

# Frequency of Thyroid Carcinoma in Multi Nodular Goiter

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## ABSTRACT

**Objective:** The objective of this study was to determine the frequency of thyroid carcinoma in patients presenting with multinodular goiter in BMCH.

**Study Settings:** Research was conducted at Department of General Surgery, Bolan Medical Complex Hospital Quetta.

**Material and Methods:** Eighty four patients from both the genders with age between 20-75 years presenting with multinodular goiter since 3 months and meeting inclusion criteria were included in this study after taking informed written consent. All the thyroidectomies were done by consultant general surgeon of the hospital. Post-operatively all the patients were managed as per hospital protocol. Post thyroidectomy specimen was sent for histopathology for diagnosis of thyroid malignancy as per operational definition. All the other findings of study variables such as age, gender, place of residence, BMI (weight in Kg/Height in m<sup>2</sup>), family history of malignancy, diabetes, hypertension, smoking (>5 cigarettes/day for 2 years) and duration of goiter were noted in a predesigned proforma.

**Results:** The mean age of the patients was 37.4±14.0 years. Majority (n=48, 57.1%) of the patients were aged between 25-50 years, followed by 23 (27.4%) patients aged <25 years and 13 (15.5%) patients aged >50 years. There were 17 (20.2%) male and 67 (79.8%) female patients with a male to female ratio of 1:4. Family history of thyroid malignancy was positive in 11 (13.1%) patients. Thyroid carcinoma was detected in 12 (14.3%) patients with multinodular goiter. When stratified, the frequency of thyroid carcinoma was significantly higher among smokers (29.2% vs. 8.3%; p-value=0.014) and those with positive family history of thyroid cancer (36.4% vs. 11.0%; p-value=0.047). However, no statistically significant difference was observed across various subgroups of patients based on age (p-value=0.978), gender (p-value=1.000), BMI (p-value=1.000), duration of goiter (p-value=0.928), place of residence (p-value=1.000), diabetes (p-value=0.928) and hypertension (p-value=0.858).

**Conclusion:** In the present study, we observed that a substantial proportion of patients with multinodular goiter had concealed thyroid carcinoma particularly smokers and those with positive family history which warrants careful pre-operative evaluation of such patients for thyroid malignancy so that it may be identified well in time and appropriate management may be initiated to improve outcomes in future practice.

**Keywords:** Multinodular Goiter, Thyroid Carcinoma, Positive Family History, Smoking

## INTRODUCTION

Multinodular goiter (MNG) is highly common endocrine disorder affecting 500-600 million people worldwide.<sup>1</sup> Its annual incidence and prevalence in non-endemic regions is 0.1-1.5% and 4- 6%, respectively. In endemic regions, it affects more than 10% of a given population.<sup>2</sup> In Pakistan, Thyroid carcinoma is responsible for 1.2% of all malignant tumors cases and though it may be relatively rare among other cancers, it represents the most frequent form of cancer of the endocrine glands. When it comes to the incidence of thyroid malignancy in MNG, the traditional view was that MNG is relatively benign, with a higher incidence of malignancy attributed to solitary thyroid nodules. However, recent review of literature has showed that rates of thyroid cancer in MNG has risen from 3 in older studies to 35 in recent studies, thereby requiring a shift in the approach towards treatment of MNG.<sup>4,5</sup>

According to previous studies in surgical specimens of MNG 5-10% were found to harbor a carcinoma, whereas recent studies have shown a significant incidence (22%) of thyroid carcinoma in patients with MNG showing a benign FNA report.<sup>6,7</sup> Keeping in view that the treatment options of MNG vary between L-T4 suppressive therapy, radioiodine (I131) uptake ablation and surgery, one would be forced to conclude that in the light of new evidence all MNG cases should have a lower threshold for surgery as a treatment option to prevent dissemination of malignant disease. Some authors have suggested total thyroidectomy for MNG, particularly in endemic iodine-deficient regions.<sup>8-10</sup>

