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A clinico-pathological study of thyroid nodules and correlation among ultrasonographic, cytologic, and histologic findings

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ABSTRACT

Background: Nodular thyroid is a common occurrence affecting 5% of the population. **Aims and Objectives:** To find the prevalence of thyroid nodules, to study the clinico-biochemical profile of the patients with thyroid nodules and to establish a correlation between pre-operative ultrasonography and fine-needle aspiration cytology (FNAC) with post-operative histopathologic findings. **Materials and Methods:** A prospective observational study was conducted in a tertiary care hospital in Kolkata over 1.5 years. Patients with clinically detectable nodules posted for surgery were evaluated clinically, biochemically, ultrasonographically (USG), and cytologically with FNAC. Histopathologic examination (HPE) was done post-surgery. Comparison was done between those with benign and malignant nodules. Correlation was done between pre-operative USG, FNA, and post-operative HPE of the nodules. **Results:** Out of 322 cases during the study period, the prevalence of clinically detectable thyroid nodule posted for surgery was 39 (12.58%). Most of the patients were euthyroid (94.9%), had nodules in left lobe (41.5%). Most of the nodules were heteroechoic (56.5%) and majority were THY3 nodules (48.7%) on FNAC. On HPE, malignancy was found in 20.5% of the nodules. Compared to benign nodules, malignant nodules were more commonly larger, on the left lobe, solid, hypoechoic, with spiculated margins, punctate calcification, and having associated neck nodes ($p_{all} < 0.03$). Out of 11 cases, which were radiologically predicted to be malignant, 10 had THY ≥3 on FNA, and 8 were malignant on HPE. USG had a sensitivity, specificity, positive, and negative predictive value of 87.5%, 87.1%, 63.63%, and 96.43% in predicting malignancy. **Conclusion:** Pre-operative ultrasonography for thyroid nodules can predict malignancy with sufficient sensitivity and specificity and can obviate the need for unnecessary FNAC in many cases and also suggest imminent need for surgery rather than FNAC in very high risk cases.

Key words: Thyroid nodule; Ultrasonographically; Fine-needle aspiration cytology; Malignancy; Thyroid cancer; Histopathology

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INTRODUCTION

Thomas Wharton coined the term thyroid which means-shield shaped in 1656. Thyroid is the largest endocrine gland in the human body.[1] This gland can be affected by numerous pathologies, many of which ultimately lead to enlargement of the gland. The enlargement is either generalized (goiter) or nodular.[2] According to autopsy studies, thyroid nodules are quite common, affecting up to 50% of the population.[3] However, the prevalence of palpable nodule is comparatively much less, only 4–7%.[4] Different imaging techniques increase the sensitivity for detection of the thyroid nodules to as high as 67% using ultrasonography (USG).[5]

Thyroid nodules are solid or fluid filled lumps that form within the thyroid gland.[6] Nodules could be solitary or multiple, functional or non-functional. Most of the nodules

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are benign in the form of toxic or non-toxic nodular goiter, benign tumors like adenoma or thyroid cysts; only 8–10% are malignant.[7] Malignant thyroid tumors could be papillary, follicular, medullary, anaplastic thyroid carcinoma or lymphoma, and rarely metastatic nodules. Often they are noticed incidentally. Early detection and treatment of malignant tumors provide good prognosis in most thyroid cancers. Thyroid carcinoma is uncommon, making up 1% of all cancers.[8,9] Differentiated thyroid cancers including papillary and follicular carcinoma make up 90% of all thyroid malignancies.[10,11]

Ultrasonography is one of the preferred imaging nowadays which can differentiate between solid and cystic nodules, detect non palpable nodules, and evaluate cervical lymph nodes.[11,12] It can differentiate between benign and malignant nodules to some extent.

