

Original Research

Incidence pattern of differentiated thyroid cancer in patients of multinodular goitre-a cross sectional study

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ABSTRACT:

Background: Multinodular goitre is very widespread all throughout the world, especially in developing countries. In recent research, the incidence of differentiated thyroid cancer among individuals with multinodular goitre has increased. **Aims and objectives:** To find out how common differentiated thyroid cancer is in patients with multinodular goitre. **Materials and methods:** This is a cross-sectional study conducted on a convenient sample of 120 patients with multinodular goitre at the ENT Ward of Hitech Medical College and Hospital from October 1, 2019 to September 30, 2020. To confirm the diagnosis, a clinical history and examination, fine needle aspiration, and postoperative histopathological testing were performed. **Results:** The average age of the patients was 43.9 years old, with 10 men and 110 women. 26 (21.7%) of multinodular goitre patients had differentiated thyroid cancer, while 94 (78.3%) had benign goitre, according to a fine needle aspiration test. Multinodular goitre patients' histology revealed that 40.8 percent of them had colloid goitre, 17.5 percent had micro-papillary carcinoma, and 37.5% had follicular adenoma. Smoking and ionising radiation were found to be significantly linked with differentiated thyroid cancer in multinodular goitre patients. **Conclusions:** Multinodular goitre patients have a significant prevalence of differentiated thyroid cancer.

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INTRODUCTION

MULTI-NODULAR GOITER

Goiter, or an enlarged thyroid gland, can be caused by a number of different things. Toxic or nontoxic, diffuse or nodular, and solitary or many, goitres can be classed. An enlarged thyroid gland with many nodules is frequently referred to as "multi" [1].

In terms of histology, MNG is defined as an overly large thyroid gland with severely altered follicles, both physically and functionally. Several disorders can lead to goitre, which is an increase in the size of the thyroid gland. Toxic or non-toxic goitres, diffuse or nodular, can all be classified as goitres. An enlarged thyroid gland with many areas of nodularity, MNG, is characterised as a thyroid enlargement with follicles that are morphologically and functionally drastically altered: it usually develops over years.

Many countries have MNG as an endemic disease, particularly in regions with low iodine intake [2]. The development of MNG is influenced by a number of factors.

EPIDEMIOLOGY

There are an estimated 500 to 600 million persons worldwide that suffer from MNG [3]. There are an estimated 54 million people in India who have goitre, and another 167 million who are at risk. When MNG affects more than 10% of a community, it is considered endemic [1]. Women and the elderly are more likely than men to develop non-endemic goitre [4]. Females outnumber men by a ratio of three to one in both endemic and non-endemic areas [1]. Goiter nodules appear earlier in endemic goitre and later in sporadic goitres, however the patient may not be

aware of their presence until their late 40s and 50s [5]. There are pockets of endemic goitre in numerous states in India's sub-Himalayan region. [6]

Sixty-four percent of the participants in a research in Baghdad had a multinodular goitre, whereas 22% had a diffuse goitre and 12.6% had a solitary nodule. There was a finding of Thyrotoxicosis in 21.5 percent of the population. 6.3 percent of those tested positive for thyroid cancer were women, with women outnumbering men in the study (80%). Eighty percent of breast cancer patients had papillary carcinoma. It was found in 6.3% of patients, all of whom were female [7].

DIAGNOSIS OF DIFFERENTIATED THYROID CANCER

It is most typical for patients or doctors to find an unnoticeable nodule during a physical examination that shows rapid growth and no symptoms of malignancy. U/S and FNA are used to diagnose thyroid carcinoma. Clinical or U/S. suspicion of cancer may necessitate FNA, which is conducted following U/S guidelines. [8]

DIFFERENTIATED THYROID CANCER AND MULTI-NODULAR GOITER

Multi-nodular goitre (MNG) has previously been assumed to have a prevalence of between 5% and 10% of patients, but subsequent research have found that ITC prevalence rates range from 8.6% to 22%. Detection of ITC in autopsies has been reported to be on the rise, with an estimated increase from 6 percent in 2003 to 20% in 2012 [9]. An autopsy dataset with a 50% frequency of thyroid nodules might explain this observed rise. [10]. According to Bae et al., more than 23% of patients with F-fluoro-deoxyglucose positron emission tomography examinations who also had incidentally discovered thyroid lesions had malignancy. [11] High-resolution ultrasonography has also been shown to detect asymptomatic thyroid nodules in 13% of individuals investigated, with a malignancy rate of 29% [12]. After a strumectomy for what was thought to be benign MNG, it is not uncommon to discover that a patient has thyroid cancer (TC) on histopathology. It is therefore necessary to take into account the presence of ITC when making a decision about the extent of MNG surgery that should be undertaken [12].

