

Original Research Article

Association between multi nodular goitre and thyroid malignancy at a tertiary care centre

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Received: 31 October 2021

Accepted: 01 December 2021

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ABSTRACT

Background: Over the past few decades, the incidence of thyroid cancer has dramatically increased. Thyroid malignancy in multinodular goitre is considered to be high and these occult malignancies are detected only in post operative histopathological analysis. The study helps in finding association between multinodular goitre and thyroid malignancy. Objective was to find the association between multinodular goitre and thyroid malignancy in those who underwent total thyroidectomy.

Methods: A cross sectional study conducted in department of general surgery, KIMS hospital, Bangalore. The 236 randomized cases of multinodular goitre who underwent total thyroidectomy were selected. Patients underwent thorough clinical examination pre operatively and were reassessed in post-operative period following surgery. Later, histopathology report on thyroidectomy specimen of the patients were obtained. This report was considered the gold standard for the diagnosis of thyroid malignancy.

Results: Occult malignancies were commoner in middle aged females. Most of the patients in the study underwent total thyroidectomy. The prevalence of thyroid malignancy in our study was found to be 7.2%. In the study, 17 incidental malignancies were papillary carcinomas. It revealed a highly significant relation between the lymphocytic thyroiditis and occult malignancy ($p < 0.0001$)

Conclusions: The prevalence of malignancy in multinodular goitre is 7.2%. The only variant of incidental malignancy detected in histopathological examination of excised thyroid was papillary carcinoma. There is a statistically significant association between presence of thyroiditis in preoperative FNA and presence of occult malignancy carcinoma.

Keywords: Incidental thyroid malignancy, Occult thyroid malignancy, Thyroiditis

INTRODUCTION

Studies have shown that the prevalence of occult thyroid malignancy in patients with multi nodular goitre ranges from 5-13%. Thyroid malignancy is the most common malignancy of endocrine system, with an incidence from the ranges from 1 to 8 per 1,00,000 population. Over the past few decades, the incidence of thyroid malignancy has dramatically increased. Hence, it is important to know the association of thyroid malignancies in patients who underwent thyroidectomy with a pre-operative diagnosis of multi nodular goitre.

Objectives

The objectives were like the primary objective of the study is to find out the association between thyroid malignancy in patients diagnosed as having multi nodular goitre and underwent thyroidectomy. The secondary objectives are to find the correlation, if any, of the prevalence of occult malignancy with the following parameters that were assessed in the study-Age of the patient, gender of the patient, incidence of thyroiditis in pre operative fine needle aspiration cytology, incidence of thyroiditis in post operative histopathology specimen,

thyroid hormone status of the patient, duration of multi nodular goitre and volume of the gland.

METHODS

Study design

The study design was of cross-sectional study.

Sample size

The 236 randomised cases of multi nodular goitre who underwent thyroidectomy were selected as the sample population. Coin toss method was used for randomisation.

Study place

The study was conducted at department of general surgery in KIMS hospital, Bangalore.

Inclusion criteria

>18 years who underwent thyroid function test, fine needle aspiration cytology and ultrasonography of the neck pre operatively excluding a pre operative diagnosis of thyroid malignancy and underwent elective thyroidectomy between August 2018 and September 2019 at our institution were included in the study.

Exclusion criteria

<18 years of age, patients with incomplete pre operative investigations, patients being suspected of malignancy and patients unwilling to participate in the study were excluded from the study.

Methods used

Patients were seen in wards and thorough clinical examination was done pre operatively. Patients were reassessed in post-operative ward following surgery. Later, the histopathology report on thyroidectomy specimen of the patient was obtained. Histopathological examination involved examining the entire gland in 5mm slices. This report was considered the gold standard for the diagnosis of thyroid malignancy.

Statistical analysis

Data was entered into a master chart prepared using Microsoft Excel 2010 and statistical analysis was done with the help of statistical package for the social sciences (SPSS) with the assistance of a statistician. Graphs and tables were made with the help of Microsoft word 2010. Quantitative variables were represented as mean and standard deviation and categorical variables as frequency and percentage to find out association between risk factors and outcome Chi-square test for qualitative

variables was used. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 236 patients with multi nodular goitre were enrolled in the study. All of them were diagnosed to have been suffering from a benign disease pre operatively. But 17 of them (7.2%) were found to have malignant focus within the gland (Figure 1). The rest (92.8%) were found to be benign. All the malignant neoplasms were papillary micro-carcinoma.

