine disease, with a gender ratio (women to men) of 3:1. Incidental thyroid malignancy, preoperatively diagnosed as benign tumor**,** is a common problem after thyroid surgery. Therefore, the present study was conducted to investigate the role of total thyroidectomy in the diagnosis of types of thyroid cancer after surgery, preoperatively diagnosed as multinodular goiter, and to determine the risk factors of thyroid malignancy in multinodular goiter.

Methods: This prospective study was conducted on 120 patients who were divided into malignant and benign groups based on thyroid tumor diagnosis. All patients underwent total thyroidectomy under general anesthesia. Patients were selected based on complete history, clinical examination, laboratory and radiological findings, as well as ultrasound-guided FNA and ultrasound machine used to confirm the diagnosis of thyroid cancer and lymph node metastasis.

Findings: Among the 120 selected patients, 20 patients were excluded and the remaining 100 patients were divided into two groups: 13% malignant and 87% non-malignant group, which were involved in nodular hyperplasia, inflammatory and benign tumors. The median age for the malignant group (40 years) was higher than the non-malignant group (30 years). Thyroid carcinoma was diagnosed in 46.2% of men and 53.8% of women (p=0.045). In addition, male gender compared to female gender has 2.7 times the analysis as a risk factor for thyroid cancer (relative risk=2.714).

Conclusion: According to the results of this study, total thyroidectomy in patients with multinodular goiter lowers the risk of reoperation because of the presence of hidden malignancy in this benign disease (MNG). Male gender is an important risk factor for thyroid cancer and age factor has no significant association with thyroid cancer post-operatively. Ultrasonography-guided FNA, ultrasound machine, and clinical examinations are not enough for final diagnosis of thyroid cancer preoperatively.

Keywords: *Goiter, Multinodular, Thyroid Cancer, Thyroidectomy, Early Detection of Cancer.*

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Introduction

Multinodular goiter (MNG) is the most prevalent endocrine systemic disease and reaching to about 500×10^6-600×10^6 globally (1). The sex ratio of MNG is 3 females to 1 male in both endemic and non-endemic area (2), and elderly age group is common age involved in non-endemic area (3). The term "goiter" is simply defined as increased growth which consequently leads to increased size of thyroid gland. Goiter has many classified terms that may be related to thyroid function (toxic and nontoxic goiter), and growth style (diffuse or nodular goiter, and multinodular or solitary goiter). MNG means there are multiple nodules in goiter's thyroid gland (4).

Thyroid nodules can be diagnosis by clinical examination (2%-6%) and radiological method (ultrasonography) (19%-68%) (5), and most of their histopathology reports are benign tumor and only 7%-15% of them have risk of malignancy (6, 7). Thyroid nodules are essentially evaluated for abnormal thyroid function and if it is associated with malignancy, in which thyroid cancer are detected by histopathology biopsy (4%-6.5%), papillary microcarcinoma (their diameter<1 cm) were detected in 36% of cases after surgery (8).

The incidental thyroid malignancy is diagnosed after thyroid surgery while preoperatively it was diagnosed as benign tumor; this is representing a common problem (9-12), and may reach up to 40% of total cases of surgical thyroid surgery (13). The incidental thyroid malignancy shows their frequency 5%-10% in MNG (14, 15), and this percentage is increasing with current researches up to 8.6%-22% (16, 17) in comparison up to 20% in autopsy histopathological diagnosis (18).

The increasing thyroid malignancy is related to the development of radiological investigation and there are real elevated cases of thyroid papillary cancer (19). Also, radiological investigation shows that about 40% of clinical diagnoses of solitary nodule of thyroid gland really have MNG (20). Therefore, optimal goals of surgery in MNG are a matter of contention and discussion, which are mainly related to elevated frequency of incidental thyroid malignancy in MNG and increasing frequency thyroid malignancy in recurrent goiter (17). Consequently, various researchers aim to do total surgical removal of thyroid gland for patients with MNG, and specifically in iodine deficiency area (endemic area) (21). At the same time, the efficacy detection of malignancy by fine needle aspiration is low in MNG due to existence of many nodules in thyroid gland (22). On the other hand, current researches concluded that the presence of solitary thyroid nodule increase risk of carcinoma in MNG (23). In contrast, multinodular goiter patients are more at risk to have cancer when these patients have single solitary nodule than multiple nodules (24). This study aims to evaluate the diagnostic role of total thyroidectomy for detection of thyroid cancer types postoperatively which are diagnosed preoperatively as MNG, and determine risk factors of thyroid malignancy in MNG at Imam Al-Sadiq General hospital.