Because of the rising prevalence of ITC and the occurrence of TC in recurrent goitre among MNG patents [10], the appropriate surgical technique for these patients is still up for debate. MNG patients with endemic iodine deficiency may benefit from a complete thyroidectomy, according to some researchers [13]. The increased prevalence of ITC in this thyroid pathology and the high recurrence rate following this treatment have been documented during long-term follow-up as disadvantages of partial thyroidectomy for MNG [13,14]. The recurrence rate following a subtotal thyroidectomy for MNG is

roughly 50%, according to some experts; however, this rate is dependent on the length of observation. A total of 180 months of follow-up time was used in this investigation. After a subtotal thyroidectomy, several researchers have argued that keeping thyroid tissue in the operation bed is a bad idea. According to their findings, some of these individuals may require a second operation in the future because to ITC in a recurrent goitre, which is associated with a poorer prognosis and an increased risk of complications [15]. One thousand thirty-one thyroidectomy tissues were evaluated for the existence of papillary thyroid microcarcinoma by John et al [16]. In this group of patients, the most prevalent surgical indication was MNG, given the prevalence of ITC. Although malignancy was suspected in just 31.4 percent of the cases, the researchers detected 94 cases of papillary thyroid micro-carcinoma.

Some preoperative investigations, particularly fine-needle aspiration biopsy (FNAB), have a lower diagnostic value when many nodules are present in the thyroid gland, resulting in the discovery of TC on postoperative histological evaluation in many individuals [17]. Papillary thyroid microcarcinoma is a common complication of MNG surgery, according to some researchers [18]. Dominant MNG nodules may have the same cancer risk as a lone nodule, according to Tollin. The following finishing operation is commonly required [19] if post-operative histology detects thyroid cancer after a less radical procedure has been undertaken.

AIMS AND OBJECTIVES

To determine the incidence rate of differentiated thyroid carcinoma among patients with multinodular goiter in ENT Ward of Hitech Medical College and Hospital.

PATIENTS & METHODS

STUDY DESIGN & SETTINGS

This study is a cross sectional study carried out in ENT Ward of Hitech Medical College and Hospital during the period from 1st of October, 2019 to 30th of September, 2020.

STUDY POPULATION

All patients with multinodular goiter admitted to ENT Ward of Hitech Medical College and Hospital were the study population.

INCLUSION CRITERIA

1. Adults (age above 18 years).
2. Multinodular goiter.
3. Suspicion of malignancy (hard, irregularity, rapid growth and micro-calcifications)

EXCLUSION CRITERIA

Sixty eight patients were excluded.

1. Toxic diffuse goiter.
2. Solitary nodule.

3. Undifferentiated thyroid cancer.
4. Associated carcinoma of other organ.
5. Recurrent carcinoma of thyroid.

SAMPLING

A convenient sample of 120 patients with multinodular goiter admitted to ENT Ward of Hitech Medical College and Hospital and surgically operated by multiple specialized surgeons was selected after eligibility to inclusion and exclusion criteria.

DATA COLLECTION

The data was collected by researcher from the patients with MNG and filled in a prepared questionnaire. The questionnaire was designed by the supervisor and researcher. The questionnaire included the followings.

1. Demographic characteristics of MNG patients: Age and gender.
2. Social characteristics of MNG patients: Residence, educational level, ethnicity and religion.
3. Smoking status.
4. Family history of thyroid diseases.
5. History of exposure to ionizing radiation.
6. TFT at time of diagnosis.
7. FNA findings.
8. Postoperative Histopathology report.