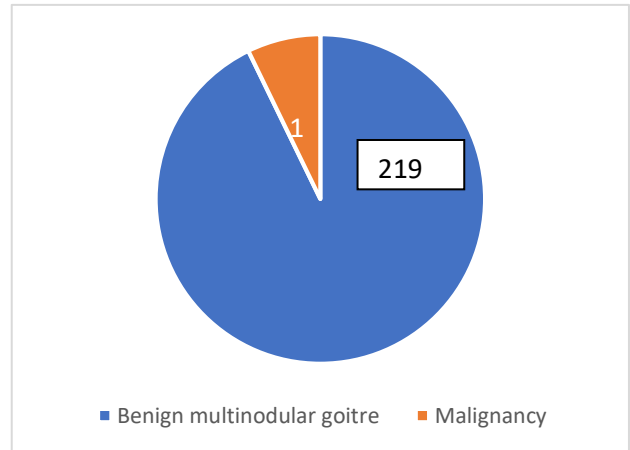


Figure 1: Histopathology.

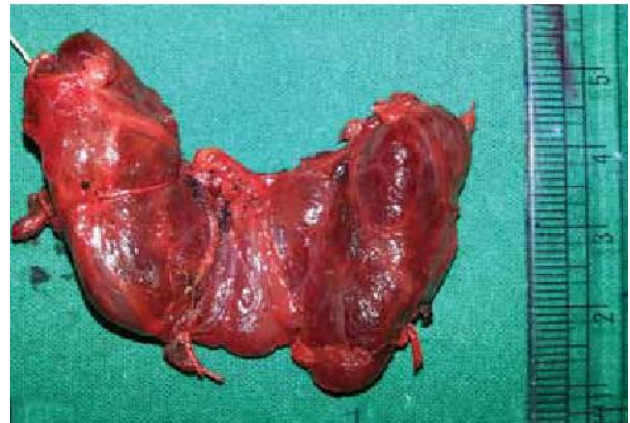


Figure 2: Gross picture of total thyroidectomy.

Type of malignant neoplasm

All the incidental malignant neoplasms obtained were papillary carcinoma. All except one were papillary micro carcinomas with a maximum diameter of 8.5 mm and a minimum diameter of 3 mm. All papillary micro carcinomas had clear margins, had no capsular or vascular invasion. One incidentally detected papillary carcinoma had vascular invasion. This was the only patient who needed to undergo completion thyroidectomy according to NCCN guidelines. None had any positive neck nodes.

Thyroiditis and malignancy

In the pre operative FNA, 18 patients were found to be having a picture of lymphocytic thyroiditis. On post operative analysis, it was found that out of these patients, 5 were harbouring occult papillary micro carcinoma. There was a strong association of lymphocytic thyroiditis in pre operative FNA and occult thyroid malignancy.

Table 1: Correlation between lymphocytic thyroiditis in pre operative FNA and incidental thyroid cancer.

Lymphocytic thyroiditis in pre operative FNA	Histopathology		
	Benign	Malignant	Total
Present	13	5	18
Absent	206	12	218
Total	219	17	236

$P < 0.0001$, Odds ratio=6.603, 95% CI=2.020-21.580.

Lymphocytic thyroiditis in HPE

The same association was noted for post operative lymphocytic thyroiditis. There were 36 cases with a background of thyroiditis in postoperative histopathological analysis. Out of this, 7 patients had occult malignancy.

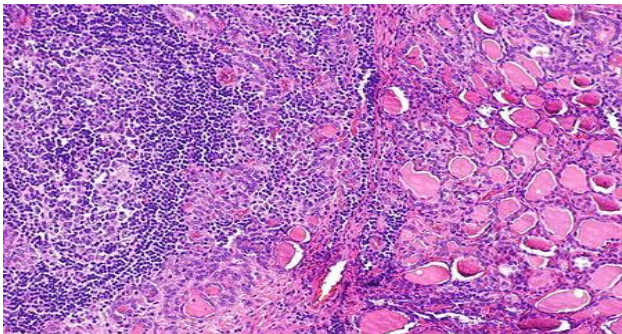


Figure 2: Hashimoto's thyroiditis. Large pink Hurthle cells and lymphocytes are seen.

Table 2: Correlation between thyroiditis in post operative HPE specimen and incidental malignancy.

