ORIGINAL ARTICLE

Diagnostic Evaluation of Ultrasound and Cytology for Solitary Thyroid Nodules in a Tertiary Care Setup in India

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Abstract

Aim and objective: To determine the sensitivity, the specificity, the positive predictive value (PPV), and the negative predictive value (NPV) of ultrasound and cytology to detect malignancy for solitary thyroid nodules.

Materials and methods: Prospective observational study conducted at a tertiary care hospital in India. The patients with solitary thyroid nodule, aged more than 12 years with consent of the patients/their parents and planned to undergo surgery, were included in the study. The patients were evaluated with history, examination, sonography, and cytology. Then, they planned for surgical hemi-/total thyroidectomy depending on indications, and the thyroidectomy specimens were sent to Department of Pathology for routine processing.

Results: A total of 140 patients were considered for recruitment, but 80 patients were operated, and their data were analyzed. Sonographic findings were reported using thyroid imaging reporting and data system (TIRADS) classification, and the sensitivity was 75.00% with a specificity of 84.62% and PPV, NPV, and diagnostic accuracy of 72.41, 81.25, and 81.25%, respectively. Cytology was assessed by the Bethesda system for reporting thyroid cytopathology (TBSRTC), and considering Bethesda IV, V, and VI as true positives and Bethesda II as benign, the sensitivity and the specificity were 89.5 and 78.4%, respectively. When a composite analysis was performed, the sensitivity and the specificity of TBSRTC and TIRADS combined were 100 and 36%, respectively. The PPV and NPV were 45 and 100%, respectively, with the accuracy of 58.5%.

Conclusion: The American College of Radiology TIRADS is a sensitive method to detect malignancy in thyroid nodules in Indian population with good specificity and PPV. Fine needle aspiration cytology (FNAC) was observed to be a sensitive technique having achieved a high sensitivity and NPV with a low specificity and PPV. The composite test (incorporating TIRADS and TBSTRC) had 100% predictive value for benign and malignant pathology.

Keywords: Bethesda, Diagnostic evaluation, Sensitivity, Solitary thyroid nodule, Thyroid imaging reporting and data system.

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Introduction

Thyroid swelling is the most common presentation of a thyroid disorder to the endocrine surgeon. The prevalence of thyroid nodules depends upon the method of estimation used. It ranges from 4 to 7% with palpation alone, compared to 20–76% with high-resolution ultrasound.[1–3] This correlates with the reported prevalence at surgery and autopsy with ranges between 50% and 65%.[4,5] The use of high-resolution ultrasound techniques has led to overdiagnosis and overtreatment of thyroid nodules.[3] Not all of them require surgical intervention. The malignancy is found in 5–15% of cases of thyroid nodule, depending on sex, age, and exposure to other risk factors. Mere diagnosis of thyroid nodule adds anxiety to the patient and needs to know the risk of malignancy (ROM) in nodule and further management plan. There is a need to make a confident preoperative diagnosis of benign or malignant nodule. This put the brakes on unnecessary thyroidectomies done for benign asymptomatic thyroid nodules and simultaneously not leaving behind the malignancy. For categorization of ultrasonography (USG) features in thyroid nodules, the thyroid imaging reporting and data system (TIRADS) is used. The purpose of TIRADS is to group the nodules into different categories with a designated percentage of malignancy.[5] Of the various TIRADS available, the American College of Radiology TIRADS (ACR-TIRADS) has emerged as standard method for reporting thyroid sonography findings.[6] Cytological evaluation of thyroid nodules is a rapid, easy, and inexpensive diagnostic procedure. In 2007, the Bethesda system for reporting thyroid cytopathology (TBSRTC) was introduced and subsequently revised in 2017.[7] TBSRTC classifies all thyroid aspirates into six categories, with each category having an associated ROM and guidelines for management. This prospective observational study was designed in a cohort of solitary thyroid nodules, with the objective of evaluating the diagnostic utility of sonography and cytology in student television network (STN) with the final diagnosis as made on histopathology.

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Materials and Methods

Study Design

Prospective observational study conducted at a tertiary care hospital in India with the primary objective of determining the sensitivity, the specificity, the positive predictive value (PPV), and the negative predictive value (NPV) of ultrasound and cytology to detect malignancy for solitary thyroid nodules.

Inclusion Criteria and Exclusion Criteria

The patients with solitary thyroid nodule, aged more than 12 years with consent of the patients/their parents and planned to undergo surgery, were included in the study. The definition of STN used was "A discrete lesion in the thyroid gland that is radiologically distinct from the surrounding parenchyma." Patients with thyrotoxicosis, conservatively managed STN, and patients unfit for surgery were excluded.