The aim of this study is to highlight the frequency of malignancy associated with multinodular goiter. In MNG previously prevalence of thyroid cancer has been reported between 5-10% but more recently very high prevalence has been reported as 8.6-22%.<sup>11-13</sup> Increase in prevalence of MNG may be associated with higher prevalence of thyroid nodules.<sup>14,15</sup>

Thyroid enlargement and nodule formation describe the clinicopathological condition known as multinodular goiter (MNG). Countries in the hilly regions of south-east Asia, Latin America,

and Central Africa all have insufficient iodine in their soil, making multinodular goiter an endemic disease in these places.<sup>10,12</sup>

Cancer rates differ from one nation to another and with different measurement techniques. Whether or not Multinodular goiter is significantly related with cancer has been a long-standing and unsolved question.<sup>6</sup> Historically, doctors have considered multinodular goiters to have a lower risk of cancer than single thyroid nodules.<sup>13,8</sup>

Furthermore, local study on this topic is very limited and outdated, so it is important to generate local evidence which help in identification of high risk population and early management of such patients may reduce morbidity and mortality due to thyroid cancer in our region. The results of our study will help clinicians and policymaker to make well informed decision and devised management and diagnostic strategies in order to reduce complication to thyroid cancer. Moreover result of our study will open the pathway for future research regarding its risk factor.

## MATERIAL AND METHODS

**Study Design:** This was a cross-sectional study.

**Study setting & Duration:** It was conducted at Department of General Surgery, Bolan Medical Complex Hospital Quetta for a period of six months w.e.f 03/02/2022 to 02/08/2022.

**Sample Size:** WHO sample size calculator was used to calculate sample size of this study. By using prevalence of thyroid malignancy in patient with multinodular goiter 31.8%,<sup>15</sup> margin of error 10% and confidence level 95%. The required sample size for this study was 84.

**Sampling Technique:** Selection of patients was done through consecutive non-probability sampling.

**Inclusion Criteria:** Patients inclusion criteria was both genders with age between 20-75 years presenting with multinodular goiter since 3 months.

**Exclusion Criteria:** However, patients with solitary nodule, metastatic lymphadenopathy, Graves' disease, undifferentiated

thyroid carcinoma, recurrent carcinoma of thyroid and associated carcinoma of other organ were excluded from the study.

**METHODOLOGY**

A written informed consent was taken from every patient before including them in this study. All the thyroidectomies were done by consultant general surgeon of the hospital. Post-operatively all the patients were managed as per hospital protocol. Post thyroidectomy specimen was sent for histopathology for diagnosis of thyroid malignancy as per operational definition. All the other findings of study variables such as age, gender, place of residence, BMI (weight in Kg/Height in m<sup>2</sup>), family history of malignancy, diabetes, hypertension, smoking (>5 cigarettes/day for 2 years) and duration of goiter were noted in a predesigned proforma.

**Data Analysis:** Data was collected using a standard proforma for all the patients and SPSS version 22.0 was used for data analysis. Mean ±SD has been calculated for numerical variables like age, BMI and duration of goiter. While frequency and percentage of categorical variables was calculated i.e. gender, place of residence, family history of malignancy, diabetes, hypertension, smoking and thyroid malignancy. Data has been stratified for age, gender, BMI, duration of goiter, place of residence, family history of malignancy, diabetes, hypertension and smoking to address effect modifiers. Post-stratification, Fisher's exact test/ chi-square test has been applied taking p-value ≤0.05 as significant.

