

Original Research Article

Triple diagnostic test in the evaluation of thyroid nodules

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ABSTRACT

Background: Thyroid nodules are a common endocrine disease whose prevalence in India is approximately 12.2%. Although most patients with suspected nodules have benign conditions, the overestimation of malignancy leads to the performance of unnecessary procedures. No clinical, radiological and cytological parameters has singularly shown significant impact on clinical practice and post-operative histopathological examination remains the gold standard in the diagnosis of malignancy.

Methods: 55 patients with thyroid nodules were evaluated and the Clinical assessment findings were recorded by McGill thyroid nodule score, ultrasonography findings using TIRADS and FNAC findings by the Bethesda system. The triple test was then used to classify them and these results were compared with the HPE of the post-operative specimen.

Results: The sensitivity and specificity of TIRADS, FNAC were higher as compared to clinical score; clinical score had lowest sensitivity of 72.73%. The sensitivity, specificity, PPV, NPV and accuracy of triple test was 100%. Triple test had higher sensitivity, specificity and accuracy in differentiating thyroid nodules as compared to any of the three parameters used individually.

Conclusions: Triple test has higher accuracy, sensitivity and specificity in determining the nature of thyroid nodule than each of the parameters used individually and it is especially useful in follicular lesions. On the basis of the results of this study, we conclude that the triple test can reliably be used to differentiate benign and malignant nodules preoperatively.

Keywords: Triple test, Thyroid nodule, McGill, TIRADS, Malignancy

INTRODUCTION

Thyroid nodule is any lesion within the thyroid gland that is palpably or radiologically distinct from the surrounding thyroid parenchyma. In India, the prevalence of thyroid nodules is around 12.5.¹ The incidence of thyroid cancer is 8.7 per 100000 people per year and is increasing. Thyroid nodules may be classified as adenomas, carcinomas, or hyperplastic lesions. Differentiated thyroid carcinomas (DTCs), include papillary and follicular carcinomas.²

There is an overestimation of malignancy in thyroid nodules which leads to lot of unnecessary procedures thus increasing the morbidity of the patient. Definitive

preoperative categorization of thyroid nodules into benign or malignant helps to avoid unnecessary extensive surgery and potential surgery related adverse effects. While a number of clinical, radiological, and cytological parameters have been previously studied, none of them have singularly shown significant impact on clinical practice.³

As far as radiological parameters are concerned, Thyroid Imaging Reporting and Data System (TIRADS) and American Thyroid Association guidelines are considered as the main criteria for determining malignancy sonographically.⁴ The Bethesda system is used to classify FNAC results. However post-operative histopathological examination remains the gold standard in the diagnosis of

malignancy.⁵ Many studies till now have focused on a single parameter- clinical, biochemical or radiological, and very few studies have analyzed multiple parameters in combination.⁶

The aim of this study is to evaluate the accuracy of triple diagnostic test, consisting of clinical findings, USG, and fine needle aspiration cytology (FNAC) in thyroid nodules and compare the results of this test to histopathology findings taken as the gold standard.⁷

METHODS

Inclusion criteria

Patients aged 18 and older undergoing thyroid surgery.

Exclusion criteria

Patients with metastatic lesions were not included in the study.

This was an observational cross-sectional study conducted in VMMC and Safdarjung hospital, New Delhi over a period of 1.5 years from September 2018 to March 2020. Patients who were to undergo surgery for thyroid nodule in the department of surgery, VMMC and SJH were identified and their clinical presentation, ultrasonography and FNAC findings were recorded. The patients were classified as having benign or malignant disease based on the triple parameters and the results were compared with histopathological findings, obtained from post-operative biopsy specimens. Study was undertaken after approval from institutional ethic committee and informed consent was taken from all participants.

Sample size

The study of Diani Kartini⁷ observed that sensitivity and specificity of triple diagnostic was 77% and 94%. Taking these values as reference, the minimum required sample size with desired precision of 15%, 80% power of study and 5% level of significance was 50 patients. To reduce margin of error, total sample size taken was 55.