Fine-needle aspiration cytology (FNAC) is the most accurate and cost-effective method for evaluating thyroid nodules.[12,13] However, as cancer constitutes only a small proportion of all nodules, non-ultrasound guided FNAC in all nodular thyroid patients might not be a good proposition and is not cost-effective.[14]

Aims and objectives

The aim of the study was to determine the association of pre-operative imaging, cytology with histopathology in thyroid swellings. The objective of the study was yo estimate the prevalence of nodular goiter in ENT outpatient department of a tertiary care hospital in East India, to determine the clinico-biochemical profile of patients with nodular thyroid swelling who are posted for surgery and determine the correlation between pre-operative ultrasound, FNAC, and post-operative histopathologic findings.

MATERIALS AND METHODS

This was a prospective observational study conducted in outpatient department and indoor ward of department of ENT and head neck surgery in a tertiary care hospital in Kolkata from January 2015 to July 2016.

Inclusion criteria

1. All patients with clinically detectable (palpable or visible) nodular thyroid disease who have been posted for surgery were included in the study.

Exclusion criteria

The following criteria were included in the study:

1. Patients with diffuse or non-nodular goiter
2. Toxic nodular goiter with thyrotoxicosis
3. Patients with thyroiditis.

Detailed clinical evaluation of thyroid nodules was done along with thyroid function tests from blood. This has followed by ultrasonography, FNAC and histopathology of operated nodules.

Ultrasonography of neck was done by experienced radiologist on a Philips HD 7 machine with linear probe of 7.5–12 MHz, FNAC from nodule using 23-gauge needle performed by pathologist. Post-operative histopathologic evaluation was done by two experienced pathologists.

Clinical correlation was done with ultrasound of the thyroid nodule, FNAC of the thyroid Nodule and histopathology of the excised thyroid nodules. Finally, the collected was analyzed for the required results using appropriate statistical tools and methods.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, Illinois). The two groups were compared using unpaired t-test or Mann–Whitney's U test for quantitative variables and Chi-square test, with Fisher's correction where appropriate, for categorical variables. $P \leq 0.05$ was considered significant.

RESULTS

Demographics

A total of 322 patients participated in the study. The mean age of the patients was 41.00±16.61 years (Table 1). Most of the patients were in the age group 30–39 years (61.9%). The ratio of male and female was 0.9:1.0. A total of 12.58% (n=39) of the patients were having clinically detectable thyroid nodule(s) posted for surgery. Most of the patients were euthyroid (94.9%) which was significantly higher than that of hypothyroidism (5.1%) ($Z=12.69$; $P<0.0001$).

USG findings

Most of the thyroid nodule were left sided (41.5%) followed by right sided (38.5%) and 20.5% cases had nodules in both lobes. The median number of thyroid nodules was 1.0, range, 1–3 and total of 71.8% of the patients were having single nodule. The mean size of thyroid nodule was 3.65±1.17 cm. More than half (59.0%) of the nodules were solid in consistency. Majority (56.5%) were mixed/heterogenous in echotexture followed by hypoechoic (23.1%) and isoechoic (15.4%) echotexture. Only 5.1% were anechoic. Elongated shape was seen in 17.9% of nodules. Borders were mostly smooth (84.6%) and 15.4% were spiculated. In 76.9% of the cases, calcification was absent microcalcifications were seen in 15.4% and coarse calcifications in 7.7% of the nodules. Loss of peripheral halo was seen in 12.8% of the nodules. About 28.2%

