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Differential Thyroid Cancer In Multinodular Goiter; Review Of 96 Cases

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Abstract

The global prevalence of multinodular goiter is high, with most cases occurring in developing countries. Previously published literature revealed that the incidence of differentiated thyroid carcinoma among patients with multinodular goiter has risen. This study aims to determine the frequency of differentiated thyroid cancer in multinodular goiter patients. This cross-sectional study was done among 96 patients with multinodular goiter admitted to the surgical ward in Imam Hussein Teaching Hospital/ AL-Nasiriyah-Iraq from 1 February 2021 to 31 January 2022. The mean age was 39.4 years old. Females were predominant 79/96 (82.3 %). 32% of the multinodular goiter patients had differentiated thyroid carcinoma by histopathology, while it was 21% by fine needle aspiration. The histopathology of multinodular goiter patients revealed that 67.7% had endemic goiter, 19.8% had papillary carcinoma, and 9.4% had Follicular thyroid carcinoma. Smoking and older age were both significantly associated with differentiated thyroid carcinoma in patients with multinodular goiter. **In conclusion,** with a high proportion of malignancy among multinodular thyroid goiter participants by FNA and histopathology, acceptable needle aspiration test result was a low-accurate tool for differentiated thyroid carcinoma diagnosis.

Keywords: AL-Nasiriyah, Differentiated thyroid cancer, Imam Hussein Teaching Hospital, MNG.

Introduction

The thyroid gland is among the most commonly impacted endocrine glands by various diseases. It is the largest endocrine gland (1). Goiter is a French word that means throat. Thyroid carcinoma (TC) is the most common kind of cancer of the endocrine glands, while being a very uncommon tumor. It accounts for 1% of all human neoplasia, with yearly incidence estimates ranging from 0.5 to 10 per 100,000 globally (2). Ionizing radiation, thyroid adenoma and multinodular goiter (MNG), familial history of thyroid cancer, and personal history of goiter or thyroid nodule have all been identified as risk factors(3). The American Cancer Society (ACS) predicts 52,890 new thyroid cancer cases in 2023, with 12,720 men and 40,170 women. Female Chinese inhabitants of

Hawaii had the highest incidence of thyroid carcinomas in the world (4). Papillary cancer accounts for 74-80% of all thyroid cancers. In areas where goiter is frequent, the risk of follicular carcinoma is increased (5). The Pathology of multinodular goiter starts as visibly swollen and deformed. The size of the lobes varies greatly. The gland's surface is knobby, enclosed by a stretched but intact capsule (6). A solid, rapidly developing, painless nodule detected by the patient or during a clinical examination is the most prevalent clinical marker of thyroid cancer. Thyroid cancer is diagnosed via ultrasound and fine-needle aspiration (FNA) (7). Previously, the incidence of incidental thyroid cancer (ITC) in multinodular goiter (MNG) was thought to be 5-10%; however, subsequent investigations have found higher ITC prevalence rates, ranging from 8.6 to 22 percent. Many surgeons prefer total thyroidectomy for MNG, particularly in areas where iodine deficiency is widespread (8, 9). Thyroid cancer in the multinodular thyroid is as follows: (A) Papillary carcinoma (PTC) is the most prevalent kind of well-differentiated thyroid cancer, as well as the most common type of thyroid cancer, which might be caused by radiation exposure(10). The age, gender, and stage determine its prognosis. In most cases, life expectancy is unaffected if cancer does not spread beyond the gland's capsule (11). Females and patients under the age of 40 have a better prognosis. (B) Follicular thyroid carcinoma (FTC) is the second most prevalent thyroid cancer; the majority of FTCs are slow-growing and have a pretty good prognosis (12). Differentiated thyroid cancers include follicular and papillary thyroid tumors, which together account for 95% of thyroid cancer cases (13, 3). Moreover, the most dangerous type cancer is the anaplastic carcinoma of thyroid (ATC), although ATC affected only less than 2% of all thyroid cancers and responsible for up to 40% of thyroid cancer mortality. According to reports, the total 5-year survival rate is less than 10%, and most patients do not live more than a few months following diagnosis (14,15). Review of literature revealed scarce publications regarding thyroid cancer in multinodular goiter. Consequently, this study designed to determine the frequency of differentiated thyroid cancer in multinodular goiter patients.