ASSESSMENT OF MNG PATIENTS

After taking history and information from selected MNG patients, clinical examination was done for the neck of the patients to detect the thyroid enlargements and lymph node status with assessment of vocal cord mobility by laryngoscope by ENT Physician. Fine needle aspiration was done for all studied patients by a pathologist in Pathology Department of Hitech Medical College and Hospital. After checking of patients by an Anaesthetist, the selected patients were surgically operated upon total or near total thyroidectomy by the multiple specialized surgeons.

The histopathology examination of specimens was done in all cases in Histo-Pathology Lab of the PG Department of Pathology at Hitech Medical College and Hospital

ETHICAL CONSIDERATIONS

1. The ethical approval was taken from IEC of Hitech Medical College and Hospital.
2. The researcher surgically managed the patients with Supervisor accordingly.
3. An oral informed consent was taken from the patients.

STATISTICAL ANALYSIS

All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 20 was used. Descriptive statistics presented as (mean \pm standard deviation) and frequencies as percentages. Multiple contingency tables conducted and appropriate statistical tests performed, Chi-square used for categorical variables (Fishers exact test was used when expected variables were less than 5) and Independent sample t-test was used to compare between two means. In all statistical analysis, level of significance (p value) set at 0.05 and the result presented as tables and/or graphs. Statistical analysis of the study was done by the community medicine specialist.

RESULTS

In this study, 120 patients with multinodular goitre (MNG) had a mean age of 43.9 ± 11.6 years; 6.7 percent were under 30 years old, 22.5 percent were between 30 and 39 years old, 39.2 percent were between 40 and 49 years old and 20.8 percent were between 50 and 59 years old. There were 11:1 more female patients with MNG than male patients. Table 1 and Figs. 1 and 2 showed all of these findings.

Table 1: Demographic characteristics of MNG patients.

Variable	No	%
Age mean \pm SD (43.9 ± 11 .years)		
<30 years	8	6.7
30-39 years	27	22.5
40-49 years	47	39.2
50-59 years	25	20.8
≥ 60 years	13	10.8
Total	120	100.0
Gender		
Male	10	8.3
Female	110	91.7
Total	120	100.0

Fig. 1. Age distribution of MNG patients

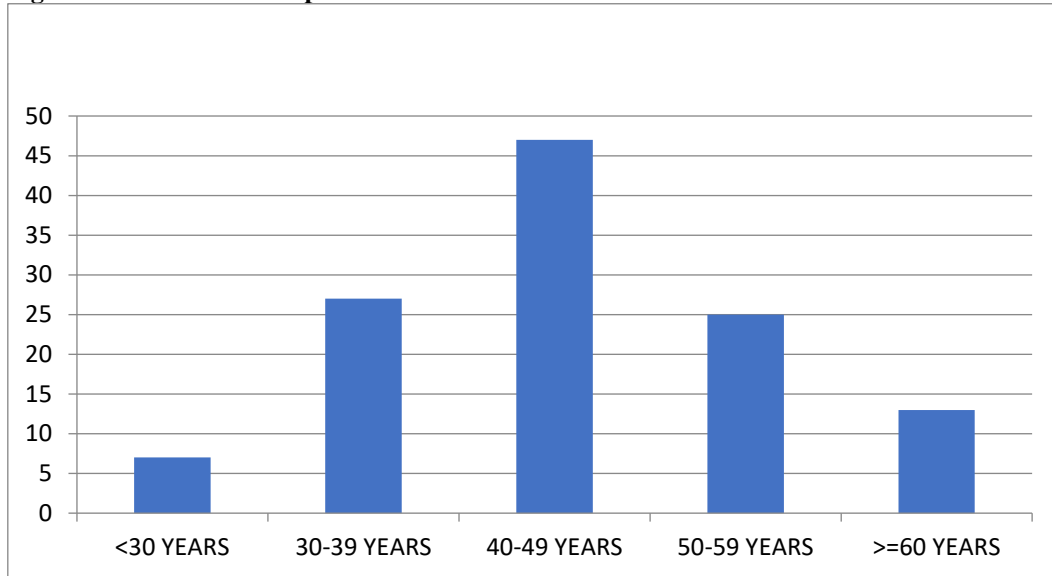
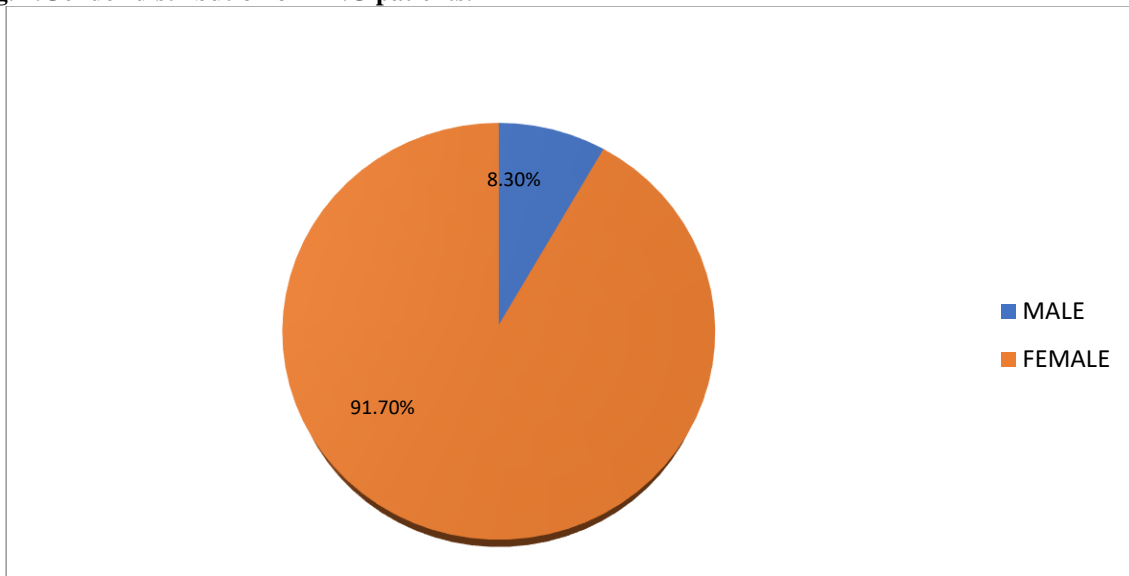


