Original Article

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Cyto-Histo-Biochemical And Ultrasonographic Correlation of Thyroid Lesions: A Multidisciplinary Approach: An Experience at Rural Tertiary Care Hospital in Southern coast of India

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ABSTRACT

Introduction: Thyroid lesions are one of the most common palpable lesions subjected for FNAC.Fine Needle Aspiration Cytology (FNAC) of the thyroid gland is now a well-established first-line diagnostic test for the evaluation of diffuses thyroid lesions as well as of thyroid nodules with the main purpose of confirming benign lesions and thereby, reducing unnecessary surgery.Apart from cytology, other investigations like ultrasonography (USG),thyroid function tests(TFTs) play a supportive for better understanding of thyroid nodules under evaluation.Also, there is some "gray zone" of thyroid cytology where the diagnostic efficacy of FNA declines sharply.Radioimaging (ultrasonography) can be helpful in grey areas of indeterminate lesions and non-diagnostic aspirates. Though USG features alone cannot predict malignancy or benignity, but techniques that combine USG features and FNA cytology are most effective and most accurate for predicting malignancy.

Aims and Objectives: We aimed to evaluate cytological features of palpable thyroid lesions and to correlate with histopathological , radiological and thyroid function tests wherever available, at a rural tertiary health care institute in southern coastal region of India.

Materials /Methods: This study was analysis of 156 cases of palpable diffuse and nodular thyroid lesions subjected to FNAC over a period of one and half year at a rural tertiary health care Institute.

Results: Thyroid lesions constituted 19.3% of total lesions subjected to FNAC in study period.Age group ranged from 13 - 77 years, maximum cases belonged to 5th decade with female preponderance . Clinically, nodular swelling accounted for 86% cases.Benign lesions detected were 75.6%. Malignant lesion accounted for 7.7% cases.Cyto-histo correlation overall was noted in 72.2% cases with benign lesions showed 76.92% were as malignant lesion showed 100% correlation. Sensitivity, specificity , positive predictive value, negative predictive value and diagnostic accuracy was 40%, 100%,100%, 78.6% and 81.3% respectively. Similarly, Overall Radio- cytological concordance was 81.03%. In hormonal correlation, majority (59%) were euthyroid. In these lesions, 60.9% were goitres whereas in cases with hypothyroidism, majority (56%) had thyroiditis.

Conclusion: FNAC is simple, cost-effective, more specific than sensitive procedure for evaluating thyroid masses, further evaluation of thyroid nodule for thyroid function status and radiological support especially in grey zone area of indeterminate lesion has a definitive role to play.

Keywords: *Thyroid Lesion, Cytology, Histopathology, Thyroid Function Tests, Ultrasonography*

Introduction

Thyroid lesions are one of the common conditions encountered in clinical practice. Fine Needle Aspiration Cytology (FNAC) of the thyroid gland is now a well-established first-line diagnostic test for the evaluation of diffuse thyroid lesions as well as of thyroid nodules with the main purpose of confirming benign lesions and thereby, reducing unnecessary surgery[1,2].Also,FNAC is easy to perform, has a low complication rates and high diagnostic value and is a cost-effective test used in the diagnosis of thyroid nodules[3,4,5].Currently, FNAC is the preferred diagnostic method for the initial stage of evaluation of thyroid nodules[5].Thus,Fine-needle aspiration cytology is the cornerstone of thyroid nodule evaluation.

The use of FNAC has resulted in a decrease in the number of patients who underwent surgical treatment by 25-50%, while increasing the percentage of malignant results in the operated group of patients[6].As a result, the incidence of malignancy at thyroidectomy has increased from 5 to 10% to 30 to 50% in the recent years[7].Although there is a large body of world literature claiming the accuracy and usefulness of thyroid cytology, there is also evidence showing possible limitations and pitfalls of this procedure[8].

Apart from cytology, other investigations like ultrasonography (USG),thyroid function tests(TFTs) play a supportive for better understanding of thyroid nodules under evaluation.

Also, there is some "gray zone" of thyroid cytology where the diagnostic efficacy of FNA declines sharply[9].

Radioimaging (ultrasonography) can be helpful in grey areas of indeterminant lesions and non-diagnostic aspirates.

Though USG features alone cannot predict malignancy or benignity, but techniques that combine USG features and FNA cytology are most effective and most accurate for predicting malignancy [10].