Materials and Methods

A descriptive cross-sectional study with analytic elements. The study was carried out in the Surgical Ward of Imam Hussein Teaching Hospital/ AL-Nasiriyah-Iraq during the period from 1st of February, 2021 to 31st of January 2022. All procedures were done according to the Helsinki Declaration and later amendments for human research. All patients received complete information about the aim and nature of the study and signed an informed consent form before enrollment in the study. The research plan was approved by the ethical committee, College of Medicine /Al-Muthanna University 2022. The 96 patients were involved in this study including adult patients (over 18 years, with multinodular goiter and have factors raising the suspicion of malignancy (hard, irregularity, rapid growth and micro-calcifications). 44 patients were excluded due to have toxic goiter, solitary nodule or proved thyroid cancer with metastasis. A purposive (Convenient) sampling technique was adopted because of time limitations. The data collected through a self-administered form distributed to all patients with multinodular goiter included in the sample who completed a pre-constructed questionnaire sheet. The questionnaire was designed by the researchers, the data included the demographical characteristics (Age, gender, residency, marital status), past medical history, FNA finding and histopathological finding. Following the intake of history and information from chosen multinodular thyroid goiter patients; necks of the patients were examined clinically to determine thyroid enlargements and lymph node status as well as a

laryngoscope assessment of vocal cord mobility by an ENT specialist. A pathologist in the hospital performed fine needle aspiration on all of the patients who examined. Following a thorough examination by an anesthesiologist, the patients were surgically operated on for total or near total thyroidectomy by a team of expert surgeons. The histopathology examination of specimens was done in some cases in hospital; others are handled by Histopathologist in a private laboratory. The data were coded and each questionnaire assigned with a serial identifying number then entered by the researchers into the computer using (SPSS) version26. Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of the difference in different percentages (qualitative data) was tested using the Pearson Chi-square test. Statistical significance was considered whenever the P-value was equal to or less than 0.05.

Results

The majority of the participants in our study were females 79 (82.3 %). The mean age was 39.4 years old with a ± SD of 11.2. (69.8%) was living in an urban area. About half of the participants had a low educational level, while 28% had a secondary school education, and 23.9% finished their college or post-graduation degree. A family history of thyroid diseases was found among 15 participants. For comorbidity factors, 27.1% of the participants had diabetes, 36.5% of them were Hypertensive, and 21.9% were smokers (Table 1).

Table. 1: Demographic characteristics of participants (N=96)

Demographic characteristics	**Value**	**Number (N = 96)**	**%**
Age	< 30 years old	9	9.4
	30 - 50 years old	51	53.1
	> 50 years old	36	37.5
Age (Mean ± SD)	39.4±11.2 years		
Sex	Male	17	17.7
	Female	79	82.3
Residency	Urban	67	69.8
	Rural	29	30.2
Education	Illiterate	16	16.7
	Primary school	30	31.3
	Secondary school	27	28.1
	College and post-college	23	23.9
Family history of thyroid diseases	No	81	84.4
	Yes	15	15.6
Diabetes Mellitus	No	70	72.9
	Yes	26	27.1
Hypertension	No	61	63.5
	Yes	35	36.5
Smoking	No	63	65.6
	Yes	21	21.9
	X-Smoker	12	12.5

Figure. 1 reveals that more than two-thirds of the participants (70%) lived in an urban area, while the rest (30%) lived in a rural area. Figure. 2 shows that 31 (32%) of the participants had differentiated malignant thyroid by the gold-standard histopathology, while 65 (68%) had benign thyroid cells.