Fig. 2. Gender distribution of MNG patients.



Most of the MNG patients studied were found to reside in urban areas, with only 23.3 percent of them found to reside in rural settings. MNG patients' educational attainment was broken down as follows: 29.2% were illiterate, 55.8% were in the primary school grades, 10.8% were in the secondary grades, and 4.2% were in the college or university grades. All of the patients with MNG who were part of the research were Arabs or Muslims. Table 2 displayed all of these findings.

Table-2: Social characteristics of MNG patients.

Variable	No.	%
Residence		
Urban	92	76.7
Rural	28	23.3
Total	120	100.0
Educational level		
Illiterate	35	29.2
Primary	67	55.8
Secondary	13	10.8
Higher education	5	4.2
Total	120	100.0
Ethnicity		

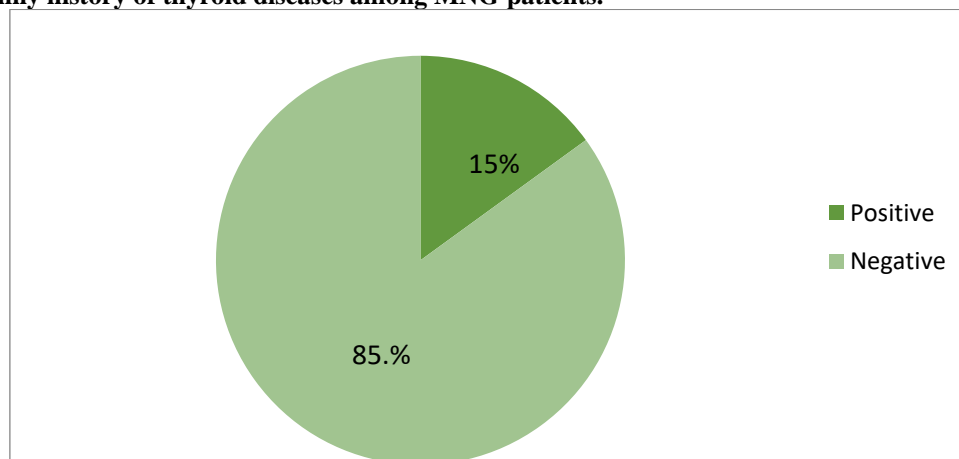
Arab	120	100.0
Kurdish	0	
Turkmen	0	
Total	120	100.0
Religion		
Muslim	120	100.0
Christian	0	
Others	0	
Total	120	100.0

Nearly two thirds (65.8%) of MNG patients did not smoke, while 15.8% of them were active smokers and 18.3% were former smokers. One-fifth of MNG patients had a family history of thyroid cancer, while only one-third of MNG patients had a family history of radiation exposure. There is a detailed breakdown of these findings in Table 3 and Figure 3.