Lymphocytic thyroiditis in post operative HPE	Histopathology		
	Benign	Malignant	Total
Present	29	7	36
Absent	190	10	200
Total	219	17	236

$P < 0.002$, odds ratio=4.568, 95% CI=1.618-13.000.

Age distribution

The mean age of all the patients enrolled in the study was found to be 44.5 ± 11.7 years. The mean age of those found to have malignancy was 45 ± 9.6 years and those who didn't have malignancy was 44.4 ± 11.9 years. There

was no significant association ($p=0.763$). The youngest individual who underwent thyroidectomy was 18 years of age and the eldest was 88 years old. The youngest person with malignancy was 36 years old and eldest was 67 years of age.

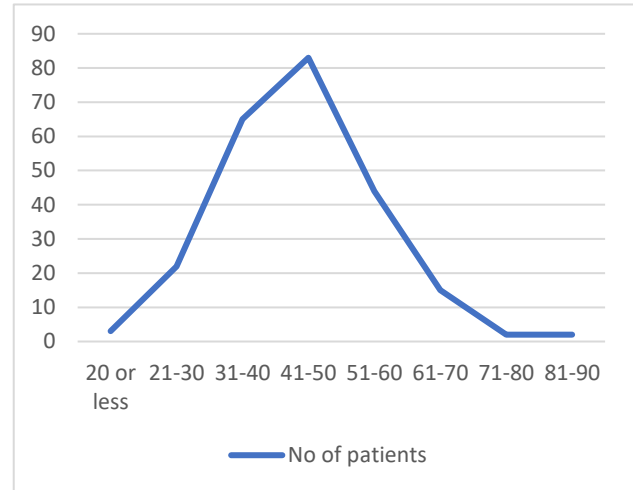


Figure 3: Age distribution of patients.

Gender distribution

There was a female predominance in the study population. Of all 236 patients, 204 were female and only 32 were males. Among the patients with occult malignancy, only one was male and rest 16 were females. An association with female gender was not statistically significant ($p=0.553$).

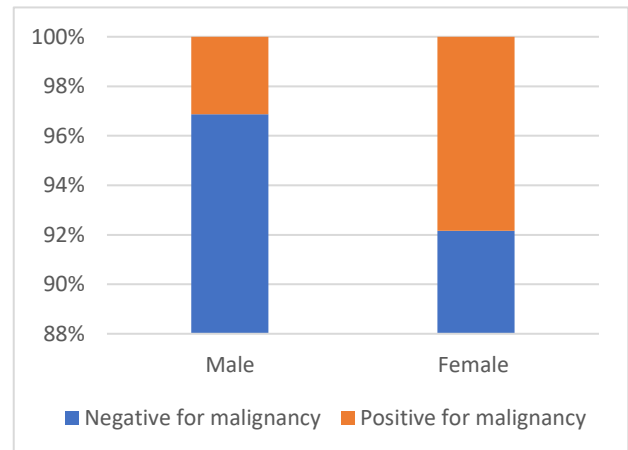


Figure 4: Gender distribution of patients.

Volume of gland

Ultrasonography size of the gland was used to calculate the volume of thyroid gland preoperatively. The mean volume of excised thyroid glands was found to be 34.4 cubic centimetres. The mean for patients with malignancy was 32.0 cubic centimetres and for those without malignancy was 34.6 cc. The largest gland excised was

184.6 cc and the smallest was 1.9 cc. the largest one with malignancy was 65.9 cc and smallest was 5.7 cc.

Duration of multinodular goitre and incidental malignancy

The mean duration of thyroid swelling in patients with multinodular goitre was 5.12 ± 5.15 years and those with incidental malignancy was 4.94 ± 3.44 years. There was no significant relationship between the duration of thyroid swelling and the probability for incidental malignancy ($p=0.8876$).

Table 3: Duration of MNG and incidental malignancy.

Variables	Histopathology	
	Benign	Malignant
Mean duration (years)	5.12	4.94
Standard deviation	5.154	3.344

Recurrence of MNG after previous thyroidectomy and malignancy

There were 7 people who underwent completion thyroidectomy for recurrence after previous thyroidectomy. None of them had occult malignancy.

Thyroid hormonal status and malignancy

Out of the 236 patients enrolled in the study, 217 were euthyroid. 18 were hyperthyroid and 1 was hypothyroid. The 3 of the patients with occult malignancy had hyperthyroidism and none had hypothyroidism. There was no significant association with thyroid hormonal status and malignancy.