Table 1: Comparison of benign and thyroid nodules

Parameter	Benign (n=31)	Malignant (n=8)	P
Gender	M: F=4:27	M: F=2: 6	0.39
Number of nodules			0.26
Solitary	21	7	
Multinodular	10	1	
Location			0.01
Left lobe	9	7	
Right lobe	14	1	
Both	8	0	
Size of nodule			0.002=12.89;
<2 cm	1	0	
2–4 cm	26	2	
>4 cm	4	6	
Content of nodule			0.17
Solid	15	2	
Cystic	16	6	
Echotexture			0.33
Anechoic	2	0	
Hypoechoic	6	4	
Isoechoic	5	1	
Mixed	18	3	
Shape of nodule			0.1
Elongated	4	3	
Not elongated	27	5	
Border of nodule			<0.01
Smooth	30	3	
Spiculated	1	5	
Calcification of nodule			0.006
Absent	27	3	
Coarse	2	1	
Punctate	2	4	
Loss of perinodular halo			NA
Absent	27	8	
Present	4	0	
Vascularity			0.047
Absent	17	5	
Increased central	3	3	
Increased peripheral	11	0	
Presence of cervical lymphadenopathy			0.004
Present	1	3	
Absent	30	5	
FNAC			<0.0001
THY>3	0	6	
THY=3	17	2	
THY<3	14	0	

nodules had peripheral vascularity whereas 15.4 had central vascularity.

FNAC findings

Mostly THY3 nodules (48.7%) were found through FNAC followed by THY2 (35.9%). Only 2.6% were THY5.

Histopathologic findings

On post-operative histopathologic examination, most of the nodules were found to be colloid goiter (48.7%) (Table 2). Malignancy was found in 20.5% of the cases. Out of the malignant cases, 17.9% were papillary carcinoma and 25.6% were follicular adenomas/carcinoma.

Comparison of radiologic and FNA findings of benign and malignant nodules

On Chi-square analysis, there were no significant differences in age and gender of patients with benign or malignant nodules. There was a significant higher proportion of malignant nodules on left lobe (87.5% of malignant nodules were on left lobe), P<0.01.

There was also a significant association between size of nodule and malignancy of the patients (P=0.0016). Most of the malignant nodule were with size >4 cm (n=6/8, 75%). The risk of malignant nodule was 20.25 times more among the patients with size of nodule >4 cm as compared with the patients with size of nodule ≤4 cm (OR–20.25 [2.98, 137.31]; P= 0.0003).

Most of the malignant nodules were solid (87.5%). The risk of malignant nodule was 7.11 times more among the patients with solid nodule as compared with the patients with cystic nodule, P=0.0027. Most of the malignant nodule were hypoechoic (75.0%) followed by mixed/heterogenous echotexture (25.0%). However, the differences in echogenicity of benign and malignant nodules did not reach significance. Furthermore, we did not find a significant association between shape of nodule and final diagnosis of the patients (P=0.10).

Higher proportion of malignant nodules than benign nodules had spiculated margins than smooth margins (62.5% vs. 3.33%, P=0.003). The risk of malignant nodule was 50 times more among nodules with spiculated margins as compared with the patients with smooth margins (OR–50.00 [4.30, 581.31]; P= P=0.00006). Malignant nodules had higher prevalence of punctate calcification than benign nodules (50% vs. 6.67%, P=0.006) Since one of the cell frequencies was zero Chi-square test of halo sign could not be done. There was significant association between vascularity of nodule and final diagnosis of the patients (P=0.0473).

The presence of neck nodes on USG was more common in malignant nodules compared to benign nodules (37.3% vs. 3.2%, P=0.004) and the risk of malignant nodule was 18.00 times more among the patients with neck node as compared with the patients without neck node and the risk was significant (OR–18.00 [1.54, 209.27]; P= P=0.004).

Performance of USG and FNAC in predicting malignancy

After checking all the individual sonological signs, the radiological characterization was done for each of the

Table 2: Sensitivity, specificity, positive, and negative predictive values of pre-operative USG and FNAC in predicting malignancy in thyroid nodules*

Parameter	HP diagnosis			FNA diagnosis		
	Benign	Malignant		THY<3	THY=3	THY>3
USG diagnosis						
Benign	27	1	USG diagnosis of malignancy	13	1	14
Malignant	4	7	Sensitivity 87.5%	1	5	5
			Specificity 87.1%			
			PPV 63,3%			
			NPV 96.4%			
FNA diagnosis						
THY<3	14	0	FNA diagnosis of malignancy			
THY=3	17	2	Sensitivity 75%			
THY>3	0	6	Specificity 75%			
			PPV 100%			
			NPV=93.9%			

