

FREQUENCY AND HISTOPATHOLOGICAL SPECTRUM OF MALIGNANCY IN NON-TOXIC MULTINODULAR GOITRE: A CROSS- SECTIONAL STUDY

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DOI: <https://doi.org/10.5281/zenodo.21485232>

Keywords

Article History

Received: 01 May 2025

Accepted: 01 July 2025

Published: 14 July 2025

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Abstract

Objective:

To examine the histopathological range of thyroid malignancy and its frequency in patients with Non-Toxic Multinodular Goitre (NTMNG) undergoing surgery.

Material & Methods:

This descriptive cross-sectional study examined the sample population in the Surgical Unit II, Department of General Surgery, of Jinnah Postgraduate Medical Centre (JPMC), Karachi. The sample population included 113 patients with euthyroid NTMNG who underwent a clinically indicated thyroidectomy within six months of NTMNG surgery after obtaining ethical approval from the institution. Demographic and clinical details were entered. Data related to the procedure and the histopathology of the thyroid were also documented. The categorical variables, for which comparisons were required, were analyzed by using appropriate exact tests. A P-value of <0.05 was taken to indicate the presence of a significant relationship.

Results:

The average age of the study population was 44.3 (range, 35-52) years. There were 94 females (83.2% of the total population). 10.6% (n=12) (95% CI 6.2% to 17.6%) were diagnosed with malignancy after histopathological examination. Of those confirmed with malignancy (n=12), 10 cases (83.3%) were diagnosed with papillary carcinoma and 2 cases (16.7%) were diagnosed with follicular carcinoma. Multinodular goitre, which was bilateral (p=0.034), compressive

goitre symptoms ($p<0.001$), and palpable cervical lymphadenopathy ($p<0.001$) were significantly associated with malignancy. Lymphadenopathy and the compressive symptom of goitre were also significantly associated with the nature of surgery ($p=0.001$). Family history of malignancy was not significantly associated with multinodular goitre.

Conclusion:

Approximately one in ten surgically managed patients with NTMNG had malignancy on final histopathology, most commonly papillary carcinoma. Cervical lymphadenopathy and suspicious clinical presentation should prompt careful preoperative risk stratification.

INTRODUCTION

The incidence of thyroid cancer is rapidly increasing worldwide. Being the most prevalent endocrine cancer, its prevalence is partly spurred by technological advancements.^{1,2} Imaging technologies are now more sensitive and more capable of detecting small and differentiated tumours. Multinodular goitre is a thyroid disorder characterized by repeated growth of hyperplastic nodules. Non-toxic multinodular goitre (NTMNG) refers to a multinodular thyroid disorder that occurs in the absence of hyperthyroidism. NTMNG can result in a swelling of the neck, difficulty in swallowing and breathing, hoarseness in the voice, and may be due to aesthetic concerns.³⁻⁵ Despite most thyroid nodules being benign, a malignant diagnosis may be of concern due to delayed treatment or may be more aggressive after a limited intervention. Modern nodule assessment involves clinical exam, serum levels of thyroid-stimulating hormone, high-resolution ultrasound, and risk-stratified fine-needle aspiration, and in selected indeterminate lesions, molecular testing.^{4,6} A 2022 meta-analysis reported that the pooled risk of malignancy for multiple nodules was not statistically different from that of solitary nodules. In one large surgical series, carcinoma was found in 31.7% of multinodular gland.^{7,8} Reported frequencies of malignancy vary widely due to differing referral patterns, different iodine status, eligibility criteria, preoperative cytology, and papillary microcarcinoma. There have also been changes in histological taxonomy under the new 2022 World Health Organization classification scheme, which separates benign tumors, low-risk neoplasms, and malignant follicular cell-derived tumors.⁹ Recent

thyroidectomy series have, however, reported that papillary carcinoma is the most common malignant subtype in multinodular goiter.¹⁰⁻¹²

Pakistan studies have shown a notable variation in the rates of malignancy in multinodular goiter in which surgery was performed are 8%, 11.6%, and 31.8%.¹³⁻¹⁵ Case-close surveys are therefore clinically important for guiding patient information and evaluation of suspicious clinical features, as well as determining the extent of surgery. Thus, this study aimed to investigate the spectrum and histopathologic variations of malignancy in patients undergoing surgery for NTMNG in a tertiary surgical unit in Karachi.