Sample Size

The sensitivity of both TIRADS and TBSRTC was high as observed previously in different studies, and the specificity of these tests was 50–70 and 60–95%, respectively, considering TIRADS and TBSRTC as two independent proportions, to detect the significant difference in specificity (as compared to histopathology) 70 vs 90%, we required 82 histopathologically negative cases for our study with 90% power. To get 82 histopathologically negative (i.e., benign) cases, we required 92 cases of thyroid swelling.

Methodology

The patients who presented to surgery outpatient department during study period with STN will be evaluated with history, examination, and investigation. Those with solitary thyroid nodule who met inclusion criteria were considered for study. All patients underwent sonography of neck at the Department of Radiodiagnosis with a superficial 7–15 MHz linear transducer. The sonographic features of the thyroid, including the nodule, were noted; any neck nodes were also evaluated. The findings were noted, and nodule was categorized as per ACR-TIRADS. The patients underwent a USG-guided fine needle aspiration cytology (FNAC) of the thyroid nodule based on ATA guidelines,[8] and cytology smears were assessed and categorized as per TBSRTC system. The patients also underwent preoperative workup, including thyroid profile and indirect laryngoscopy along with routine investigations. The surgical hemi-/total thyroidectomy depending on indications was then performed. The indications of hemithyroidectomy were Bethesda II (>1 cm when patient wants surgery), Bethesda III (diagnostic hemithyroidectomy), Bethesda IV (diagnostic hemithyroidectomy), and papillary thyroid carcinoma less than 1 cm (microcarcinoma). For total thyroidectomy, indications were FNAC-proven carcinoma (Bethesda V, VI), FNAC-proven papillary carcinoma thyroid, with size of nodule more than 1 cm, and intraoperative decision in patients with follicular neoplasm, where infiltration of surrounding structures seen suggests carcinoma. The thyroidectomy specimens were sent to the Department of Pathology for routine processing. It was fixed in neutral buffered formalin. Appropriate sections were taken from the nodule, its capsule, and the adjoining thyroid. The sections were paraffin-embedded, then viewed, and reported by an expert pathologist.

Statistical Analysis

The data were entered in Microsoft Excel sheet for data entry. The data were entered and analyzed with Stata software. And the sensitivity, the specificity, the PPV, and the NPV of both diagnostic tests were calculated and compared with histopathology as gold standard.

Results

A total of 140 patients were considered for recruitment, with a clinically palpable solitary thyroid nodule out of which 30 patients had more than one nodule on ultrasound and were excluded. Out of the remaining 110 patients, 16 refused consent to undergo further investigations and were excluded. Out of the 94 patients, 90 had an operable nodule and were recruited in the study. However, due to the limited availability of the routine OT in the COVID-19 pandemic, only 80 patients were operated and their data were analyzed.

Of the total 80 study subjects, 66 (82.5%) were female and 14 (17.50%) were male patients in the study. Their ages included in the study were all more than 12 years. So, we had few patients in extremes of ages, that is, 3 (3.75%) in less than 20 years and 6 (7.5%) in more than 60 years age group. Almost two-third of patients (65%) were in young age (20–40 years). None of the patients had history of thyroid malignancy or radiation exposure in the past. The nodule was more common on left side in 54 (67.50%) patients than right side in 26 (32.50%) patients. Cervical lymph nodes were present in 5 (6.25%) patients. None of patients had retrosternal extension. Most patients were euthyroid. Nine patients were on thyroxine and biochemically euthyroid on medication. Two patients had subclinical hypothyroidism. None of our patients had tracheal deviation and/or compression.

The USG findings were noted as per ACR-TIRADS (TR) category. Among total population, 24 (30%) nodules were categorized as TR2, 27 (33.75%) in TR3, 23 (28.75%) in TR4, and 6 (7.50%) in TR5 categories. Three (3.90%) patients had cervical lymphadenopathy (levels III and IV) on USG, and these patients underwent FNAC of lymph node. The functional cervical lymph node dissection was performed during surgery. On initial cytology examination, there were eight cases which were unsatisfactory for evaluation. On repeat aspiration, three were recategorized into higher categories. The final distribution of cases into the various Bethesda (B) categories was 5 (6.25%) in B I, 31 (38.75%) in B II, 19 (23.25%) in B III, 15 (18.75%) in B IV, 1 (1.25%) in B V, and 9 (11.25%) in B VI. The surgeries performed were (66, 82.5%) hemi-thyroidectomies, out of which 59 were open and 7 were endoscopic. Total thyroidectomy was done in 9 (11.25%) cases. And lymph node dissection along with total thyroidectomy was done in 5 (6.25%) cases. After hemithyroidectomy, 14 (17.5%) patients needed completion thyroidectomy. The completion thyroidectomy was performed 6 weeks after first surgery.