**RESULTS**

The patients had a mean age of 37.4±14.0 years within the range of 20-75 years. The study sample had 57.1% (n=48) patients in the range of 25-50 years, followed by 23 (27.4%) patients aged <25 years and 13 (15.5%) patients aged >50 years as given in Table 1. There were 17 (20.2%) male and 67 (79.8%) female patients and the study population had a male to female ratio of 1:4. BMI of these patients was 27.8±3.7 Kg/m<sup>2</sup> in the ranged from 22.1 Kg/m<sup>2</sup> to 33.5 Kg/m<sup>2</sup>. 26 (31.0%) patients were obese, 34 (40.5%) patients were diabetic and 40 (47.6%) patients were hypertensive. 24 (28.6%) patients were smoker while family history of thyroid malignancy was positive in 11 (13.1%) patients. Duration of disease ranged from 1 to 6 years with a mean of 3.7±1.7 years. 56 (66.7%) patients had rural while 28 (33.3%) patients had urban residence. These findings have been summarized in Table 2.

Thyroid carcinoma was detected in 12 (14.3%) patients with multinodular goiter as shown in Table 3. When stratified, the frequency of thyroid carcinoma was significantly higher among smokers (29.2% vs. 8.3%; p-value=0.014) and those with positive

family history of thyroid cancer (36.4% vs. 11.0%; p-value=0.047). However, the various subgroups of patients had no significant difference based on age (p-value=0.978), gender (p-value=1.000), BMI (p-value=1.000), duration of goiter (p-value=0.928), place of residence (p-value=1.000), diabetes (p-value=0.928) and hypertension (p-value=0.858) as shown in Table 4 & Table 5.

Table 1: Age of Study Cohort

Characteristics	Participants n=84
Age (years)	37.4±14.0
• <25 years	23 (27.4%)
• 25-50 years	48 (57.1%)
• >50 years	13 (15.5%)

Table 2: Basic Characteristics of Study Cohort

Characteristics	Participants n=84	Characteristics	Participants n=84
Gender		BMI (Kg/m <sup>2</sup> )	27.8±3.7
• Male	17 (20.2%)	• Non-Obese	58 (69.0%)
• Female	67 (79.8%)	• Obese	26 (31.0%)
Diabetes		Hypertension	
• Yes	34 (40.5%)	• Yes	40 (47.6%)
• No	50 (59.5%)	• No	44 (52.4%)
Smoking		Family History	
• Yes	24 (28.6%)	• Positive	11 (13.1%)
• No	60 (71.4%)	• Negative	73 (86.9%)
Duration of Disease (years)	3.7±1.7	Residence	
• ≤3 years	36 (42.9%)	• Rural	56 (66.7%)
• >3 years	48 (57.1%)	• Urban	28 (33.3%)

Table 3: Frequency of Thyroid Carcinoma in Patients with Multinodular Goiter n=84

Thyroid Carcinoma	Frequency (n)	Percent (%)
Yes	12	14.3 %
No	72	85.7 %
Total	84	100.0 %

Table 4: Comparison of Thyroid Carcinoma across various Age Groups of Patients with Multinodular Goiter

Subgroups	n=84	Thyroid Carcinoma n (%)	P-value
Age			
• <25 years	23	3 (13.0%)	0.978
• 25-50 years	48	7 (14.6%)	
• >50 years	13	2 (15.4%)	
• Urban	28	4 (14.3%)	

Chi-square test/Fisher's exact test, \* observed difference was statistically significant

Table 5: Comparison of Thyroid Carcinoma across various Subgroups of Study Variables in Patients with Multinodular Goiter

Subgroups	n=84	Thyroid Carcinoma n(%)	P-value	Subgroups	n=84	Thyroid Carcinoma n(%)	P-value
Gender				BMI			
• Male	17	2 (11.8%)	1	• Non-Obese	58	8 (13.8%)	1
• Female	67	10 (14.9%)		• Obese	26	4 (15.4%)	
Diabetes				Hypertension			
• Yes	34	5 (14.7%)	0.928	• Yes	40	6 (15.0%)	0.858
• No	50	7 (14.0%)		• No	44	6 (13.6%)	
Smoking				Family History			
• Yes	24	7 (29.2%)	0.014*	• Positive	11	4 (36.4%)	0.047*
• No	60	5 (8.3%)		• Negative	73	8 (11.0%)	
Duration of Disease				Residence			
• ≤3 years	36	5 (13.9%)	0.928	• Rural	56	8 (14.3%)	1
• >3 years	48	7 (14.6%)		• Urban	28	4 (14.3%)	