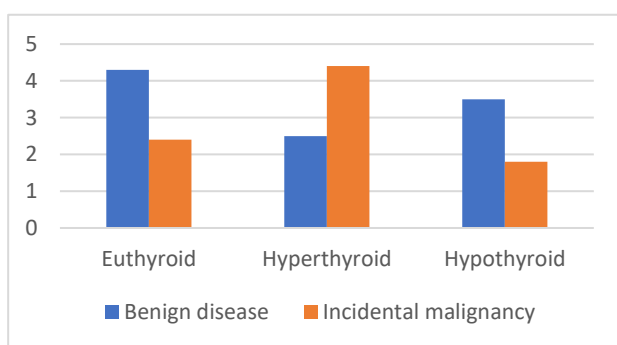


Figure 4: Thyroid hormonal status and incidental thyroid carcinoma.

DISCUSSION

The protocols for managing thyroid neoplasms are constantly evolving. There have been recent changes about to the practice of management of thyroid neoplasms which reflect the need for on-going research and modification of practice in the field. In the study, we

analysed 236 cases of patients with multi nodular goitre and tried to discover the association of occult malignancy in the excised gland. Possible correlations with other significant parameters are also investigated.

The prevalence of thyroid malignancy in our study found to be 7.2% Mittendorf et al from Cleaveland reported similar rate (7%) in their study of 54 people.¹ A similar study in an India setting Gangappa et al from Bangalore medical college with the sample size of 116 patients found a slightly increased prevalence of malignancy (11.2%).² Another retrospective study from South Africa which was published in 2014, analysed 166 thyroidectomies and found a prevalence of malignancy of 5.7%.³ A more recent Indian study Karthik et al has pointed out a slightly lower rate of 5.8%.⁴ Similar studies on the prevalence of malignancy they detected were as follows-Rehman et al 3.87%, Nanjappa et al 12%, Hanumanthappa et al 10%.⁵⁻⁷ The prevalence of malignancy in multi nodular goitre in the present study, thus well correlates with the results previously obtained.

All the above-mentioned studies have found the papillary carcinoma to be either exclusive or the predominant variant of incidental carcinoma that was detected post excision. The only other neoplasm that is occasionally described is follicular carcinoma. Karthik et al described 2 cases of follicular carcinoma against 6 cases of papillary carcinoma.³ This is probably because follicular carcinomas seldom stay occult. In the present study, all the 17 incidental malignancies were papillary carcinomas. And all except one were papillary micro carcinomas without vascular or capsular invasion.

Papillary micro carcinomas are papillary carcinomas which are 1 cm or less in diameter. They usually have a stellate configuration similar to the lesions. Formerly known as occult sclerosing carcinoma are non-encapsulated sclerosing tumour, whereas others show partial or near total encapsulation, with or without tumour outside the capsule.^{8,9} Its microscopic features and the loss of heterozygosity mutational profile so far investigated are similar to papillary carcinoma. RET/PTC is common and BRAF mutations have been identified, although they are less frequent than in larger tumours. Papillary micro carcinoma is reported to be common incidental finding (25% or more, depending on the thoroughness of the examination) in thyroid glands removed for other reasons and in population-based autopsy studies.^{10,11} However, recent studies show a prevalence of 2.1% probably owing to an over diagnosis due to improved imaging cytological modalities.¹² International agency of research on cancer has emphasized this issue in recent articles.¹³ Distant metastases are exceptionally rare and the prognosis is generally excellent.¹⁴ A proposal made at a thyroid cancer meeting in Porto and colloquially referred to as 'the proto proposal' is to avoid term 'carcinoma' for this tumour when occurring in adults in its typical form, and to replace by the term papillary micro tumour.

Table 4: Comparison of present study to other similar studies.

Variables	Present study	Mittendorf et al	Gangappa et al	Bombil et al	Karthik et al
Year	2017-2018	1990-1998	2013-2014	2005-2010	2011-2012
Duration (years)	18 months	8		5	18 months
Design	Cross sectional	Retrospective	Randomized prospective	Retrospective	Cross sectional
Sample size	236	54	116	166	155
Prevalence of malignancy (%)	7.2	7	11.2	5.7	5.8