MATERIAL & METHODS

This study was a descriptive cross-sectional study performed at Surgical Unit II, Jinnah Postgraduate Medical Centre. The study was conducted over a period of six months after receiving the ethical clearance from the respective committee. The sample size was determined using the OpenEpi Version 3 for a single population proportion, with a presumed occurrence of malignancy of 8%, a 95% confidence interval, and an absolute error of 5%. The sample size was set at 113 participants recruited using non-probability purposive sampling.

Participants included patients who had NTMNG as defined by a thyroid that was enlarged with at least two discrete nodules that were considered to have normal thyroid function, along with the thyroidectomy that was followed by a conclusive histopathology. Participants who had a normal thyroid function but had a thyroid nodule, who had a thyroid nodule of a singular nature, and who had no histopathology were excluded.

A written, informed consent was obtained after which each participant was assigned a unique study identifier. The information obtained by the study included the history of duration of neck swelling and compressive symptoms, as well as family history of thyroid disease, and if found, was noted. The treatment of choice for patients who had a multinodular thyroid was total, subtotal, or lobar thyroidectomy based on the findings of the patients' thyroid function tests and the clinical judgment of the surgeons. The excised tissues also underwent definitive histopathological examinations.

Data Analysis was performed in IBM SPSS Statistics version 26. Continuous variables were presented as mean $\pm$ SD (M $\pm$ SD) with range. Categorical variables were expressed as frequency and percentage. The proportion of Primary Malignancy was reported with a 95% Wilson CI. The association with Malignancy was assessed by two-sided Fisher exact test for 2x2 tables and a Fisher-Freeman-Halton exact test for larger

contingency tables. This was done as some expected cell counts were small. A p-value of less than 0.05 was considered statistically significant. Before enrolment, ethical approval for the study was granted by the Institutional Review Board of JPMC. Coded study identifiers were used to maintain the confidentiality of the participants.

RESULTS

There were 113 participants, and all of them had complete records of their demographics, clinical, operative, and histopathological data. The average age of the participants was 44.3 $\pm$ 8.9 years (range 29-61), and 94 (83.2%) were females. The average duration of Goitre was 4.0 $\pm$ 1.4 years, and the average TSH was 2.15 $\pm$ 0.24. Bilateral multinodular enlargement was found in 83 (73.5%) of the participants, and palpable cervical lymphadenopathy was found in 10 (8.8%). The operation that was performed most frequently was a total Thyroidectomy (n=57; 50.4%)(Table 1).

Table 1: Demographic, clinical and operative characteristics (n=113)

Characteristic	Value
Age, years	44.3 $\pm$ 8.9 (29-61)
Age <40 years	41 (36.3)
Age $\geq$ 40 years	72 (63.7)
Female sex	94 (83.2)
Male sex	19 (16.8)
Duration of goitre, years	4.0 $\pm$ 1.4 (1-7)
Duration $\leq$ 3 years	43 (38.1)
Duration >3 years	70 (61.9)
TSH	2.15 $\pm$ 0.24 (1.60-2.60)
No compressive symptom	60 (53.1)
Dysphagia	24 (21.2)
Dyspnoea	22 (19.5)
Hoarseness	7 (6.2)
Positive family history	16 (14.2)
Diffuse multinodular enlargement	30 (26.5)

Characteristic	Value
Bilateral multinodular enlargement	83 (73.5)
Palpable cervical lymphadenopathy	10 (8.8)
Total thyroidectomy	57 (50.4)
Subtotal thyroidectomy	31 (27.4)
Lobectomy	25 (22.1)

