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Frequency of Malignancy in Retrosternal Multinodular Goiter

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ABSTRACT

Retrosternal Multinodular Goiter (MNG) was a condition often associated with benign thyroid disease, but it may harbor undetected malignancies. Accurate diagnosis was essential to avoid complications during and after surgery. **Objective:** To determine the frequency of malignancy in patients undergoing total thyroidectomy for retrosternal multinodular goiter. **Methods:** This retrospective observational study included data of 80 patients, aged 40 years or more who underwent total thyroidectomy for retrosternal multinodular goiter. Data of patients with smoking history, recurrent goiter, previous neck surgeries, solitary nodules, metastatic lymphadenopathy, Graves' disease, known carcinoma thyroid, or associated carcinoma of other organs were excluded. Thyroidectomy was performed via cervical incision, with or without sternotomy. Histopathological examination of the excised thyroid tissue was conducted. Data were analyzed using SPSS version 25.0. The quantitative variables were shown in tables as mean ± standard error, and qualitative data as frequency (percentage); N (%). **Results:** According to the results, 14 (17.5%) patients were aged 40-50 years, 47 (58.75%) were aged 51-60 years, and 19 (23.75%) were aged 61-70 years. Histopathological examination revealed thyroid malignancy in 10% of the cases. **Conclusion:** A notable percentage of patients with retrosternal multinodular goiter were found to have malignancy that was not detected in preoperative investigations.

INTRODUCTION

Thyroid enlargement is a slow process with gradual development of symptoms of secondary hormonal dysfunction, obvious neck swelling, and pressure symptoms. The most common symptoms are shortness of breath, discomfort during sleep, swallowing difficulty, and hoarseness of voice, which are caused by esophageal and tracheal compression [1]. Worldwide, about 500 to 600 million people are affected by multinodular goitre, which is one of the most common endocrine diseases [2]. Retrosternal goiter is defined as an enlargement of the thyroid gland that extends below the sternal notch [3]. Clinically, a goiter is considered retrosternal if the lower border of the thyroid is not palpable when the neck is fully extended [4]. Approximately 20% of patients undergoing thyroidectomy have retrosternal extension. It is slowly progressive and commonly presents after the fifth decade of life [5]. The reported rate of retrosternal goiter varies between 5% to 22% due to differences in the definition of retrosternal goiter [6]. These are typically found in the anterior mediastinum, with rare cases occurring in the posterior mediastinum, which is an important consideration for surgical planning [7]. Due to its slow growth, it often remains asymptomatic and is frequently an incidental finding on radiological investigations [8, 9]. Relevant clinical history, physical examination, and radiological investigations are used as diagnostic tools for retrosternal goiter [10, 11]. Retrosternal and primary intrathoracic goiter are considered two separate entities based on their blood supply. Primary intrathoracic goiters receive their blood supply directly from thoracic vessels and the aorta, with no connection to the thyroid gland in the neck [12]. Recent studies indicate that malignant transformation may occur in long-standing multinodular goiter, with rates varying from 3% to 35% [13]. The mainstay treatment of retrosternal multinodular goiter is surgery through Kocher's neck incision, with sternotomy

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required in only 1-11% of cases [14]. It is widely acknowledged that a key environmental factor for an increase in thyroid nodules is iodine deficiency. Thyroid enlargement was discovered in 15.0% and 22.6% of the ultrasonographic exams in Denmark's mildly and moderately iodine-deficient regions, respectively. In 30% of the examinations in both locations, thyroid nodules were observed; however, in areas with significant iodine deficiency, nodules were larger and more frequently palpable. In a study, 9.8% of people with mild iodine deficiency and 14.6% of those with significant iodine deficiency had palpable goiters[15].

Previous research on Multinodular Goiter (MNG) suggests that malignancies in these goiters may often be overlooked during preoperative evaluations [8]. Despite advancements in diagnostic imaging techniques, identifying malignant transformations within retrosternal MNG remains a challenge, potentially leading to inadequate surgical planning and outcomes [11]. Given the prevalence of retrosternal MNG and its association with thyroid malignancies, particularly in various populations, it is essential to examine the incidence of malignancy in this condition.

The current study aimed to fill a gap in the literature by providing updated and region-specific data on the frequency of malignancy in patients undergoing total thyroidectomy for retrosternal MNG in Peshawar, Pakistan and to compare the clinical and pathological features between benign and malignant type of retrosternal MNG in these patients.