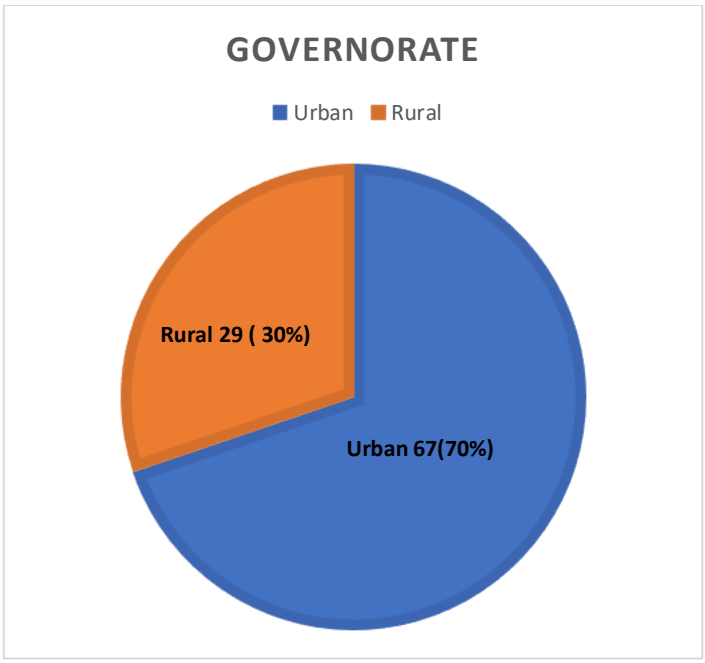

Figure.1: the distribution of the participants according to the geographical area.

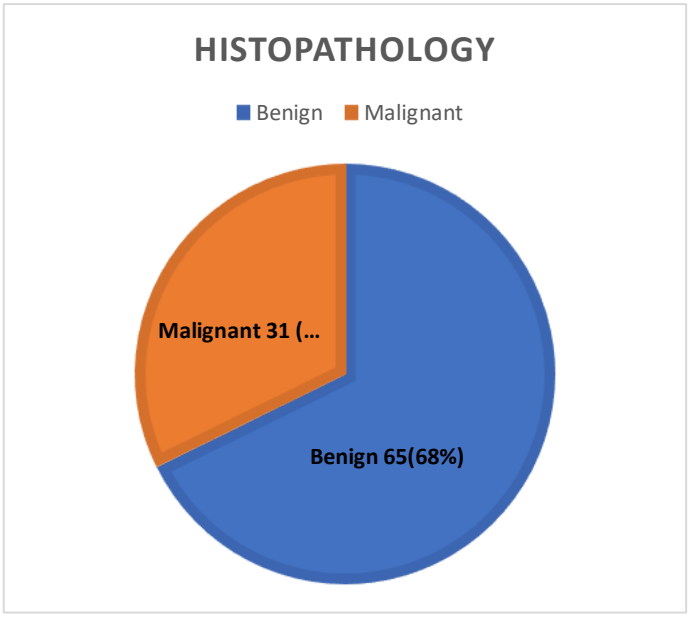

Figure. 2: Distribution of the participant's histopathology

According to the result of fine needle aspiration cytology, malignancy among multinodular goiter was found among 20 (20.8%) of the participants, and the remaining 76 (79.2%) were benign, as shown in (Figure. 3).

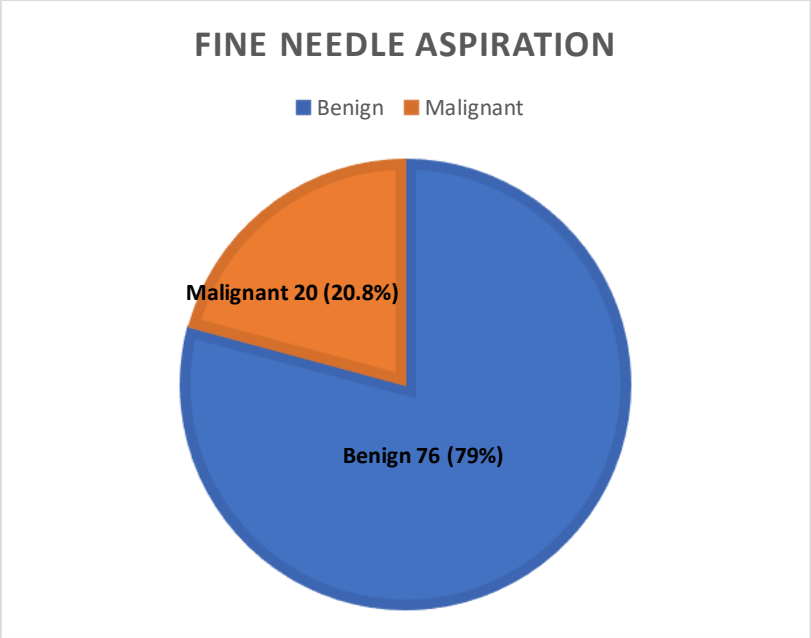

Figure. 3: Distribution of the participant's fine needle aspiration results.

Goiter was found in 65 (67.7%) of the participant's histopathology, followed by Papillary carcinoma in 21 (21.9%), Follicular thyroid carcinoma in 9 (9.4%), and only one case (1.0%) had Hurthle cell carcinoma (Figure 4).