Table 3: Clinical history of MNG patients.

Variable	No.	%
Smoking status		
Smoker	19	15.8
Ex-smoker	22	18.3
Non-smoker	79	65.8
Total	100	100.0
Family history of thyroid malignant diseases		
Positive	18	15.0
Negative	102	85.0
Total	120	100.0
History of exposure to ionizing radiation		
Positive	3	2.5
Negative	117	97.5
Total	120	100.0

Fig. 3. Family history of thyroid diseases among MNG patients.



At the time of diagnosis, all MNG patients were euthyroid. Twenty-six MNG patients (21.7 percent) had differentiated thyroid carcinoma, while eighty-seven MNG patients (78.3 percent) were found to be benign. MNG patients' histopathology revealed colloid goitre in 40.8%, follicular adenomas in 37.5%, micro-papillary carcinoma in 17.5%, and follicular carcinoma in 4.16% of cases. These findings were depicted in Table 4 and Figs. 4 and 5, respectively.

Table 4: Investigations findings of MNG patients.

Variable	No
TFT at time of diagnosis	
Euthyroid	120
Total	120
FNA findings	
Differentiated carcinoma	26

Benign	94
Total	120
Histopathology findings	
Colloid goiter	49
Micro-papillary carcinoma	21
Follicular adenoma	45
Follicular carcinoma	5
Total	120

Fig. 4.FNA findings.

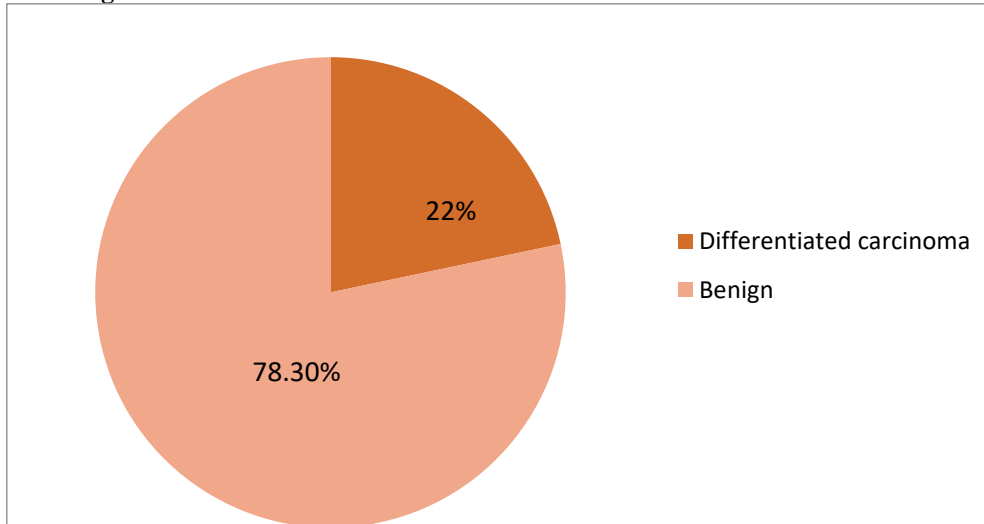
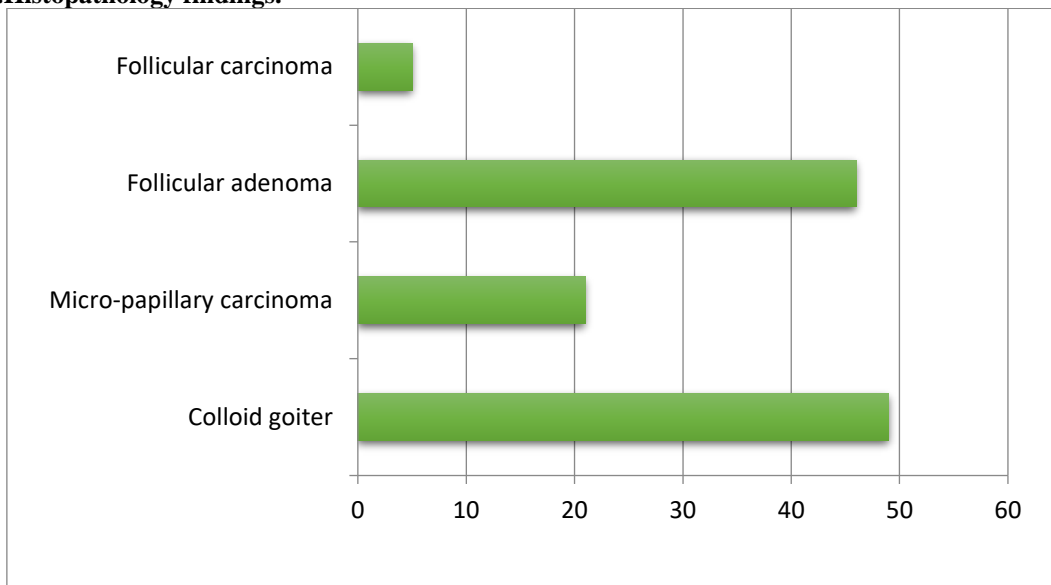