METHODS

This retrospective study was conducted using hospital medical records from 1st July 2022 to 30th June 2023 at the Medical Teaching Institution Lady Reading Hospital, Peshawar. A non-probability consecutive sampling technique was employed to select patients. Data of 80 patients aged 40 to 70 years were included in the study, as retrosternal goiter commonly presents in later decades of life. The study was approved by the Institutional Review Board (IRB) of Medical Teaching Institution Lady Reading Hospital, Peshawar (288/LRH/MTI). Patients were excluded if their records indicated a history of neck irradiation, recurrent goiter, a family history of thyroid cancer, evidence of malignancy, or suspicion of malignancy based on preoperative Fine-Needle Aspiration Cytology (FNAC). Records with incomplete medical histories or missing laboratory data were also excluded. Data from medical records were analyzed, including preoperative and postoperative clinical, biochemical, radiological, and pathological findings. Information retrieved from the records included surgical procedures performed, early postoperative complications, thyroid scintigraphy results, thyroid hormone profiles, thyroid Ultrasonography (US) findings, FNAC results, and histological diagnoses. Based on the final histological analysis of the surgical specimens, participants were categorized into two groups: Group A included patients with benign diagnoses, and Group B consisted of those with malignant diagnoses. Statistical analysis was performed using Version 25.0 of the Statistical Package for Social Sciences (SPSS). Descriptive statistics such as percentages and frequencies were used for categorical variables. Fisher's exact test was employed to assess associations between qualitative variables. A p-value of < 0.05 was considered statistically significant.

RESULTS

This study consisted of 80 patients who underwent thyroidectomy for retrosternal multinodular goiter without known malignancy. All patients underwent comprehensive preoperative and postoperative evaluations, which included clinical, biochemical, radiological and histopathological studies. The mean age of the patients was 56.11 ± 7.53 years, with an age range of 40 to 70 years. The majority of the patients were females (60%, 48 patients), while 32(40%) patients were males. Age distribution analysis revealed that 14(17.5%) patients were in the 40-50 years age range, 47(58.75%) patients were in the 51-60 years age range, and 19(23.75%) patients were in the 61-70 years age range. The mean BMI of the patients was 26.13 kg/m^2, (Table 1).

Table 1: Demographic characteristics of study participants

Gender	N (%)/(Mean ± SD)
Men	32 (40%)
Female	48 (60%)
Age (Years)	
40-50	149 (17.5%)
51-60	47 (58.75%)
61-70	19 (23.75%)
Age	56.11 ± 7.53
BMI (Kg/m^2)	26.13 ± 2.02

All patients came with a complaint of thyroid swelling. Among them, 50(66.6%) patients had dyspnea, 14.4 % (15 patients) were asymptomatic, 10(12.5%) patients had painful swelling and 5(6.3%) patients experienced dysphagia. Six patients required median sternotomy, while 74 patients were operated through a cervical neck incision. The duration of stay for these patients was 3 ± 1 days, and follow-up was conducted for up to 6 ± 3 months (Table 2).

Table 2: Symptoms, Signs, and Surgical Details of study participants

Abnormal	Total (N = 80)	Benign (Group A, N = 72)	Malignant (Group B, N = 8)	p-Value
Swelling	80 (100.0%)	72 (100.0%)	8 (100.0%)	1.000
Swelling with Dyspnea	50 (66.6%)	45 (62.5%)	5 (62.5%)	1.000
Swelling with No Symptoms	15 (18.8%)	15 (20.8%)	0 (0.0%)	0.332
Swelling with Pain	10 (12.5%)	8 (11.1%)	2 (25.0%)	0.286

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Swelling with Dysphagia	5 (6.3%)	4 (5.5%)	1 (12.5%)	0.415
Median Sternotomy	6 (7.5%)	4 (5.5%)	2 (25.0%)	0.048*
Cervical Neck Incision	74 (92.5%)	68 (94.4%)	6 (75.0%)	0.048*
Hospital Stay (Mean ± SD)	3 ± 1 Days	3 ± 1 Days	4 ± 1 Days	0.031*
Follow-up Duration (Mean ± SD)	6 ± 3 Months	6 ± 3 Months	6 ± 2 Months	0.715

(*P < 0.05 indicates statistical significance).

Figure 1 presented frequency of malignancy.