Chi-square test/Fisher's exact test, \* observed difference was statistically significant

**DISCUSSION**

A clinicopathological condition known as multinodular goitre (MNG) is characterised by an enlarged thyroid gland and the development of nodules. A goitre is described as a thyroid gland that weighs more than 20–25g or has a volume greater than 19–25ml for men and women, respectively.<sup>16</sup> Counties in the hilly regions of South-East Latin America, Asia, and Central Africa are among those where MNG is prevalent due to the low iodine content of the soil in

these places.<sup>17,18</sup> The thyroid gland's easily observable location makes MNG diagnosis typically simple.<sup>19</sup> Being an essentially benign disease the treatment is usually straight forward including L-T4 suppressive therapy, radioiodine (I<sup>131</sup>) uptake ablation and surgery.<sup>18,20</sup>

In the United States, thyroid cancer ranks fifth among all cancers, with approximately 62,000 new cases both in men and women in 2015.<sup>21</sup> Globally, the incidence is still increasing. The

prevalence of thyroid cancer has been increasing quickly, making it a major issue on a global scale.<sup>22,23</sup> A preoperative risk assessment that considers clinical, imaging, and cytological information is helpful in decisions about initial treatment.<sup>24,25</sup> There is now growing body of evidence that a substantial proportion of patients with multinodular goiter have concealed thyroid carcinoma which is diagnosed after surgical excision and histopathology of specimen.<sup>26</sup> This delayed diagnosis adversely affects the prognosis of patient and warrants appropriate diagnostic workup before planning and implementing a treatment in patient with multinodular goiter.<sup>19</sup> But, available evidence regarding frequency of thyroid carcinoma among patients with MNG varied among existing studies, necessitating the present study to give baseline local statistical data for more researches in this area and provide an insight into the magnitude of the problem.

The objective of this study was to determine the frequency of thyroid carcinoma in patients presenting with multinodular goiter in BMCH.

Patients with multinodular goiter had a mean age of 37.4±14.0 years. Previously in a similar study, likewise mean age of the patients was reported by Khan et al. (2016) as 36.9±12.2 years in Pakistan at PIMS, Islamabad and 35±2.2 years by Ahsan et al. (2013) at Jinnah Postgraduate Medical Centre, Karachi.<sup>13,14</sup> Moreover mean age in MNG patients was reported as 37±12.5 years in another local study at Hayatabad Medical Complex, Peshawar by Anwar et al. (2012).<sup>16</sup> Mean age in MNG patients reported by some other authors is 36.8±13.3 years in India by Jena et al. (2015), 36.5±12.3 years by Hossani et al. (2014) and 38.9±15.3 years by Rashid et al. (2016) in Bangladesh, 35±7.9 years by Jat et al. (2019) in Saudi such population and 38.1±13.9 years in Ethiopia by Asmelash et al. (2019).<sup>17,18,19</sup>

Majority (n=48, 57.1%) of the patients with multinodular goiter in this study had age in the range of 25-50 years, next to them were 27.4% (n=23) patients with age less than 25 years and remaining 15.5% (n=13) patients aged >50 years. In a similar Pakistani study, Anwar et al. (2012) reported results matching with our findings as frequency of patients with age >50 years was 11.8%, 25-50 years were 52.0% and less than 25 years age were 36.2%.<sup>16</sup> Age distribution reported in MNG patients by Saqlain et al. (2018) also supports our findings.<sup>22</sup> Shrestha et al. (2014) also reported comparable frequency in Nepali population as 22.0% with age <25 years, 64.0% had age range of 25-50 years while their remaining 14.0% study population had age >50 years.<sup>23</sup> Hossain et al. (2014) in Bangla reported frequency for these age slabs as 24.0%, 66.0% and 10.0% respectively.<sup>18</sup>