Fig. 5.Histopathology findings.



According to age and gender, there was no statistically significant difference between MNG patients with differentiated cancer and those with benign MNG. In Table 5, you'll see a summary of these findings.

Table 5: Distribution of demographic characteristics according to FNA findings.

Variable	Carcinoma		Benign		P
	No	%	No	%	
Age					0.1 ^{aNS}
<30 years	3	11.5	5	5.3	
30-39 years	2	7.7	25	26.6	
40-49 years	10	38.5	37	39.4	
50-59 years	9	34.6	16	17.0	

60 years	2	7.7	11	11.7	
Mean ± SD (years)	45.1 ± 12.6		43.5 ± 11.3		0.5 ^{bNS}
Gender					0.5 ^{aNS}
Male	3		7	7.4	
Female	23		87	92.6	

According to their residence and educational level, there was no significant difference between MNG cancer patients and those with benign MNG. Table 6 summarised all of these findings.

Table 6: Distribution of social characteristics according to FNA findings.

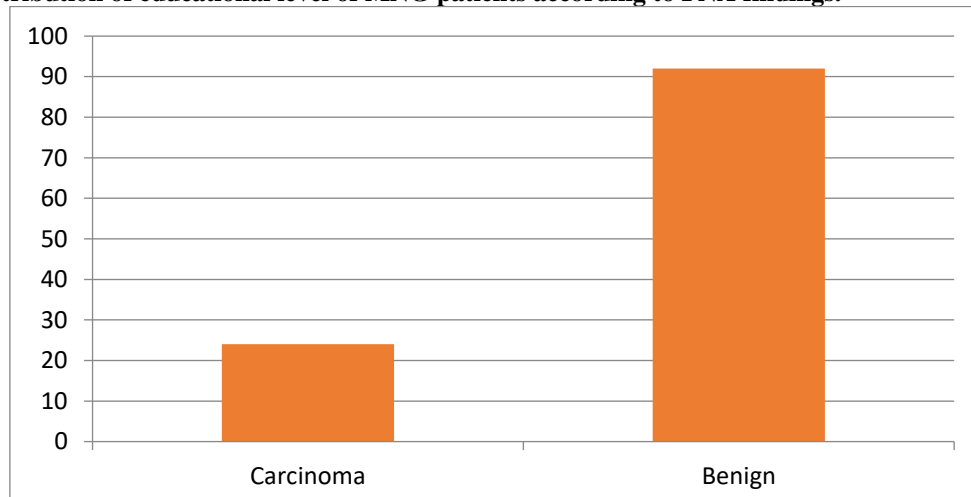
Variable	Carcinoma		Benign		P
	No	%	No	%	
Residence					0.3 ^{aNS}
Urban	18	69.2	74	78.7	
Rural	8	30.8	20	21.3	
Educational level					0.7 ^{bNS}
Illiterate	8	30.8	27	28.7	
Primary	13	50.0	54	57.4	
Secondary	3	11.5	10	10.6	
Higher education	2	7.7	3	3.2	

The current smoking status of MNG patients was strongly linked to the development of differentiated carcinoma (p 0.001). There was no significant difference in family history of thyroid disease between MNG patients with differentiated carcinoma and benign MNG. P 14 0.02 showed an association between MNG patients' history of ionising radiation exposure and the development of differentiated carcinoma. Table 7 and Fig. 6 show all of these findings.