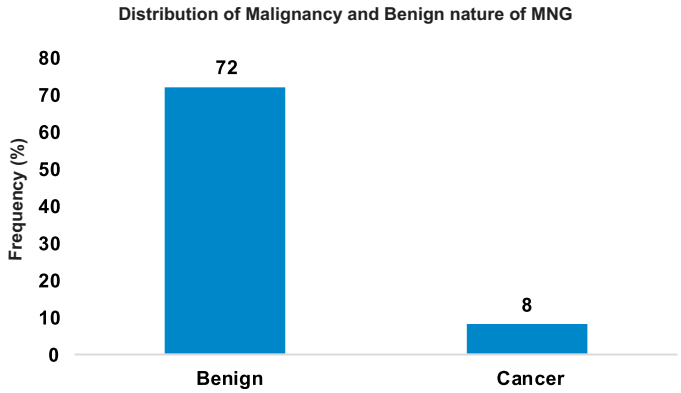

Figure 1: Frequency of Malignancy among Study Participants

Histopathological examination revealed that 10% (8 patients) had thyroid malignancy, while 90% (72 patients) were diagnosed with benign thyroid disease. Among the malignancy, 6.25% was papillary, 2.5% Follicular and 1.25% was undifferentiated thyroid malignancy (Table 3).

Table 3: Post-Operative Diagnosis Based On Histopathology

Diagnosis	Total (N = 80)	Benign (Group A, N = 72)	Malignant (Group B, N = 8)	p-Value
Colloid Goiter	72 (90.0%)	72 (100.0%)	0 (0.0%)	<0.001*
Papillary Carcinoma	5 (6.25%)	0 (0.0%)	5 (62.5%)	<0.001*
Follicular Carcinoma	2 (2.5%)	0 (0.0%)	2 (25.0%)	<0.001*
Undifferentiated Thyroid Malignancy	2 (2.5%)	0 (0.0%)	2 (25.0%)	<0.001*

(*P < 0.05 indicates statistical significance).

Regarding postoperative complications, only 1 patient (1.25%) developed postoperative hoarseness, which resolved by the second postoperative month, with normal vocal cord movements observed on a laryngoscopy examination. Two patients (2.5%) experienced secondary hemorrhage, and 3 patients (3.75%) developed a surgical site infection, which was treated with antibiotics (Table 4).

Table 4: Post-Operative Complications

Complications	Total (N = 80)	Benign (Group A, N = 72)	Malignant (Group B, N = 8)	p-Value
No Complications	73 (91.2%)	69 (95.8%)	4 (50.0%)	<0.001*
Hemorrhage	2 (2.5%)	1 (1.4%)	1 (12.5%)	0.126
Infection	3 (3.75%)	2 (2.8%)	1 (12.5%)	0.214
Recurrent Laryngeal Nerve Injury	1 (1.25%)	0 (0.0%)	1 (12.5%)	0.048*
Recurrence	1 (1.25%)	0 (0.0%)	1 (12.5%)	0.214

(*P < 0.05 indicates statistical significance).

There were 12.5% of the males and 87.5% of the females in the thyroid cancer group, whereas benign group had16.7% of the males and 83.3% of the females. In this comparison, the P-value was 1.00, meaning that there was no discernible change in the distribution of sexes between the two groups. Age distribution analysis showed that the highest incidence of thyroid cancer occurred in patients aged 40-50 years (37.5%), while the highest incidence in the benign group was among those aged 51-60 years (50%) (Table 5).

Table 5: Comparison of Sex and Age in Patients with and without Thyroid Malignancy (n=80)

Variables	Benign Group N (%)	Cancer Group N (%)	p-Value
Sex			
Male	12 (16.7%)	1 (12.5%)	1.00
Female	60 (83.3%)	7 (87.5%)	
Age (Years)			
40-50	11 (15.28%)	3 (37.5%)	0.368
51-60	36 (50%)	3 (37.5%)	
61-70	25 (34.72%)	2 (25.0%)	

All patients with thyroid malignancy presented with neck swelling, with some cases showing additional symptoms such as dyspnea (37.5%) or dysphagia (12.5%). Notably, swelling without any additional symptoms was significantly more common in the benign group (P=0.012). Multinodular goiter was predominantly seen in the benign group (94.4%), whereas solitary thyroid nodules were equally distributed between benign (5.6%) and cancer groups (50%) (P=0.001), highlighting a potential diagnostic marker. Post-operative complications were more in thyroid malignant cases as compared to benign cases (Table 6).

Table 6: Comparing the Signs/Symptoms, Diagnosis and Postoperative Complications of Patients with and without Thyroid Malignancy (n=80)

Symptom/Sign	Benign Group N (%)	Cancer Group N (%)	p-Value
Swelling with No Symptoms	25 (34.72%)	0 (0%)	0.012
Swelling with Dyspnea	33 (45.8%)	3 (37.5%)	
Swelling with Pain	10 (13.9%)	0 (0%)	
Swelling with Dysphagia	4 (5.6%)	5 (62.5%)	
Diagnosis			
Multinodular Goiter	68 (94.4%)	4 (50%)	0.001
Solitary Thyroid Nodule	4 (5.6%)	4 (50%)	