*Abbreviations used: USG: Ultrasonography, FNAC: Fine-needle aspiration cytology, PPV: Positive predictive value, NPV: Negative predictive value

nodules. All the nodules were categorized as either benign or malignant based on the individual radiologic parameters by two radiologists. As per USG findings, out of 39 cases, 11 was designated to be malignant and rest to be benign. Out of 11 cases which were radiologically predicted to be malignant, 10 had THY ≥3 based on FNAC findings and 8 were proved to be truly malignant as per histopathology. There was significant association between FNAC type and prediction through USG (P=0.0024). Three-fourths (75%) of the malignant nodule was THY >3 for FNAC. Most of the THY >3 (83.3%) was predicted as malignant by USG.

On the other hand, out of 28 radiologically benign nodules, all 28 were truly benign. Three cases were declared malignant based on US findings but ultimately proved malignant. A total of 96.4% of the benign nodules and 12.9% of the malignant nodules were predicted as benign and malignant by USG respectively. Ultrasonography was found to be 87.5% sensitive and 87.09% in predicting malignancy preoperatively with 63.63% PPV and 96.43% NPV.

DISCUSSION

We conducted a cross-sectional study of 322 subjects among whom the prevalence of nodular thyroid disease was 12.58%. This is higher than the worldwide reported prevalence of about 8.5%[15] but similar to other Indian studies citing a prevalence of 12.2% in the community.[16] In our study, 71.8% actually had solitary nodules on USG while 28.2% of clinically solitary thyroid nodules were multinodular as proved by ultrasonography. Palpation of the thyroid gland during routine physical examination is the easiest and least expensive method for detection, albeit the least sensitive. Findings from palpation alone suggest that the prevalence of thyroid nodules in the general population ranges from 4% to 7% in the United States. In the Framingham Study, 6.4% of women and 1.5% of men had palpable thyroid nodules.[17] Using a 7.5-MHz transducer, a non-biased population-based study in Hyvinkaa, Finland, detected nodules in 27% of women and 15% of men.[18] Autopsy studies have shown that 50% of consequent autopsies had thyroid nodules.[19]

There are limited studies from India on the epidemiology of thyroid nodules. In a study involving 14,762 schoolchildren, aged 6–18 years, with a countrywide representation, the overall prevalence of goiter was 23.0% with a higher frequency in girls. The cytologic diagnoses in 1,312 successful cases were colloid goiter (92.8%), Hashimoto's thyroiditis (4.6%), focal lymphocytic thyroiditis (1.7%) and hyperplastic goiter (0.9%). The authors concluded that there is possibility of significant role of environmental goitrogens in the causation of goiter in the post iodization period.[20]

In our study, 94.9% were euthyroid and 5.1% hypothyroid. As toxic nodules are rarely malignant, they were excluded from this study. We found that 20.5% of the thyroid nodules turned out to be malignant. According to nationwide data in the US, although the vast majority are benign lesions, about 5% may actually represent thyroid cancer.[21]

We found a slightly higher prevalence of malignant nodule in males compared to females but the risk was not significant. The present literature suggests a clear female preponderance of thyroid nodules,[22] which could be due to hormonal factors. Hashimoto's thyroiditis which is more common in females may lead to an increased risk of thyroid lymphomas but the association of Hashimoto's thyroiditis with differentiated thyroid cancer is not well established.[23]

In our study, most of the patients were in the age group 30–39 years (61.9%) and the proportion of malignant cases

with age <40 years was significantly higher than that of age ≥40 years. In a similar Indian study by Khan et al., majority of the patients were within 20–39 years age group.[24] Furthermore, in their study Kwong et al. concluded that with advancing age, the prevalence of clinically relevant thyroid nodules increases, whereas the risk for malignancy decreases.[25] Nonetheless, when thyroid cancer is detected in older individuals, a higher-risk histological variant is more likely.