Table 7: Distribution of clinical history according to FNA findings.

Variable	Carcinoma		Benign		P
	No	%	No	%	
Smoking status					<0.001 ^{aS}
Smoker	16	61.5	3	3.2	
Ex-smoker	3	11.5	19	20.2	
Non-smoker	7	27.0	72	65.6	
Family history of thyroid diseases					0.07 ^{aNS}
Positive	1	3.8	17	18.1	
Negative	25	96.2	27	81.9	
History of exposure to ionizing radiation					0.05 ^{aS}
Positive	2	7.7	1	1.1	
Negative	24	92.3	93	98.9	

Fig. 6. Distribution of educational level of MNG patients according to FNA findings.



When the results of histopathology and FNA were compared, a highly significant correlation ($p < 0.001$) was found. All MNG patients whose FNA results indicated cancer were also diagnosed as cancerous when the results of histopathology were examined. Table 8 summarised all of these findings.

Table 8: Distribution of histopathology findings according to FNA findings.

Variable	Carcinoma		Benign		P
	No	%	No	%	
Histopathology findings					<0.001 ^{as}
Colloid goiter	0	-	49	52.12	
Micro-papillary carcinoma	21	80.8	0	-	
Follicular adenoma	0	-	45	47.87	
Follicular carcinoma	5	19.2	0	-	
Total	26	100	94	100	

DISCUSSION

Most nodules diagnosed as benign are in fact multinodular goitre (MNG), which is still common in areas where iodine deficiency is prevalent, especially among women [20]. However, the possibility of malignancy exists, particularly for differentiated thyroid carcinoma, as both conditions share the same risk factors.

21.7 percent of patients with MNG were found to have differentiated thyroid carcinoma by FNA and histopathology in the current study. Dedifferentiated thyroid carcinoma (DTC) incidence in Al-Kindi Teaching Hospital in Iraq was 8.7 percent in the study by Matar et al. [21]. Baghdad Medical City's hospitals, which are tertiary centres, receive most of the MNG cases that are considered to be suspicious or complicated. Dedifferentiated thyroid carcinoma (DTC) was detected and confirmed in 21.3 percent of MNG by FNA and histopathology in a study by Al-Salamah et al. [22] in Saudi Arabia. Kaliszewski et al. found a lower incidence rate in their study. Thyroid cancer was found in 2.12% of patients with MNG, according to a Polish study [23]. In addition to differences in methodology and sample size, this discrepancy between two studies could be explained by differences in associated risk factors and lifestyles between communities. The incidence of thyroid carcinoma among patients with goitre was 8.8 percent in a previous Iraqi study [24] carried out over a period of three years at Al-Hilla Surgical hospital. Thyroid cancer incidence has risen in recent decades and around the world due to lifestyle changes, obesity prevalence, and higher levels of exposure to ionising radiation, as well as an increase in the prevalence of MNG due to iodine deficiency (as documented by Pellegriti et al. [20] study in Italy). It was found that the Scopa study in Greece stated that the incidence of differentiated carcinoma among MNG goitre patients was 4e17 percent worldwide, and papillary carcinoma accounts for about 80 percent of thyroid carcinomas. For MNG patients, preoperative diagnosis of differentiated thyroid carcinoma with different diagnostic materials is always inaccurate, even if fine needle aspiration is used before surgery. [17] It is common for MNG patients to have a post-operative diagnosis of thyroid cancer discovered by

histopathology. Patients with MNG have a lower incidence of differentiated thyroid carcinoma than those with a single nodule, but it is more difficult to diagnose cancer in these patients than in those with a single nodule. [20,25]