Methods

This prospective research was accomplished in Imam Al-Sadiq General hospital. The research period is extended from 10 January/2019 to 10 January/2022 (Ethical code IASGH 2021-4-105). This research involved 120 patients, and they are divided into two groups according to diagnosis of thyroid tumor; first group was malignant and second group was benign. All of them underwent total thyroidectomy under general anesthesia. The clinical documents of patients include age, sex, clinical features, and open surgical thyroid biopsy were collected.

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Patients with multinodular goiter, normal thyroid function (euthyroid state), when there are doubtful cases of carcinoma and had hard consistency, irregular outline, fast tissue growth, micro-calcifications, lymph nodes metastasis, negative ultrasonography-guided FNA of thyroid gland were included in the study and patients with toxic diffuse goiter, solitary nodule, malignancy related to other body organs, and frequent malignancy in thyroid were excluded from the study.

Full past history concerning any operation, medical disease, and drug intake was collected. General clinical examination included measuring blood pressure, pulse rate checking, respiratory rate computing, and temperature assessment. Laboratory investigation included RBS (random blood sugar), virology screen, CBC (complete blood count), RFT (renal function test), LFT (liver function test), TFT (thyroid function test), and coagulation profile.

Radiological investigations (x-ray in erect and supine for chest and abdomen, and abdominal ultrasound) were used to confirm the diagnosis. Ultrasonography-guided FNA, and ultrasonography machine (HD11 xe, Phillips Medical Systems, Bothell, WA, USA) were used to support diagnosis presence of thyroid cancer and lymph node metastasis. After thyroidectomy, all patients have been examined for histopathological analysis for diagnosis thyroid cancers types. After operation, to detect any recurrence rate of thyroid cancer were evaluated by clinico-pathologic decisions, S.thyroglobulin concentration, ultrasonography-guided FNA, and relapse of cervical lymph nodes metastasis by repeated ultrasonography for neck.

Statistical data calculation was computed by SPSS program (version 26 software). Continuous numbers were quantified as Means±SD, median, minimum, and maximum. Categorical variables were assessed by numbers and percentages. Kolmogorov-Smirnov test was applied to decide the normal distribution of data. Evaluation of continuous variables was done by Independent Samples T Test to find out if the data were normally distributed. Categorical data were estimated with Pearson's chi-squared test. $P < 0.05$ was regarded significant.

Results

The total patients involved were 120 patients, 20 patients were excluded according to exclude criteria in this research. So, remaining 100 patients were divided into malignant groups (13%) and nonmalignant group (87%), which involved nodular hyperplasia, inflammatory and benign tumor.

Table 1 shows the distribution of thyroid tumors and inflammatory thyroid diseases in patients with multinodular goiter, in which nodular hyperplasia represents the higher percentage 63%, inflammatory thyroid disease, carcinoma, and benign tumor represented 15%, 13%, and 9% respectively.

Based on the age of patients in the present study, approximately the same comparable mean age between malignant and nonmalignant groups was found, which show 37.38±9.614 and 37.71±11.823, respectively. Median age for malignant group was higher than nonmalignant group (40 and 35 years, respectively) (Table 2). Age data were divided into six groups (20-30, 31-40, 41-50, 51-60, 61-70 and 71-80 years old). 38.5% in 20-30 age group was the highest percentage observed for thyroid cancer. P-value<0.05 is insignificant between age groups (p=0.988) (Table 3).

Thyroid carcinoma was diagnosed in both sexes post-operatively, in which 46.2% were males and 53.8% were females, and the significant difference in sex group was statistically significant (p=0.045). In addition, male gender has 2.7 fold analysis as risk factor for developed thyroid cancer in comparison to female gender (Relative risk=2.714) (Table 4).