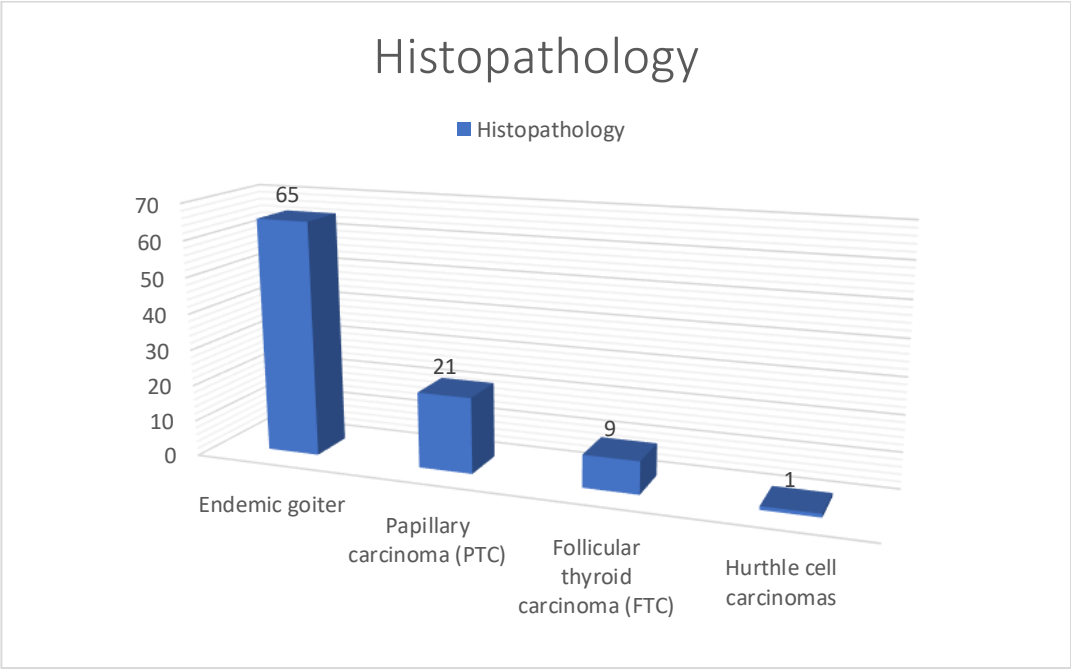

Figure. 4: Distribution of the histopathology findings of the participants**.**

There was a significant difference between the mean age of the thyroid differentiated carcinoma and benign condition as p value was less than 0.05. The other socio-demographic factor was the statistically insignificant difference between malignancy and benign thyroid multinodular goiter (Table 2).

Table. 2: The association between malignancy and benign thyroid goiter with the socio-demographic characteristics.

Variable	Value	Malignancy N=31 (%)	Benign N=65 (%)	P value
Age	< 30 years old	3 (9.7%)	6 (9.2%)	0.181
	30 - 50 years old	16 (51.6%)	35 (53.9%)	
	> 50 years old	12 (38.7%)	24 (36.9%)	
Age (Mean ± SD)		41.45±6.894	38.48±12.886	**0.002**
Gender	Male	6 (19.4%)	11 (16.9%)	0.315
	Female	25 (80.6%)	54 (83.1%)	
Residency	Urban	22 (71.0%)	45 (69.2%)	0.716
	Rural	9 (29.0%)	20 (30.8%)	
Education	Illiterate	6 (19.4%)	10 (15.4%)	0.617
	Primary school	10 (32.2%)	20 (30.7%)	
	Secondary school	9 (29.0%)	18 (27.7%)	
	College and post college	6 (19.4%)	17 (26.2%)	

There is a significant association between smokers and differentiated carcinoma of the thyroid compared to benign thyroid goiter, as the p-value was less than 0.05, as shown in Table. 3.

Table. 3: The Association Between Malignancy And Benign Thyroid Goiter With The Comorbidity Factors.