Differentiated carcinoma was found to most commonly have one histopathology type: micro-papillary carcinoma. There was a 14 percent incidence rate for thyroid carcinoma in MNG patients after thyroidectomy, with an 84% prevalence rate for papillary carcinoma, according to the Turkish study by Tas ova et al. [26] Our histopathology results also showed that follicular adenoma was a common benign finding in MNG patients. Papillary carcinoma was found to be the most common type of differentiated carcinoma among MNG patients (85.7%), and an adenoma was found to be the most common benign tumour in this study (53 percent). A study done in Iraq by Al-Hashimi, on the other hand, found that the most common form of differentiated thyroid cancer in MNG patients, namely papillary carcinoma, had undergone significant changes in thyroid pathology and surgical trends. [7]

There was no discernible difference in educational attainment between patients with carcinoma and those with benign thyroid MNG, according to our findings. According to the Aschebrook-Kilfoy et al. [27] study in China, patients with low educational levels were more likely to develop thyroid cancer than those with higher levels of education, but this finding contradicts that finding. There is a strong link between low socioeconomic status and a poor quality of life, two risk factors for thyroid cancer [28]. Low socioeconomic status of MNG patients was found to be a risk factor for thyroid carcinoma metastasis, particularly follicular type, in a study in India.

Patients with MNG who are current smokers are significantly more likely to develop differentiated carcinoma ($p < 0.001$), according to our study. Sawicka-Gutaj and colleagues [29] in Poland found that smoking had a number of negative effects on thyroid health, including an increase in the incidence of MNG and an increase in the risk of developing thyroid cancer. A study conducted in the United States by Kitahara et al. [30] found that alcohol consumption and cigarette smoking reduced the risk of papillary

thyroid carcinoma. There may be some inconsistency here due to the presence of other risk factors for smoking in our study, in addition to variations in socioeconomic factors and lifestyle. Many thyroid diseases, including multinodular goitre, have been linked to smoking cigarettes, according to the Vestergaard et al. [31] study in Denmark.

Differentiated carcinoma was found in MNG patients who had been exposed to radiation in the past (p 14 0.02), according to the results of the current study. According to Nikiforov et al. [32] study in the United States, long-term exposure to ionising radiation increases the risk of thyroid carcinoma. Thyroid cancer is a significant risk factor in the workplace, especially for those in jobs that expose them to ionising radiation, according to a study by Aschebrook-Kilfoy et al. [33]. Long-term exposure to ionising radiation has been linked to autoimmune thyroiditis and multinodular goitre by some researchers.

A study published in the journal Pathology found that MNG patients' FNA results were strongly linked to histopathology findings (p 0.001). Sharma study in India [34] found that FNA is an invasive but highly accurate diagnostic technique for the diagnosis of thyroid cancer in MNG patients with significant correlation to histopathology findings. This finding is similar to the findings of that study. However, FNA was not found to be the first line of diagnosis for multinodular thyroid disease by Gupta et al. [35] FNA with ultrasound imaging is the first-line diagnosis of thyroid cancer in Iraq because of its cost-effectiveness and non-invasiveness [7,21].

LIMITATIONS OF THE STUDY

1. As other cross sectional studies, temporal relationship is difficult to be assessed.
2. Small sample size.
3. Single center study.

CONCLUSION

Dedifferentiated thyroid carcinoma (DTC) is common in patients with multiple goitre lesions. Patients with multi-nodular goitre are more likely to have the thyroid cancerous tumour papillary carcinoma. Follicular adenoma was the most common benign thyroid tumour in patients with multinodular goitre. Risk factors for differentiated thyroid carcinoma in multinodular goitre patients included illiteracy, smoking, and radiation exposure. For differentiated thyroid, a fine needle aspiration test has a high degree of accuracy and reliability.

RECOMMENDATIONS

- Patients with multinodular goitre should be encouraged to have a fine needle aspiration cytology performed prior to surgery.
- Doctors are increasingly using fine needle aspiration to make first-line diagnoses because of

its high level of confidence and strong correlation to histopathology.

- surgeons should take into account factors such as illiteracy, smoking and exposure to ionising radiation when performing thyroid cancer surgeries.
- Research on the incidence of thyroid cancer in patients with a multinodular goitre should be supported by large multicenter studies.

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