Clinical assessment

Clinical assessment (history and physical examination) was scored by Diane Kartini’s modification of the McGill Thyroid Nodule Score/MTNs.^{7,8} Diagnostic test using the receiver operating characteristic (ROC) procedure was performed to obtain clinical cut-off scores of diagnoses of malignant. Results of the clinical examination was considered to be malignant if scores >3.

Ultrasound

Results were classified according to TIRADS USG classification. USG result was considered malignant for TIRADS category 4,5.

FNAC

Cytological results of FNAC were divided into 6 categories based on Bethesda system for reporting thyroid cytopathology. Categories I, II, III were placed into benign whereas IV, V VI were taken malignant.

Triple diagnostic test

If clinical, USG and histopathology examinations of triple diagnostic test had malignant results, it was classified as malignant concordant whereas if all those three showed benign results, the classification was benign concordant. In cases of discordant results, the categorisation into benign and malignant was done based upon which category 2 out of 3 elements of the triple test fell into.

Statistical analysis

This study used computer program Statistical package for social sciences (SPSS) 22 for statistical calculations. Chi-square test was used to obtain receiver operating characteristic (ROC) curve and was performed between each element of triple diagnostic test to the gold standard. Multivariate analysis using logistic regression test was done in order to reveal the diagnostic value of the triple diagnostic test. In the analysis of this diagnostic test, each variable was divided into 2 groups: malignant and benign.

RESULTS

In present study, majority (60.00%) of patients belonged to ≤30 years followed by 31-40 years (23.64%), 41-50 years (9.09%) and >60 years (5.45%). Majority (85.45%) of patients were females and only 8 out of 55 patients were males. Swelling in neck was the most common complaint amongst patients, 4 patients had toxic symptoms and only two patients had pressure symptoms. No patient had family history of thyroid cancer. Clinical score predicted benign in 85.45% of cases and malignancy in 14.55% of cases.

Table 1: Distribution of clinical score of study subjects.

Clinical score	Frequency	Percentage
0	39	70.91
1	4	7.27
2	3	5.45
3	1	1.82
4	8	14.55
Benign	47	85.45
Malignant	8	14.55

Ultrasonography was done for all the study subjects and TIRADS was used to categorize the findings. In majority (43.64%) of patients, TIRADS category was 1 followed by 2(36.36%) and 4 (14.55%). TIRADS category was 5 in only 3 out of 55 patients. TIRADS predicted benign in 80% of cases and malignancy in 20% of cases.

All patients were subjected to FNAC irrespective of their TIRADS category after confirmation of euthyroid status.

In majority (63.64%) of patients, FNAC category was 2 followed by 3 (16.36%), 5 (9.09%) and 6 (7.27%). FNAC was category 4 in only 2 out of 55 patients. FNAC predicted benign in 80% of cases and malignancy in 20% of cases.

Table 2: Distribution of TIRADS category of study subjects.

TIRADS category	Frequency	Percentage
1	24	43.64
2	20	36.36
3	0	0.0
4	8	14.55
5	3	5.45
Benign	44	80.00
Malignant	11	20.00

The results of all three parameters were compared and patients were categorized into benign and malignant by the triple diagnostic test. In majority (80.00%) of patients, triple test predicted benign. Triple test predicted malignant in only 11 out of 55 patients. The results of each of the three parameters and the results of the triple test were compared with HPE, taking the later as gold standard.

Table 3: Distribution of HPE of study subjects.

HPE	Frequency	Percentage
Follicular adenoma	7	12.73
Follicular carcinoma	2	3.64
Multinodular goitre	2	3.64
Nodular colloid goiter	35	63.64
Papillary carcinoma	9	16.36
HPE		
Benign	44	80.00
Malignant	11	20.00

Table 4: Diagnostic test to find out sensitivity, specificity, NPV and PPV of clinical score, TIRADS, FNAC and triple test to predict malignancy.