We found male to female ratio of patients in study population as 1:4. Our findings are supported by results of other studies as Ahsan et al. (2013) reported female predominance in MNG patients as 1:4.1.<sup>14</sup> Female predominance was also reported by Ahmad et al. (2013) as 1:4, Anwar et al. (1:3.5), Khan et al. (1:3) and Ullah et al. (1:3).<sup>27,16,13,8</sup> Moreover, in similar Indian studies Krishna et al. (2019), Jena et al. (2015) and Gautam et al. (2017) also reported female predominance as 1:3.4, 1:3.8 and 1:4 respectively.<sup>28,17,29</sup> However, Rashied et al. (2016) reported relatively higher female predominance with a male to female ratio of 1:6.6 in Bangladesh.<sup>19</sup>

In the present study, thyroid carcinoma was detected in 12 (14.3%) patients with multinodular goiter. When frequency of thyroid carcinoma was stratified its risk was significantly less among non-smokers as (8.3% vs. 29.2%; p-value=0.014). But stratification on the basis of negative and positive family history, negative family history had significantly less risk (11.0% vs. 36.4%; p-value=0.047). Furthermore, insignificant difference was observed across various subgroups of patients based on age (p-value=0.978), gender (p-value=1.000), BMI (p-value=1.000), duration of goiter (p-value=0.928), place of residence (p-value=1.000), diabetes (p-value=0.928) and hypertension (p-value=0.858).

Findings in this study matches with results of another similar local study where Anwar et al. (2012) observed comparable

frequency of malignant thyroid lesion among patients presenting with multinodular goiter at Hayatabad Medical Complex, Peshawar and reported it to be 14.4%.<sup>16</sup> A comparable frequency has been reported by Nadeem et al. (2013) who observed thyroid carcinoma in 14.9% of patients with MNG presenting at Sheikh Zayed Medical Hospital Rahim Yar Khan.<sup>30</sup> Ullah et al. (2014) observed a comparable frequency of 15.0% at Khyber Teaching Hospital, Peshawar.<sup>8</sup> Asokan et al. (2020) and Palo et al. (2016) observed comparable frequency of thyroid carcinoma among Indian patients with MNG and reported it to be 14.0% and 17.0% respectively.<sup>[165,166]</sup> Similar frequency of 13.0% has been reported by Shrestha et al. (2014) in Nepalese patients with multinodular goiter.<sup>23</sup> Yong et al. (2017) observed this frequency to be 14.3% in Singapore while Fama et al. (2018) reported it to be 12.1% in Italy.<sup>31,30</sup>

The current study adds to the body of locally and globally published research evidence on the subject. The present study's tight exclusion criteria and large sample size of 84 cases were its strongest points. We stratified the data for different effect modifiers as well. In the present study, we observed that a substantial proportion of patients with multinodular goiter had concealed thyroid carcinoma particularly smokers and those with positive family history which warrants careful pre-operative evaluation of such patients for thyroid malignancy so that timely identification and appropriate management may improve the outcome of such cases in future practice.

However, cross-sectional design of the study was a very strong limitation where we didn't follow the cases to evaluate final outcome of such patients. Moreover, we didn't consider histopathological subtype of tumor that may be used for stratification of risk in such cases and planning its management. Therefore, in future clinical research, such a study is highly recommended.

## CONCLUSION

In the present study, we observed that a substantial proportion of patients with multinodular goiter had concealed thyroid carcinoma particularly smokers and those with positive family history which warrants careful pre-operative evaluation of such patients for thyroid malignancy so that it may be identified well in time and appropriate management may be initiated to improve outcomes in future practice.

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