Comorbidity factors	Value	Malignancy N=31 (%)	Benign N=65 (%)	P value
Family history of thyroid Disease	No	29 (93.5%)	52 (80.0%)	0.119
	Yes	2 (6.5%)	13 (20.0%)	
Diabetes Mellitus	No	20 (64.5%)	50 (76.9%)	0.259
	Yes	11 (35.5%)	15 (23.1%)	
Hypertension	No	17 (54.8%)	44 (67.7%)	0.211
	Yes	14 (45.2%)	21 (32.3%)	
Smoking	No	7 (22.6%)	56 (86.2%)	**0.012**
	Yes	16 (51.6%)	5 (7.7%)	
	X-Smoker	8 (25.8%)	4 (6.1%)	

Table.4 shows that there was statistically significant association between histopathological finding as malignant or benign thyroid multinodular goiter with the FNA finding (Table 4).

Table 4 The Association Of Fine Needle Aspiration Results With The Histopathology Finding**.**

Variable		Histopathology		P value
		Malignancy N=31 (%)	Benign N=65 (%)	
Fine needle aspiration	differentiated thyroid carcinoma	12 (60.0%)	8 (40.0%)	0.004
	Benign goiter	19 (25.0 %)	57 (75.0%)	

However, Table 5 shows that the FNA's sensitivity to diagnose differentiated carcinoma in multinodular goiter was 60%, specificity 75%, and overall accuracy 71.9% (Table 5).

Table. 5: the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of the fine needle aspiration test in diagnosis of differentiated carcinoma among multinodular goiter patients.

Performance	Differentiated carcinoma by FNA in Multinodular goiter
Sensitivity	60.0%
Specificity	75.0%
Positive predictive value	38.7%
Negative predictive value	87.7%
Accuracy	71.9%

Discussion

Multinodular goiter (MNG) still seems common in iodine-deficient areas, particularly among women. Although the majority of these nodules are benign, the possibility of malignancy exists, particularly for differentiated thyroid cancer, as both illnesses share the same risk factors (16). According the results of the current study, participants between 30 and 50 years were the most common age group for carcinoma associated with multinodular goiter. This result was compatible with the finding reported by Yogish *et al.*,(2019) (17) study that patients between 31 and 40 years of age (38.09%) were most commonly affected by thyroid gland carcinoma. However, the differences between benign and malignant goiter in this age group were found to be insignificant. Females were the predominant gender, 79 (82.3%), in the current study compared to males, 17 (17.7%). This finding was close to that of Mishra *et al.*, (2022)(18), a study done in India in 2021, which found that the majority of the participants in that study were females (110), against only (10) males with multinodular goiter with differentiated cancer. The majority of the participants in this study lived in an urban area (69.8%) while the rest were from a rural area, and this compatible with a previous study done in Baghdad by Ghadhban *et al.*,(2018) (19) in the urban area patients represented about (76.7%) in his study. About one-third of our study participants had a primary school education level, followed by 28.1% who had a secondary school education level and 23.9% who finished college or post-college education level. These results were almost the same as those of the Satapathy *et al.*, (2014) (20) study, which reported that the low socioeconomic status of multinodular goiter patients was a risk factor for metastasis with thyroid carcinoma, especially follicular type. However, the current study finding was not significant. Xu *et al.*, (2012) (21)reported that 9 (4.8%) had a first-degree family history of thyroid cancer, La Quaglia *et al.*, (2000) (22) reported that (10%) of the patients in his study had a family history; these results were higher proportion than the current study result that found the family history was found in about 15.6% of the participants of the current study; however, the current study found that there was no association between family history of previous thyroid disease with the development of differentiated thyroid cancer and this was against the result mentioned in a study done in Italy by Botrugno *et al.*, (2011) (23) that the family history of thyroid disease seemed to be one of the factors associated with an increased risk of incidental carcinoma. At the same time, Ghadhban *et al.*,(2018) (19) found that there was no association between a family history of thyroid disease and the development of differentiated thyroid cancer. These differences might be due to the effect of sociodemographic features in different countries on the genetic expression related to thyroid diseases. Also, the current study's