Diagnostic Test Evaluation

The TR1 category refers to normal thyroid gland, so no further follow-up or workup was done. So, this category was excluded from any further calculation. The TR2 (benign) and TR3 (probably benign) were considered as true negative, and TR4 (suspicious for malignancy) and TR5 (malignant) were considered true positive for malignancy for the diagnostic test evaluation. Based on this, a two-by-two table was constructed and the parameters for TIRADS system were calculated. The sensitivity was 75.00% with a specificity of 84.62% (Table 1). The FNAC findings are recorded as 6 TBSTRC categories. The B I is nondiagnostic category, and no definitive categorization can be done. So, this category is not considered for evaluation of FNAC as diagnostic test. A diagnosis of neoplasm (benign or malignant) equates a surgical outcome. The B III and B IV categories are indeterminate with varying associated risks of malignancy. Hence, sensitivity, specificity, NPV, and PPV for FNAC results were calculated considering various categories into true positive. Category I was omitted from these calculations. Considering only BV and VI as true positive and rest all as true negative, the sensitivity was calculated to be 43.48% and specificity 100%. The sensitivity and the specificity of TBSRTC in our study population were also calculated considering B IV, V,

Table 1: Diagnostic evaluation of sonography taking histopathology as gold standard

Histopathology		
Ultrasound	*Malignant*	*Benign*
Suspicious/malignant (TR4,5)	21	8
Benign (TR2,3)	7	44
Parameters	*Value*	*95% CI*
Sensitivity	75%	55.13–89.31%
Specificity	84.62%	71.92–93.12%
Positive predictive value	72.41%	57.27–83.72%
Negative predictive value	81.25%	70.97–89.11%
Diagnostic accuracy	81.25%	70.97–89.11%

Table 2: Diagnostic evaluation of cytology with different cutoff points for malignancy

Considering Bethesda V and VI as true positive		
Parameter	*Value*	*95% CI*
Sensitivity	43.48%	23.10–65.60%
Specificity	100%	93.70–100%
Positive predictive value	100%	92.40–100%
Negative predictive value	81.43%	75.32–86.28%
Diagnostic accuracy	80.22%	69.80–88.30%
Considering Bethesda IV, V, and VI as true positive		
Parameter	*Value*	*95% CI*
Sensitivity	89.50%	66.90–98.70%
Specificity	78.40%	61.82–90.26%
Positive predictive value	69%	54.20–80.80%
Negative predictive value	93.30%	78.70–98.10%
Diagnostic accuracy	82.30%	69.70–91.20%
Considering Bethesda III, IV, V, and VI as true positive		
Parameter	*Value*	*95% CI*
Sensitivity	92.86%	76.50–99.12%
Specificity	61.70%	46.20–75.20%
Positive predictive value	56.63%	47.24–65.66%
Negative predictive value	94.13%	80.55–82.27%
Diagnostic accuracy	72.60%	61.08–82.27%

and VI as true positives and Bethesda II as benign. The sensitivity and the specificity were 89.5 and 78.4%, respectively. The PPV and NPV are depicted in Table 2. The additional analysis with BIII as true positive resulted in sensitivity and specificity of 92.86 and 61.70%, respectively.

Composite Test

The composite test results were calculated categorizing the test results into benign, indeterminate, and malignant groups and comparing with final histopathology. For the calculation of composite test, nodules with B = II and TR = 2 were combined as benign, and B = V/VI or TR = 5 as malignant results, and the rest as indeterminate category. Thus, the combined test sensitivity, specificity, and validation are calculated considering indeterminate category as true positive and true negative, respectively. So, results of the composite test (combined TBSRTC and TIRADS) can be expressed in three diagnostic categories, such as the definite benign, the indeterminate, and the definite malignant group (Table 3). So, the nodules categorized as benign on composite test result were all benign, and those categorized as malignant were all malignant (100% PPV). Sixteen (34.8%) of the nodules in indeterminate category were malignant. Considering indeterminate as not malignant on composite test, the sensitivity and the specificity of TBSRTC and TIRADS combined were 100 and 36%, respectively. The PPV and the NPV were 45 and 100%, respectively, with the accuracy of 58.5%.