Majority of patients in this study were euthyroid. Of the patients with malignancy, 100% were euthyroid. According to global and national data, most patients with thyroid cancers are euthyroid, followed by hypothyroid. Rarely, patients with Graves' disease and a dominant cold nodule may have underlying thyroid cancer which could behave in a more aggressive manner.[26] Hypothyroid patients with Hashimoto's disease and a dominant nodule or a rapidly enlarging goiter may also have lymphoma of the thyroid and require FNAB.[27]

According to the analysis of our study, only four signs were statistically significant to predict malignancy, these were a size more than 4 cm at initial presentation, spiculated border, punctate calcification, and presence of neck node. The risk of malignant nodule was 20.25 times more among the patients with size of nodule >4 cm as compared with the patients with size of nodule ≤4 cm. The nodules, which are malignant, tend to grow fast and thus present with a large size. According to study by Kamran et al., increasing thyroid nodule size impacts cancer risk in a nonlinear fashion. A threshold is detected at 2.0 cm, beyond which cancer risk is unchanged. However, the risk of follicular carcinomas and other rare thyroid malignancies increases as nodules enlarge.[28] Our results were also comparable to the result of study by Hoang et al., but they also concluded that benign nodules can often be very large too.[29] McCoy et al. also opined that nodule size more than 4 cm is a predictor of malignancy.[30]

We found that the risk of malignancy was 1.77 times more in solid nodules compared to cystic nodules, corroborating with the previous studies.[30] The cystic nodules, which were malignant, were complex cystic nodules. Purely cystic and honeycomb lesions are almost always benign.[31]

Most of the malignant nodule were hypoechoic (50.0%) followed by mixed (37.5%). Hypoechoic nodules most commonly harbor malignancy among the solid nodules. The sensitivity and specificity of this sign has been found to be variable in literature.[3,32] As per our results, hypoechogenicity was 71.4% sensitive in detecting malignancy. In the study by Gopinathan et al., malignant nodules, both carcinoma and lymphoma, typically appeared solid and hypoechoic when compared with normal thyroid parenchyma.[33] In spite of high positive predictive value of a markedly hypoechoic nodule for malignancy, the sensitivity reportedly low, ranging from 26 to 41%.[34-36] Furthermore, approximately 30–55% of benign nodules were also found to be hypoechoic in previous studies thereby decreasing the usefulness of this US marker.

There was no significant association between shape of nodule and risk of malignancy of the nodule.

Risk of malignancy was 50 times more in nodules with spiculated border and the specificity of this sign was 100% in our study. The finding of Moon et al. was quite similar with 91.8% specificity.[37] Furthermore, punctuate calcification had a specificity 90% in predicting malignancy which also perfectly corroborates with the previous studies.[38] However, the sensitivity for this sign was poor (44.4%). Older studies have reported a variable but low sensitivity for this sign, ranging between 29% and 51.4%.[39,40]

No malignant nodule in our study had a perinodular halo. A complete, uniform halo around a nodule is highly suggestive of benignity. Even if the halo is incomplete, it is 4 times more likely to be benign. However, 15–30% of malignant nodules may also show a halo limiting the utility of this sign.[38] In this study, there was significant association between vascularity of nodule and final diagnosis of the patients. Despite extensive overlap in the color Doppler appearance of benign and malignant thyroid nodules, a predominantly peripheral flow pattern is considered as a feature of a benign nodule, and a malignant nodule tends to have a predominantly central chaotic blood flow. Studies have shown that solid hypervascular thyroid nodules have a high likelihood of malignancy (nearly 42%).[40] In our study, the risk of malignant nodule was 18.00 times more among the patients with neck node as compared with the patients without neck node and the risk was significant. The presence of neck node has been found to be highly specific (96.7%) to detect malignancy, though the sensitivity is poor (37.5%). The plausible explanation of this low sensitivity is that, many a malignancy does not have nodal metastasis at the time of initial presentation.[41]