Similarly,TSH measurement can be part of the initial workup in every patient with a thyroid nodule and be used as a guide for further management. Lower levels of TSH are associated with a lower risk of papillary thyroid cancer in patients with thyroid nodular disease[11].Recent studies have investigated the relationship between serum TSH concentration and thyroid cancer. TSH was found to be an independent predictor of malignancy in thyroid nodules[12]. The risk of malignancy rises in parallel with serum TSH, even within the normal range, and higher TSH levels were found to be associated with advanced-stage thyroid cancer[11,12].

Thus, the aim of this study was to correlate cyto-histo,cyto-biochemical and cyto-radiological evaluation to give us broader and better evaluation of palpable thyroid nodules wherever these modalities were available.

Materials and Methods

This analytical study comprised of 156 cases of palpable diffuse and nodular thyroid lesions subjected to FNAC in Department of Pathology over a period of one and half year at a rural tertiary health care Institute after obtaining ethical clearance from institute Human ethics committee. Data regarding clinical features, concise history, thyroid function tests and USG features were obtained from cytology requisition forms and medical records section and analyzed.

Cytological evaluation was done on May Grunwald Geimsa (MGG) and Hematoxylin and Eosin(H&E) stained slide and reporting based on Bethesda classification.[3] Benign group consisted of Colloid goitre, thyroiditis, cyts (colloid cyst/thyroglossal cyst), whereas the indeterminant group consisted of lesions with follicular archietecture with two subgroup -atypia of undetermined significance (AUS)/ follicular lesion of undetermined significance (FLUS) and another was FN(follicular neoplasm)/SFN (suspicious for follicular neoplasm). Malignant group consists of suspicious for malignancy and malignant cytology without any overt follicular architecture.

For biochemical correlation, results of thyroid function tests were categorized as euthyroid, hypothyroid and hyperthyroid and findings were correlated with cytological diagnosis.

For radiological correlation, features of benign and malignancy were noted. In ultra-sonography, imaging features significantly associated with the incidence of malignancy were microcalcification, hypervascularity, hypoechoic, irregular shape, ill-defined margins, absence of halo/rim and solid appearance[13]. Conversely,predominantly cystic lesion with no microcalcifications, isoechogenicity and spongiform appearance (defined as aggregations of multiple microcysts in more than 50% of the nodule) are features highly suggestive of benignity[14,15].

Statistical Methods: Percentage was used for descriptive statistic to explain the distribution and simple data interpretation. To test the efficacy of FNAC against gold standard histopathology, diagnostic test like sensitivity, specificity, positive and negative predictive value and accuracy was applied.

Results

Thyroid lesions constituted 19.3% of total lesions subjected to FNAC in the study period. Age group ranged from 13 to 77 years and maximum cases belonged to 5th decade. Thyroid lesions showed female preponderance with ratio of 6.09:1 over males. Mean age for male and female were 41.6years and 42.02 years respectively with no statistical significance. Most common clinical presentation was nodular swelling (86%).Benign lesions accounted for 75.6% on FNAC and Goitre was the most common lesion diagnosed on FNAC , accounting for 56.4% cases followed by thyroiditis (15.4%) and cystic lesion (3.8%). Indeterminate lesions which falls under grey zone area in thyroid FNAC accounted for 16(10.3%)cases – Ten were FLUS and six were FN/SFN. Malignant cases were Twelve(7.7%) on cytology. Ten cases (6.4%) were labelled unsatisfactory due to low cellularity or hemorrhagic smears.[Table 1]

Cyto-histocorrelation:[Table 2] FNAC diagnostic categories were compared with corresponding histopathological diagnosis. Out of 156 FNACs, histopathology was available in 36(23%).In 118 benign cytology cases, histology was available in 36 cases, and cyto-histo concordance was seen in 20 (77%).Out of 6 cases of colloid goitre on cytology , two showed incidental Papillary micro-carcinoma with surrounding colloid goitre changes on histology and four were follicular variant of Papillary carcinoma on histology which accounted for false negative cases.[Fig:1,2]

In 16 indeterminate cases of cytology, histology was available in 6 cases, 4 cases of FLUS showed adenomatoid nodule with colloid goitre and two cases of follicular neoplasms turned out to be follicular carcinoma.[Fig:1,2]

In four malignant cytology cases, cyto-histo concordance was 100%. Thus, overall cyto-histo concordance was seen in 72.2% cases.

Accordingly, sensitivity, specificity , positive predictive value, negative predictive value and diagnostic accuracy was calculated and found to be 40%, 100%,100%, 78.6% and 81.3% respectively.