Final histopathology was Malignant in 12 patients, giving a frequency of 10.6% (95% CI 6.2%-17.6%). Malignant Histopathologies were 10/12 (83.3%) Papillary Carcinoma and 2/12 (16.7%)

Follicular Carcinoma. Of the Malignant Tumours, the average size was 2.02 ± 0.34 cm, and the lymph nodes were

Table 2: Histopathological findings and malignant tumour characteristics (n=113)

Finding	Overall value	Additional description
Benign histopathology	101 (89.4)	—
Malignant histopathology	12 (10.6)	95% CI 6.2–17.6
Papillary carcinoma	10 (8.8)	10/12 (83.3) of malignancies
Follicular carcinoma	2 (1.8)	2/12 (16.7) of malignancies
Malignant tumour size, cm	2.02 ± 0.34	Range 1.5–2.6
Lymph-node involvement	9 (8.0)	9/12 (75.0) of malignancies

The frequency of malignancy did not significantly differ according to age, gender, duration of goitre, or family history. In cases of bilateral goitre, malignancy was more likely than in cases of diffuse multinodular goitre (14.5% vs 0%; $p = 0.034$). Malignancies were also more likely among certain symptom categories ($p < 0.001$) and were

associated with the presence of cervical lymphadenopathy (100% vs 1.9%; $p < 0.001$). Total thyroidectomy was performed in every malignancy, resulting in a link between surgery and the histopathological findings ($p = 0.001$). This was a result of clinical choice and should not be seen as a consequence of the surgery (Table 3).

Table 3: Association of demographic and clinical factors with malignant histopathology (n=113)

Factor	Category	Malignant n/N (%)	p-value
Age	<40 years	2/41 (4.9)	0.206
	≥40 years	10/72 (13.9)	
Sex	Male	2/19 (10.5)	1.000
	Female	10/94 (10.6)	
Duration	≤3 years	3/43 (7.0)	0.531
	>3 years	9/70 (12.9)	

Factor	Category	Malignant n/N (%)	p-value
Symptoms	None	0/60 (0.0)	<0.001*
	Dysphagia	8/24 (33.3)	
	Dyspnoea	0/22 (0.0)	
	Hoarseness	4/7 (57.1)	
Family history	No	12/97 (12.4)	0.211
	Yes	0/16 (0.0)	
Examination	Diffuse MNG	0/30 (0.0)	0.034
	Bilateral MNG	12/83 (14.5)	
Cervical nodes	Absent	2/103 (1.9)	<0.001
	Present	10/10 (100.0)	
Surgery	Lobectomy	0/25 (0.0)	0.001*
	Subtotal	0/31 (0.0)	
	Total	12/57 (21.1)	

DISCUSSION

Of the 113 patients who underwent surgery for NTMNG, 10.6% were found to have malignant histopathology. This is approximately 1 in 9 thyroidectomies. Of those cases, the majority (83.3%) were of papillary type. The majority of the cases that were studied were of a single centre. The lead estimation was of fair precision for a unit of that type, as indices indicate that (95% CI: 6.2% - 17.6%).

The observed frequency is closely aligned with recent Pakistani reports. Zahid et al. detected malignancy in 8.0% of 154 surgically treated multinodular goitres while Amin et al. reported a figure of 11.6%, while a study of a series of retrosternal goitres reported a malignancy prevalence of 10.0%.^{13,15,16} A Balochistan study in 2023 reported a figure of 14.3%, while Naeem et al. reported a figure of 31.3% in a study from Rawalpindi.^{14,17} Most recently, in a study of 520 patients from Karachi, malignancy was reported in 16.0%.¹⁸ There is also great variation in international studies, with a reported figure of 14.4% from a 2026 Italian study, a 31.7% figure from a Serbian study, a 13.9% figure from a South Indian study, and a Greek total thyroidectomy