There was significant association between FNAC type and prediction through USG (P=0.0024). Most of the THY >3 (83.3%) were predicted as malignant by USG. Corroborating with present literature, there was significant association between FNAC type (THY) and HP findings of the patients and 75% of the malignant nodule was for THY >3. In a similar study by Makwana et al., FNAC showed colloid goiter in 57 patients, papillary carcinoma in two patients, and follicular adenoma in six patients and histopathological report showed four cases of papillary

carcinoma, four cases of follicular carcinoma, six cases of follicular adenoma, five cases of thyroiditis, and the rest being colloid goiter.[42] Our results are also comparable to a recent study done by Popli *et al*., they found the sensitivity, specificity, and positive predictive value of ultrasonography to be 81.8%, 87.2%, and 59.0%, respectively, to detect malignancy in thyroid nodules.[43]

Our study had the limitation that while individual radiologic parameters were mentioned, a consolidated formal TIRADS score was not given for the nodules. Sample size was small. In addition, sonological diagnoses are prone to observer variation. For the lymph nodes, we only mentioned their presence and did not characterize specific suspicious features of the nodes.

Diagnosis and management of thyroid disorders in the resource poor Indian sub-continent remain suboptimal. Ultrasonography has emerged as the imaging procedure of choice for thyroid nodules and is simple and widely available at a low cost. When done by an experienced sonologist, ultrasonography can predict malignancy with sufficient sensitivity and specificity. Thus, if a nodule looks undoubtedly benign in USG, it can be observed even without doing a FNAC. On the other hand, when a nodule looks malignant, surgery could be offered without FNAC. It is only the borderline or confusing nodules that require cytology to determine the course of management. Based on combination of radiologic characteristics, scoring systems like the TIRADS have been developed and found to have significant correlation with BETHESDA scoring system for FNAC as well as histopathologic findings. Appropriate management protocol for thyroid nodules entails adequate use of accurate imaging procedures and following prescribed guidelines for thyroid nodule management at all levels of health-care facilities.

Limitations of the study

While making a sonological diagnosis of a nodule (benign or malignant), no cutoff value or scoring system for the presence of different individual signs was used. Thus these sonological diagnoses are prone to observer variation. Only the presence of neck nodes has been taken as a sonological criterion in this study. Specific features of a node could not be elucidated and incorporated into this study due to lack of operational feasibility. TIRADS scoring was not used in this study to classify thyroid nodules. The sample size was small.

CONCLUSION

Diagnosis and management of thyroid disorders in the resource poor Indian sub-continent remain suboptimal. Ultrasonography has emerged as the imaging procedure of choice for thyroid nodules as it not only reproduces better regional anatomy and better correlation of true thyroid dimensions with the image, but also because of its simplicity, low cost, and lack of need for radioisotope administration. When done by an experienced sonologist, it can predict malignancy with sufficient sensitivity and specificity. Thus, if a nodule looks undoubtedly benign in USG, it can be observed even without doing a FNAC. On the other hand, when a nodule looks malignant, surgery could be offered without FNAC. It is only the borderline or confusing nodules that require cytology to determine the course of management.

Based on combination of radiologic characteristics, scoring systems like the TIRADS have been developed and found to have significant correlation with BETHESDA scoring system for FNAC as well as histopathologic findings. More widespread and accurate application of this or more refined systems during routine ultrasound of nodules could prevent unnecessary interventions. Appropriate management protocol for thyroid nodules entails adequate use of accurate imaging procedures and following prescribed guidelines for thyroid nodule management at all levels of health-care facilities.

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RS- Concept and design of the study, prepared first draft of manuscript; **GCG-** Interpreted the results; reviewed the literature and manuscript preparation; **RR**- Concept, coordination, statistical analysis and interpretation, preparation of manuscript, and revision of the manuscript.

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