Cyto-Biochemical Correlation: [Table 3] Thyroid function tests were available in 118(75.6%) cases. Majority of them were euthyroid (78%) and most of them showed colloid goitre (60.8%) on FNAC.Hypothyroidism accounted for 18.6% and majority of them (54.5%) were showing features of thyroiditis on FNAC.But four cases of colloid goitre on cytology which turned out to be Papillary carcinoma on histopathology (false negative on FNAC) were showing hypothyroidism.

Cyto-Radiological Correlation: [Table4] Ultrasonography findings were available in 116(74.3%).In cystic lesions on cytology, USG was very useful in diagnosing origin of four cystic lesion as thyroglossal cyst contributing to 100% cyto-radio correlation. Similarly, in ten non-diagnostic aspirates on FNAC, radiology provided diagnosis of colloid goitre in eight cases.In malignant cases also there was 100% cyto-radio-histology correlation.

In ten cases of FLUS, six cases in which USG was available showed findings of colloid goitre which showed concordance with histopathology cases. In six cytologically diagnosed FN/SFN, USG was available in four cases, with two showing follicular adenoma .But histology showed follicular carcinoma. Other two cases showed colloid goitre.

In sixteen indeterminate cases, with suspicious of follicular lesion of on cytology ,USG was available in ten cases,showed adenoma features in two,malignancy features in two (FC on HPE), remaining six showed goitreous features. Thus, radiological features were more conclusive in indeterminate cases.

Thus, overall cyto-radio concordance was found to be 77.6% in 116 cases. Four cases of colloid goitre on cytology which turned out to be Papillary carcinoma on histopathology (false negative on FNAC) were showing hypothyroidism

Table 1: Cytological diagnosis of Palpable thyroid lesions.

Cytological Diagnosis	N=156	Percentage (%)
Benign (n=118) Colloid goitre Thyroiditis Cystic lesion	 88 24 06	75.6 = 56.4 15.4 03.8
Indeterminate(n=16) AUS/FLUS FN/SFN	 10 06	10.3
SM/Malignant(n=12) PTC Medullary	 10 02	7.7
Non-diagnostic- (n=10)	 10	 6.4
Total	**156**	**100%**

Table 2: Cyto-histopathology correlation in thyroid lesions.

Cytological Diagnosis(n=156)	No. of cases with HPE available (n=36)(its correlation with FNAC)	Correlated with FNAC n (%)
Benign-total (118) Colloid goiter(88) Thyroiditis (24) Cystic lesion(06)	26= 22(16-CG,4-FVPTC,2=PMC+goitre) 02 02	20= (77) 16 (73) 02 (100) 02 (100)
Indeterminant- Total (16) AUS/FLUS (10) FN/HN/SFN(6)	06= 04 (ANCG) 02 (FC)	 00 02 (100)
Malignant-total(12) PTC (10) MTC (02)	04= 02 02	 02 (100) 02 (100)
Unsatisfactory (10)	0	
Total	**36**	**26 (72.2)**

CG=colloid goitre,FVPC=Follicular variant of papillary carcinoma,PMC=Papillary microcarcinoma,PTC=papillary thyroid carcinoma,ANCG=Adenomatoid nodule with colloid goitre,AUS=atypia of undetermined significance,FLUS=follicular lesion of underteminate significance,FN=follicular neoplasm,HN=hurtle cell neoplasm,SFN=suspicious for follicular neoplasm,MTC=medullary thyroid carcinoma

Table 3: Cyto-Biochemical correlation.

THYROID FUNCTION TESTS	No. of cases evaluated (n=118)	Percentage(%)	Cytological diagnosis n (%)
Euthyrodism	92	78%	Colloid goitre 56 (60.8%)
Hypothyroidism	22	18.6%	Thyroiditis 12 (54.5%)
Hyperthyroidism	04	3.4%	Goitre 04 (100%)

Table 4: Cyto-Radiological correlation.

Cytological diagnosis (n=156)	Radiological diagnosis available (Total n=116)	Correlated with FNAC	Not correlating with FNAC n (Radio Diagnosis)	Histopathology available
Benign(118) Colloid goitre (88) Thyroiditis (24) Cyst (06)	 72 18 04	 64 (88.8%) 14 (77.8%) 04 (100%)	 08 (6PTC+ goitre, 2Thyroiditis) 04 (goitre)	 06 (PTC) 02 02
Indeterminant (16) FLUS (10) FN/SFN/ HN (06)	 06 04	 06(CG) 02(FA)	02(CG)	06 (CG) 02(FC)
Malignant (12)	04	04 (100%)	-	04(2PTC,2MTC)
Non diagnostic (10)	08	-	08 (CG)	-
Total	**116**	**94(81.03%)**	**22(18.97%)**	

FA=follicular adenoma,FC=follicular carcinoma,CG= colloid goitre,PTC=Papillary thyroid carcinoma,MTC=medullary thyroid carcinoma

Table 5: Cytological diagnosis rendered in thyroid lesions in Indian studies.