Diagnostic test	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Diagnostic accuracy
Clinical score	72.73 (39.03 to 93.98)	100 (91.96 to 100.00)	0.86 (0.74 to 0.94)	100 (63.06 to 100.00)	93.62 (82.46 to 98.66)	94.55
TIRADS	100 (71.51 to 100.00)	100 (91.96 to 100.00)	1 (0.94 to 1.00)	100 (71.51 to 100.00)	100 (91.96 to 100.00)	100.00
FNAC	100 (71.51 to 100.00)	100 (91.96 to 100.00)	1 (0.94 to 1.00)	100 (71.51 to 100.00)	100 (91.96 to 100.00)	100.00
Triple test	100 (71.51 to 100.00)	100 (91.96 to 100.00)	1 (0.94 to 1.00)	100 (71.51 to 100.00)	100 (91.96 to 100.00)	100.00

Table 5: Inter-rater kappa agreement between triple test and HPE.

Triple test	HPE		Total	P value	Kappa
	Benign (n=44)	Malignant (n=11)			
Benign	44 (80.00%)	0 (0.00%)	44 (80.00%)	<.0001	1.000
Malignant	0 (0.00%)	11 (20.00%)	11 (20.00%)		
Total	44 (80.00%)	11 (20.00%)	55 (100.00%)		

Very good agreement exists between HPE and triple test with kappa 1 and p<0.0001. Among 11 patients diagnosed as malignant via HPE, all the patients had similar findings in triple test. Overall concordance rate was 100.00% and overall discordance rate was 0.00% between HPE and Triple test

DISCUSSION

The sensitivity and specificity of TIRADS, FNAC were higher as compared to clinical score; sensitivity 100% (71.51% to 100.00%) and specificity 100% (91.96% to 100.00%). In differentiating thyroid nodules, clinical score had lowest sensitivity of 72.73%. Although several studies show that physical examination is a poor predictor of malignancy, clinical examination was specific and

relatively sensitive in making a diagnosis of malignancy in this study.^{9,10} But all the parameters had specificity of 100.00%. Sampling bias may be responsible for the higher values of sensitivity and specificity of the individual parameters in this study

The sensitivity, specificity, PPV, NPV and accuracy of triple test was 100%. This shows that triple test had higher sensitivity, specificity and accuracy in differentiating thyroid nodules as compared to any of the three parameters used individually.

Some grey areas in thyroid nodules have always been controversial. These may include Bethesda Category 3 - Atypia of unknown significance/ Follicular lesion of unknown significance, Bethesda category 4- suspicious for follicular neoplasm.¹¹ The diagnosis of follicular lesions has always been challenging.^{12,13} The addition of TIRADS to these lesions may help in such cases of uncertainty. The combination of three parameters in triple assessment is even more useful in distinguishing benign and malignant follicular lesions.

In this study there were 9 patients of Bethesda category 3 whose triple test and HPE showed benign nature. This shows a malignancy rate of 0 in Bethesda category 3 lesions in this study. In other studies that compared FNAC findings and HPE, the estimate rate of malignancy in Bethesda category 3 lesions to be between 25-30%.¹⁵ But the use of triple test in this study was effectively able to categorize all the Bethesda category 3 lesions as benign which was in complete agreement with HPE.

However, there is a need for more studies with larger sample sizes. If these studies can avoid bias and reduce confounding factors, they can help in validation.

CONCLUSION

Thyroid nodules often present a diagnostic and management dilemma for the surgeon, pathologist, endocrinologist, and patient as well. While many diagnostic tools have been developed, most of these are either based on radiological, pathological or biochemical findings. There is need for a single reliable test that can amalgamate all these tools to help determine preoperatively the nature of a thyroid nodule before planning patients for surgery.

The results from this study have shown that the accuracy, sensitivity and specificity of triple test in determining the nature of thyroid nodule was higher than each of the parameters individually. In cases where radiological, pathological and clinical findings are contrasting, the triple test is especially helpful as it combines all of the variables assessed in the individual tests. In nodules belonging to Bethesda categories 3 and 4 which usually pose a diagnostic challenge, triple test can provide a more accurate categorization as benign or malignant. On the basis of this study, we conclude that the triple test, owing

to its high accuracy, sensitivity, specificity and can reliably be used to differentiate benign and malignant nodules preoperatively.

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