Table 3: Descriptive table for the composite test

	Benign on histopathological examination (HPE)	*Malignant on histopathological examination (HPE)*	*Total*
Benign	17	0	17
Indeterminate	30	16	46
Malignant	0	12	12
Total	47	28	75

Discussion

The significance of thyroid swelling lies in the ROM, which is higher in the solitary thyroid nodule.[8] And the ideal algorithm of management should be certain of the ROM present in these nodules. With the recent advancement of high-frequency sonography, it has become the first investigation for thyroid nodules. Since there is no single ultrasound feature to differentiate benign from malignant nodule, there are various classification systems proposed, including various nodule characteristics. A classification was proposed by Kwak et al. on considering the ROM and subdivisions using five US criteria, called the TIRADS classification. It was validated through retrospective analysis of the available scans and FNAC. This article also described that a malignancy risk lower than 3% is expected for TIRADS 3, a risk of 3.6–91.9%.[9] Recently, ACR-TIRADS is being validated to formulate standardized system as BIRADS for breast imaging reporting, which is used in our study. In our study, the sonography findings categorized more than one-third nodules in benign (TR2) group and only 7.5% in definitive malignant (TR5) category. Almost two-third of the nodules were indeterminate (TR3,4). The test has been validated with various studies in the past. The sensitivity, the specificity, NPV, and PPV are calculated again with respect to cytology or histopathology in various studies. The values vary widely which may be attributed to interobserver variations.

Recently, Grani et al. demonstrated that the ACR-TIRADS reduced unnecessary FNACs more than other international guidelines with a very low false-negative rate (2.2%). This system suggests a higher size threshold for FNA than other guidelines while still recommending similar malignancy risks for each FNAC assessment category.[10] The FNAC is the safe, easy method with good sensitivity and so is the standard of care in thyroid nodule evaluation.[11] Moreover, the pathologists are skilled with this common investigation. The findings are reported as described in standard reporting system, TBSRTC. The sensitivity of thyroid FNAC for surgical decision ranges from 65 to 98%, with a specificity of 72–100% and reported false-negative rates of 1–11%.[12] The sensitivity and specificity were 87 and 100%, respectively, in Indian population study.[13] The sensitivity and the specificity of TBSRTC in

Table 4: Comparison of findings in our study to those reported in literature

	Studies evaluating the sonographic TIRADS classification			
Study	*Sensitivity*	*Specificity*	*PPV*	*NPV*
Our study	*75.00%*	*84.62%*	*72.41%*	*86.27%*
Range[15]	70.0–97.0%	29.0–90.0%	23.0–64.0%	87.0–99.0%
Median[15]	90.0%	57.4%	49.0%	91.0%
	Studies evaluating the cytology with TBSRTC classification			
	Sensitivity	*Specificity*	*PPV*	*NPV*
Our study	*92.8%*	*61.7%*	*56.6%*	*94.1%*
Bongiovanni et al.[14]	97%	60.2%	98%	96%
Pusztaszeri[16]	97%	50.7%	55.9%	96.3%
Cibas and Ali[7]	97%	97%	NA	NA
Keh et al.[11]	73.9%	80%	NA	NA
Wu et al.[13]	87%	100%	NA	NA

our study population were in concordance with those of literature (Table 4). This is important to note that for calculation of FNAC as diagnostic test, we have considered Bethesda III, IV, V, and VI as true positive as in different studies.[14] Considering malignant outcome for thyroid nodules with BV and VI only as true positive, sensitivity was 43.48%, specificity 100%, PPV 100%, NPV 81.43%, and accuracy 80.22% for TBSTRC. About one-third of the indeterminate cases were malignant on resection. Hence, indeterminate nodules on both these investigations may be further evaluated by repeat aspiration cytology (in cases with BIII cytology) or molecular tests or subjected to diagnostic hemithyroidectomy. We have considered diagnostic hemithyroidectomy for this group in our study.

The composite results of two diagnostic tests revealed very high predictive value. The nodules categorized as benign on composite tests result were all benign, and those categorized as malignant were all malignant (100% PPV). If we consider indeterminate category as true positive, the sensitivity, the specificity, the PPV, and the NPV of the composite tests were 42, 100, 76, and 80%, respectively. Considering indeterminate as not malignant on diagnostic tests, the sensitivity and the specificity of TBSRTC and TIRADS combined together were 100 and 36%, respectively. The PPV and NPV were 45 and 100%, respectively, with the accuracy of 58.5%. The combined test results were not analyzed in the literature. For this analysis of the composite tests, B = II and TR = 2 were considered as benign, and B = V/VI or TR = 5 as malignant, and the rest as indeterminate category. No studies have evaluated combined test results.

Conclusion

ACR-TIRADS is a sensitive method to detect malignancy in thyroid nodules in Indian population. It accurately categorized nodule in benign and malignant category with good specificity and PPV. FNAC was observed to be a sensitive technique having achieved a high sensitivity and NPV with a low specificity and PPV. The composite test (incorporating TIRADS and TBSTRC) had 100% predictive value for benign and malignant pathology. About one-third of the indeterminate cases were malignant on resection.

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