The present study revealed a highly significant relation between the lymphocytic thyroiditis and occult malignancy ($p < 0.0001$, odds ratio=6.603). The same association was confirmed by analysis of the relation of thyroiditis in post operative HPE ($p = 0.02$, odds ratio=4.568). The prevalence of LT in patients with PTC has been reported to be significantly higher than with benign thyroid tumours.¹⁵ There have been reports that patients with lymphocytic thyroiditis (LT) are at higher risk for papillary thyroid carcinoma.¹⁶ The presence of LT in patients with PTC has been associated with better prognostic outcome, lower recurrence rate and less aggressive disease at the time of surgery.¹⁷⁻¹⁹ Hung et al also observed that well-differentiated thyroid carcinoma with concomitant HT present with less aggressive clinical behaviour and low recurrence rates in 1,788 PTC patients and 209 FTC patients who underwent thyroidectomy with or without lymph node dissection. The mean tumour size of classical PTC was larger than that seen in HT concurrent with PTC group. Cancer-specific mortality was higher in classical PTC group compared to PTC with HT. Recent meta-analysis by Lee et.al has suggested a positive correlation between presence of HT and disease-free survival and overall survival in PTC.²⁰ Surgical complications were no higher in patients of PTC with coexistent HT, suggesting that the presence of HT does not affect the management of papillary thyroid cancers. The follow up patients of PTC with HT is no different from those of stage and type matched PTC.

However, it has been conversely reported that the coexistence of CLT has no protective effect on patient outcome.²¹ Thus, the pathogenesis and prognostic outcome of the existence of PTC and CLT remains controversial. The casual association between HT and PTC remains elusive and larger prospective studies are needed to support or refute this association. However, based on the evidence of available literature, it would be prudent to rule out malignancy in nodular Hashimoto's thyroiditis. The treatment of PTC associated with HT is no different from that of stage and type matched PTC and HT concurrent with PTC have a better prognosis compared to age and stage matched PTC alone.

The mean age of all the patients enrolled in the present study was 44.5 ± 11.7 years. The mean age of those found to have malignancy was 45.1 years and those who didn't have malignancy was 44.4 years. Even though malignancy was not skewed towards the older end of

spectrum. The duration of multi nodular goitre also does not seem to correlate with the risk of malignancy. The Ask it's et al study featuring a population of European Caucasian ethnicity in the geographical zones from East Macedonia to Thrace in Northern Greece found a mean age of 49.60 ± 14.65 years. The mean age for patients with incidental thyroid malignancy was 47.00 (34.50-60.50). The difference was not found to be significant. According to earlier discussed Gangappa et al study, all the patients with incidental malignancy were in an age group ranging from 27 to 43 years and all were female. Another study by Wong et al concludes that, with advancing age, the prevalence of clinically relevant thyroid nodules increases, whereas the risk of such nodules being malignant decreases. Nonetheless, when thyroid cancer is detected in older individuals, a higher-risk histological phenotype is more likely.²³ In Wong et al study, population referred for initial evaluation of nodular disease, an average of 1.9 clinically relevant thyroid nodules was detected per patient. However, when stratified by age, the extent of modularity increased in a linear fashion. Patients 20-29 years old had an average of 1.55 nodules ≥ 1 cm, whereas patients ≥ 70 years old had an average of 1.55 nodules ≥ 1 cm, whereas patients ≥ 70 years old had an average of 2.21 nodules ≥ 1 cm ($p < 0.001$). Of the 1018 (15.9%) patients diagnosed with thyroid cancer during 16-year period of the early study, 988 (97%) were confirmed by surgical histology, whereas 30 (3%) were based on positive FNA cytology without thyroidectomy. Notably, the risk that a nodule was cancerous decreased with the advancing age ($p < 0.001$). For patients age 20-29, 30-39, 40-49, 50-59, 60-69 and > 70 years, the cancer prevalence was 22.9, 21.8, 17.1, 13.0, 13.7 and 12.6 % respectively ($p < 0.001$). For comparison, when the malignancy rate was analysed "per-nodule", the youngest cohort (20-29) demonstrated a 14.8% malignant risk per nodule at diagnosis in comparison to 5.6% in the oldest cohort (> 70 y $p < 0.01$). Between the ages of 20 and 60 years, each advancing year was associated with a 2.2% reduction in the relative risk that any newly evaluated thyroid nodule was malignant in a patient (OR, 0.972; $p \leq 0.001$). This risk of malignancy stabilized after age 60 years. So, even though, the finding of present study might be counterintuitive, there is a backing of evidence from literature for the finding.