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Postoperative Complications			
Recurrent Laryngeal Nerve	0 (0%)	1 (14.29%)	0.02
Hemorrhage	0 (0%)	2 (28.57%)	
Recurrence	0 (0%)	1 (14.29%)	
Infection	1 (14.29%)	2 (28.57%)	

DISCUSSION

Enlargement of the thyroid gland evident as neck swelling was defined as goiter, which in most cases was multinodular [15]. Goiter can extend through the thoracic inlet and pass into the mediastinum, known as substernal or retrosternal thyroid gland extension. Substernal goiter may be primary or secondary [16]. The secondary type of substernal goiter originates from the cervical region and descends into the mediastinum due to the effects of negative intrathoracic pressure and gravity [17]. Primary STG, which was extremely rare, accounting for approximately 1% of all cases, arises from aberrant thyroid tissue within the mediastinum and receives its blood supply from the mediastinal vessels, as opposed to the normal superior and inferior thyroid arteries [18, 19]. The incidence of retrosternal goiter varies from 2% to 20%, largely due to the lack of a standardized definition of retrosternal goiter [20]. Surgery was the mainstay treatment in most cases of retrosternal goiter, particularly due to symptoms of airway compression. In the majority of retrosternal goiter cases, total thyroidectomy was performed. Some of the postoperative complications include transient symptomatic hypoparathyroidism, hematoma, wound infection, pneumonia, and transient laryngeal nerve paresis [21]. Thyroid cancer accounts for approximately 1% of all human cancers and was the most common endocrine malignancy. Risk factors for thyroid malignancy include female sex, exposure to ionizing radiation, and a family history of endocrine malignancy [22]. The primary objective of this study was to evaluate the postoperative outcomes and incidence of thyroid malignancy in patients undergoing thyroidectomy for retrosternal multinodular goiter. This results revealed that 10% of patients had thyroid malignancy, while 90% were diagnosed with benign thyroid disease. These findings highlight the importance of histopathological examination in retrosternal goiter cases, especially given the limitations of Fine-Needle Aspiration (FNA) in obtaining accurate samples from substernal tissue. In line with previous studies, this study demonstrated a higher prevalence of retrosternal goiter among females, with 60% of the total cases being female patients. This gender distribution was consistent with the known increased risk of thyroid diseases in females [21]. The mean age of 56.11 years in this cohort was also comparable to other studies, which report a mean age of around 50 to 60 years for patients with retrosternal goiter [23]. The results of this study show that dyspnea was present in 66.6% of patients, which reflects findings in other studies where respiratory symptoms were the most common clinical presentation of retrosternal goiter [21]. Previous research by Abdelrahman H *et al.*, who reported a malignancy rate of 10% in patients undergoing thyroid surgery for benign disease [24]. The malignancy rate in this cohort (10%) supports the concept that retrosternal goiters may have malignancies that were not easily detectable preoperatively through FNA. Thyroid cancer incidence ranged from 3 to 23% in a systematic evaluation of individuals with retrosternal goiter having thyroidectomy [25]. Patients with a single nodule and those with several nodules had similar rates of malignancy. Of the 90 patients with numerous nodules, 8 had cancer (8.9%), while 4 of the 60 patients with solitary nodules (6.7%) had cancer [26]. According to Di Crescenzo V *et al.*, cancer was found in 7 out of 97 cases of retrosternal goiter (7.6%) [27]. Another study found that there were no significant differences in the frequencies of malignancy across the groups, however papillary carcinoma was diagnosed in 76 out of 390 patients (19%) with retrosternal goiter and 200 out of 880 patients (22%, control group) with benign multinodular goiter [28]. Regarding postoperative complications, we observed a low incidence of recurrent laryngeal nerve injury (1.25%) and transient hypocalcemia (8.3%), with these complications being more frequent in the malignancy group (P=0.04 and P=0.03, respectively). This was consistent with existing literature, which indicates that more complex surgeries, such as those for malignant goiters, were linked with an increased risk of complications [21]. Additionally, the rate of wound infection (3.75%) and secondary hemorrhage (2.5%) was low, similar to the complication rates described in previous literature [23]. The higher incidence of solitary thyroid nodules in cancer patients (50% vs. 5.6% in the benign group) could be a useful diagnostic marker, as the presence of a solitary nodule was more commonly associated with malignancy [21].

CONCLUSIONS

There was a risk of malignancy in longstanding multinodular retrosternal goiter, which requires proper and timely workup, in order to devise appropriate management strategies for these patients and to prevent complications secondary to carcinoma. Further studies with larger sample size were required to further strengthen the findings of this study and to know about the actual burden of disease.

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Authors Contribution

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Writing, review and editing: AB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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