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Table 1. Frequency of histopathological reports of post-operative total thyroidectomy

Diagnosis	Number(%)
Nodular hyperplasia	63(63)
Colloid nodule	19(19)
Hyperplastic nodule	20(20)
MNG	24(24)
Inflammatory	15(15)
Lymphocytic thyroiditis	7(7)
Hashimoto's thyroiditis	8(8)
Benign tumor	9(9)
follicular adenoma	9(9)
Malignant tumor	13(13)
Papillary thyroid carcinoma	4(4)
Papillary microcarcinoma	5(5)
Follicular carcinoma with minimum invasive	1(1)
Noninvasive follicular neoplasm with papillary like feature	2(2)
Oncolytic follicular variant of papillary thyroid carcinoma	1(1)

Table 2. Descriptive analysis of age data between malignant with non-malignant groups

Parameters	Patients with Multinodular goiter		p-value
	Malignant group (n=13)	Non-malignant group (n=87)	
Age (years)			
Median	40	35	0.924*
Minimum	23	18	
Maximum	52	75	
Mean±SD	37.38±9.614	37.71±11.823	

*Independent Samples T-Test

Table 3. Comparison age groups between malignant with non-malignant groups and their significant difference

Parameters	Patients with Multinodular goiter		p-value
	Malignant group (n=13) Number(%)	Non-malignant group (n=87) Number(%)	
Age groups (years)			
20-30	5(38.5)	30(34.5)	0.988*
31-40	4(30.8)	26(29.9)	
41-50	3(23.1)	19(21.8)	
51-60	1(7.7)	9(10.3)	
61-70	0(0)	2(2.3)	
71-80	0(0)	1(1.1)	

*Chi-Square Test

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Table 4. Association of sex groups between malignant with non-malignant groups

Parameters	Patients with Multinodular goiter		p-value	Relative risk
	Malignant group (n=13) Number(%)	Non-malignant group (n=87) Number(%)		
Sex groups				
Male	6(46.2)	18(20.7)	0.045*	2.714
Female	7(53.8)	69(79.3)		

*Chi-Square Test

Discussion

Post-operation complications are the most common problems that face the surgeon after surgery, specially, when surgical complications need another surgery; consequently, this second operation might be associated with high complications in comparison to the first operation. For this reason, total resection of thyroid gland for MNG is less harmful than other operations (24). It is important to remove whole thyroid nodule during first surgery; in this procedure, the risk of recurrence is 2% because multiple nodules of thyroid are associated with more recurrence risk (25).

MNG is managed through complete clinical analysis, TSH concentration, ultrasonography, and finally, ultrasonography-guided FNA (12, 26). In normal thyroid function (euthyroid state) of patients that have no symptoms, the cancer risk is not easy to determine to give decision about final treatment (whether medical or surgical treatment) (27). Overall incidence rate is 13%; this value is similar in comparison to Shrestha et al (28) and Palo et al researches (29) that show rates of 13% and 17%, respectively. Also, many studies showed incidence rate of 17% (30-34) and 13.7% (35). Ajarma et al (27) conclude that there are insignificant association of thyroid malignancy with age, but male gender has a significant association and is regarded as a risk factor (odd ratio=2.318); compared to this study, male gender has higher risk factor (relative risk=2.712). Luo et al (36) and Kaliszewski (24) confirms that malignancy occur in MNG in association with younger age and male as risk factors. The studies of Ghadhban et al. (37) and Mishra et al. (38) on MNG shows insignificant association between cancer, age and gender groups.

Due to our limitation in hospital cases, we extracted statistical data from our case series study involving 120 patients. However, due to the small sample size, these analyses may not be reliable enough to guide clinical decisions. We need to do total (or near total) surgical removal of thyroid because of the risk of incidental thyroid cancer and to prevent multiple operations for such cancer.

In presented study, we concluded that only gender group has a significant association; age group has no significant association with thyroid cancer postoperatively. Also, age group 20-30 years old shows higher percentage of patients with cancer, and mean age are 37.71 and 37.38 for nonmalignant and malignant groups. All this finding is similar to a study by Nasr et al. (35), in which male gender is significantly associated ($p \leq 0.001$) with the occurrence of disease, and there is no significant association between gender groups, and it is more commonly in age group 20-30, and mean age of 36.72 versus 36.53 for benign and malignant group, respectively.

Conflicts of Interests: None.

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