In the present study, there was a female predominance. Of all 236 patients, 204 were females and only 32 were

males. Among the patients with occult malignancy, only one was a male and 16 were females. There is general consensus that sporadic goitre is common in females. The same goes for malignancy. A female predominance has been noted among patients who develop thyroid carcinoma in the early and middle adult years. By contrast, cases seen in childhood and late adult life are distributed equally between males and females. Papillary carcinoma is documented to be commoner in females than males.²⁴ Although more common in women, thyroid cancer typically presents at a more advanced stage and with a worse disease prognosis in men. Clinical evidence on the impact of oestrogen and other sex hormones on thyroid cancer has remained inconclusive, although numerous experimental studies have suggested that these hormones and their receptors may play a role in tumorigenesis and tumour progression. Studies of thyroid cancer cell lines suggest that an imbalance between the two-oestrogen receptor (ER) isoforms, alpha and beta, may be responsible for the cell proliferation seen with oestrogen treatment. Expression studies on thyroid tumours indicate that they express ER and possibly progesterone receptors and androgens receptors, but there is conflicting evidence as to whether or not there is a difference in receptor status between thyroid cancers, benign thyroid lesions and normal thyroid tissue. There have been few studies evaluating ERalpha/ERbeta profiles in thyroid tumours and normal thyroid tissue.²⁶

A conflicting result was reported by Bessy et al in a patient population of 2,766 women (mean age \pm SD, 52 \pm 15.2) and 964 men (mean age \pm SD, 59 \pm 13.8).²⁵ Of the 3,722 (93.5%) patients with diagnostic FNAs, 196 (5.3%) had malignant FNA cytology. Malignant FNAs were twice as frequent in patients age \leq 45 vs. those $>$ 45 (8.1% vs. 4.0%, $p<0.001$). Overall, men had more indeterminate (10.2%, vs. 6.3%, $p<0.001$) and malignant (6.7% vs. 4.8%, $p=0.034$) FNAs than women. Malignant FNAs in men were greatest in patients over age 45 (6.0% vs. 3.2%, $p=0.001$). The incidence of malignant FNAs for women peaked in their 30s (10.4%) whereas the incidence of malignant FNAs for men peaked 10 years later in their-40s (12.1%). Both men and women had the lowest incidence of malignant FNAs in their 70s (2.3% and 1.9% respectively). But the study is limited in the fact that it relied on preoperative FNAs instead of postoperative histopathology results.

Out of the 236 patients enrolled in the present study, 217 were euthyroid. 18 were hyperthyroid and one was hypothyroid. A similar finding-80% euthyroid state, 19% hyperthyroid and 1% hypothyroid was reported in another Indian study, Sanjeev et al.²⁷ Three of the patients with occult malignancy had hyperthyroidism and none had hypothyroidism. There was no statistically significant association with thyroid hormonal status and malignancy. A similar Indian study from Pondicherry, Nanjappa et al also couldn't find any evidence of relationship between toxicity and incidental malignancy. Incidental thyroid cancer was more prevalent in euthyroid patients

($p=0.029$) in their series. Another large-scale Italian study, Gelmini et al with a sample size of 739, found no significant difference in the incidence among euthyroid and hyper functioning thyroid patients. Reports in large published studies also say that the difference is not significant. While in some series higher incidence ITC was found in toxic, therefore hyperthyroidism cannot be considered a protective factor against differentiated thyroid carcinoma.²⁷

Limitations

Duration of study was only 18 months precluding a long term follow up of patients.

CONCLUSION

From the detailed analysis, we found that the association of malignancy in multi nodular goitre is 7.2%. This is comparable to recent studies done around the globe. The only variant of incidental malignancy detected in histopathological examination of excised thyroid was papillary carcinoma. There is statistically significant association between presence of thyroiditis in preoperative FNA and presence of occult malignancy. Thyroiditis in postoperative histopathology is also strongly associated to the presence of occult papillary carcinoma. Occult malignancy is commoner in middle aged females. Cases are found to be less in older individuals and men. Most of the patients in the study group underwent total thyroidectomy. Thyroid hormone status was found to bear no association with occult malignancy. The duration of illness, volume of gland and recurrent Multi nodular goitre are also found to have no association with occult malignancy.

ACKNOWLEDGMENTS

Author would like to thank to guide for his valuable guidance, encouragement, critical evaluation, prompt help and advice during the entire period of work. Also, to all patients, who in spite of all their sufferings have lent themselves to be a very valuable part of this study.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Sreenidhi GM, Jyothi S. Association between multi nodular goitre and thyroid malignancy at a tertiary care centre. *Int Surg J* 2022;9:86-92.