study reported occult carcinoma in 14.0%.^{8,19,21,23}

Variance in iodine exposure, intensity of referrals, the use of pre-operative imaging and cytology, differences in surgical indications, and the inclusion or exclusion of microscopic incidental tumours are all likely to account for the variation. There is a worldwide concordance regarding the prevalence of papillary carcinoma. In the study from Islamabad, papillary carcinoma accounted for 83.3% of the malignancies, which is the same as in our study.¹³ More recent studies of multinodular goitre have reported a papillary carcinoma prevalence of 57.4% in an Ethiopian cohort and 78.1% in the 2026 Italian cohort, and from a South Indian study, papillary carcinoma was reported in 77 of the 91 malignancies.^{19,21,22} This correlates with the current prevalence of papillary carcinoma and suggests that multinodular thyroidectomy specimens warrant detailed pathological examination.⁹ Our two cases of follicular carcinoma underscore that the spectrum is not limited to papillary carcinoma.

In this cohort, malignancy was not associated with age and sex. Still, the almost equal malignant rates of 10.5 percent in men and 10.6 percent in women, considering how predominantly female

the NTMNG patients were, is very significant. There is conflicting literature data on demographic predictors. Younger age and male sex were described by Apostolou et al. as independent predictors. Chen et al. also described younger age as associated with incidental carcinoma.^{8,11,20} On the other hand, Fernandes et al. described older age with no significant sex effect. The lack of association in this study may reflect the small number of malignancies and limited statistical power, with broad groupings, rather than an absence of demographic effect. Malignant potential was better addressed by the clinical presentation. There was a significant association of malignancy with symptom category and bilateral multinodular enlargement. Furthermore, all ten patients with cervical lymphadenopathy presented with malignancy. Lymph node involvement was seen in 9 of the 12 malignant cases. Palpable cervical lymphadenopathy has been described in 37.4% of the malignant multinodular goitres in a study from South India.²¹ The current recommendations for thyroid nodules treat the invasive symptoms, concerning ultrasound findings, and the suspicious cervical lymph nodes as indications for supplementary imaging and direct cytology. Due to the small size of several strata in the present study, these associations should be viewed as indicative of a clinically important warning sign, rather than estimating a stable effect.

All cases documented as malignant had undergone total thyroidectomy. Patients with bilateral disease, compressive features, or a suspicion of malignancy are likely to undergo total thyroidectomy. These patients are also likely to have a malignancy. Therefore, we cannot determine if the risk of malignancy is altered due to the type of surgery performed. The risk of malignancy, paired with the compressive symptoms, should determine the type of surgery. Cytology and imaging should be evaluated along with the risk factors, and the preferences of the patient should be considered.^{5,6} The frequency of 10.6% supports a need for a thorough preoperative evaluation and a detailed

histopathological evaluation for cases of non-toxic multinodular goitre.

This study was limited in the following ways. The study was designed as a single-center and non-randomized surgical cohort, and thus, the results do not apply to community cases of non-toxic multinodular goitre. The study was subjected to referral bias and selection bias. Twelve cases of malignancy were reported. This limited the statistical power of the study and resulted in hyper-sparse data. The nature of small sample sizes and slow recruitment was mitigated with the use of exact testing; however, improved precision was not achieved. Malignant cases provided only limited data on preoperative staging and no data on the risk of malignancy as assessed by ultrasound, pre-surgical cyst evaluation, iodine status, thyroid autoimmunity, or comprehensive pathological evaluation, which precluded assessment of the risk of malignancy and the state of malignancies as they were believed to be before surgery. Tumor size and lymph node involvement were reported and assessed, but only in cases of documented malignancy.

CONCLUSION

Malignancy was found in 10.6% of cases of non-toxic multinodular goitre, with the greatest incidence of malignancy being in cases of papillary thyroid carcinoma. The risk of malignancy should be assessed on a case-by-case basis. A thorough and detailed preoperative assessment should be conducted for cases of non-toxic multinodular goitre when there are concerning symptoms, bilateral disease, or cervical lymphadenopathy. Definitive histopathological evaluation is warranted in all cases.

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