sample size was smaller than the other studies. Smoking and previous smoking participants were found to be significantly associated with the development of differentiated thyroid cancer in the current study, and this finding was the same finding mentioned by Ghadhban *et al.*,(2018) (19) and Vestergaard et al., (2002) (24) studies that smoking cigarettes is a significant risk factor for many thyroid diseases including multinodular goiter. While Kitahara et al., (2012) (25) found that smoking reduced the risk of papillary thyroid carcinoma. These discrepancies might be due to the differences in socioeconomic features and lifestyles between the study's population, as well as the presence of other risk factors associated with smoking in our study. About 20.8% of the FNA findings were malignant, while 79.2% were benign in the current study, and this finding was close to the results mentioned in studies done in Iraq previously (Ghadhban *et al.*, 2018) (19), who mentioned that 21.7% of the findings were malignant in FNA. Matar *et al.*, (2016) (26) reported that the incidence of differentiated thyroid carcinoma was 8.7%; the cause for this discrepancy may be due to the incidence of Differentiated TC (DTC) increased more than threefold in the last two decades, as mentioned by Drozd *et al.*, (2020) (27). Papillary carcinoma represented 19.8% of the thyroid histopathological results, and this finding was closed to the result mentioned by Burkan *et al.*, (2021) (28) study that Papillary carcinoma was found in 18% of his study participants; also, he concluded that Papillary thyroid cancer was the primary type of differentiated thyroid cancer which was 76% and this also was close to our study finding as Papillary thyroid cancer represented the primary type of differentiated thyroid cancer in about 61.3%.; the same conclusion was mentioned by Al-Qurayshi *et al.*, (2020) (29) that (69.6%) of the participants had papillary thyroid cancer. Follicular thyroid carcinoma (FTC) in the current study was found to be the second most common type of differentiated thyroid cancer, and this result was the same conclusion mentioned by Al-Qurayshi *et al.*, (2020) (29) and Satapathy *et al.*, (2014)(20). Hurthle cell carcinomas were found in only one case in our study, and this was the result mentioned by Burkan *et al.*, (2021) (28), who had only one case among multinodular goiter participants in the study. The current study found a significant association between FNA findings and histopathology. Moreover, this association was against the result mentioned by Gupta et al., (2010) (30) that the association was clear between FNA finding with histopathology finding in the solitary nodule but not in multinodular goiter. At the same time, it was going on with the result of Ghadhban *et al.*, (2018) (19) study that was done in Iraq found a significant association between the FNA finding and histopathology in multinodular goiter patients. Thyroid fine needle aspiration was shown to have a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 60.0 %, 75.0 %, 38.7 %, 87.7 %, and 71.9 %, respectively. The sensitivity of FNA cytology is relatively low in our study compared to published studies from other countries, where the sensitivity, specificity, and accuracy of FNA cytology are greater than 94 percent, as reported by Muratli et al., (2014) (31) in their study conducted in Turkey. These cases need to thoroughly assess the situation and consider ways to increase the sensitivity of FNA cytology in the identification of multinodular thyroids and the degree of skill in cytology.

In conclusion, this study showed a high proportion of malignancy among multinodular thyroid participants by FNA and histopathology. The commonest differentiated thyroid carcinoma type among multinodular goiter patients was papillary carcinoma. The significant risk factors for differentiated thyroid carcinoma among multinodular goiter patients are the age and smoking, while gender, family history, and education level were not related to the development of malignancy among multinodular thyroid goiter

patients. The fine needle aspiration test result was not a perfectly accurate tool for differentiated thyroid carcinoma diagnosis compared to the gold standard histopathology test. The authors recommend patients with goiter follow the medical institution and ask for more advice and tests to diagnose the exact problem of his or her thyroid problem and the type of goiter they have. The researcher have to attention to multinodular goiter as a high proportion of multinodular goiter developed malignancy, mainly differentiated thyroid carcinoma. The easy use of FNA to screen patients with multilocular goiter must be accomplished with the increase of the test's accuracy, sensitivity, and specificity by further training on the ideal approach. Risk factors for thyroid carcinoma, like old age and smoking among multinodular thyroid goiter, should be taken into consideration by surgeons. Further national multi-center studies are needed to assess the morbidity and mortality among differentiated thyroid carcinoma in multinodular goiter patients and the role of early detection by FNA in decreasing morbidity and mortality.

DECLARATIONS

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Competing interests statement

The authors declare that they have no conflict of interest in publish this article.

Ethics statement

This study was approved by the ethical committee /College of Medicine /Al-Muthanna University 2022. The authors confirm that the journal's ethical policies, as noted on the journal's author guidelines page, have been adhered to. The study procedures were conducted according to the Helsinki Declaration and later amendments for human research. All patients signed an informed consent form before enrollment in the study.

Author contributions

ARA: provided the concepts, data analysis, and writing of the manuscript. **KOHA:** worked on data collection, analysis, and writing of the manuscript. **MAA:** contributed to data collection, analysis, and manuscript revision.

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