Indian studies	Nonneoplastic (%)	Malignant (including suspicious for malignancy)(%)	Indeterminant/follicular lesions (including FLUS/ Suspicious of follicular Neoplasm)(%)	Non diagnostic (%)
Handa et al [7]	87.7	3.91	3.22	5.06
Richa etal[22]	53.16	9.56	35.10	2.12
Sunita etal[18]	94.6	1.6	3.1	0.7
Bagga et al[5]	90.5	1.2	6.7	1.6
Pande et al[4]	72.03	4.69	18.79	4.47
Present study	75.6	7.7	10.3	6.4
AsliMuratli et al[19]	59.5	20.5	9.3	10.8

Table 6: Sensitivity, specificity, Accuracy, negative and positive predictive values in thyroid lesions in Indian studies and foreign studies.

Study	Number of Patients	Sensitivity	Specificity	Accuracy	Negative Predictive value	Positive Predictive value
Sengupta etal[21]	178	90	100	98.88	98.75	100
Gupta etal[17]	75	80	86.6	84	86.6	80
Sunita etal[18]	104	50	100	94.2	93.8	100
Prakash etal[23]	162	40	100	95.71	95.58	100
Pande etal[4]	112	57.14	90	80.28	83.33	70.58
Bagga etal[5]	32	66	100	96.2	96	100
Richa Sharma etal[22]	74	89.47	86.11	87.83	88.57	87.18
Foriegn Asli etal[19]	126	87.1	64.6	77.3	79.5	76.1
Fatemeh etal[20]	101	95.2	68.4	85.14	89.6	83.3
Present study	36	40	100	81.3	78.6	100

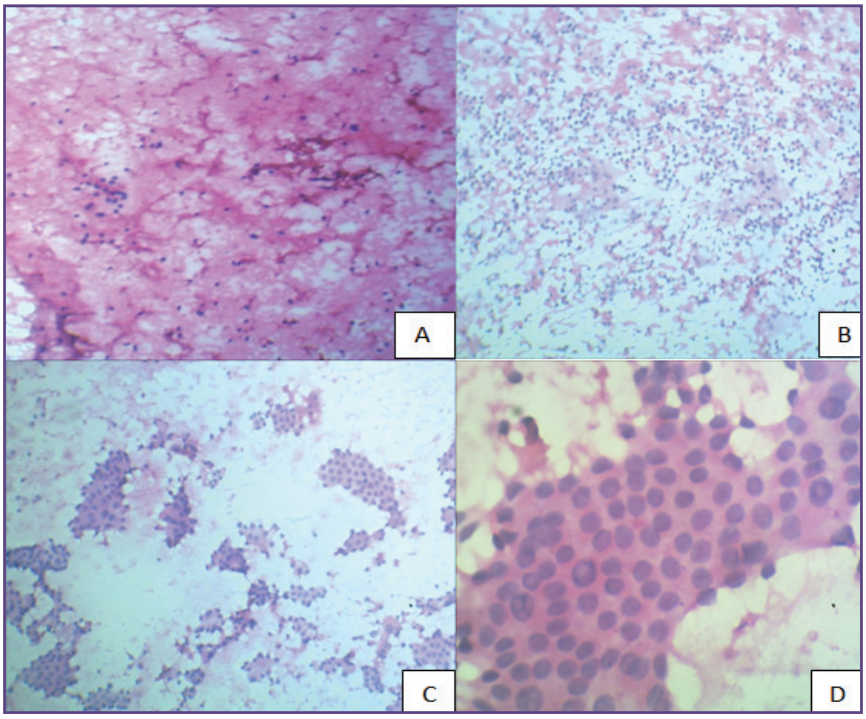

Fig. 1: A-Colloid Goitre-diffusely scattered follicular cells in background of thin colloid(H&E 10X),B- Lymphocytic thyoiditis-Follicular cells dispersed on background of denselymphocytes(H &E10X), C- Follicular Neoplasm-Repetitive microfollicular pattern of follicular cells (H &E 10X), D-Papillary thyroid carcinoma-showing overlapping,intranuclear inclusions(H&E 40X)

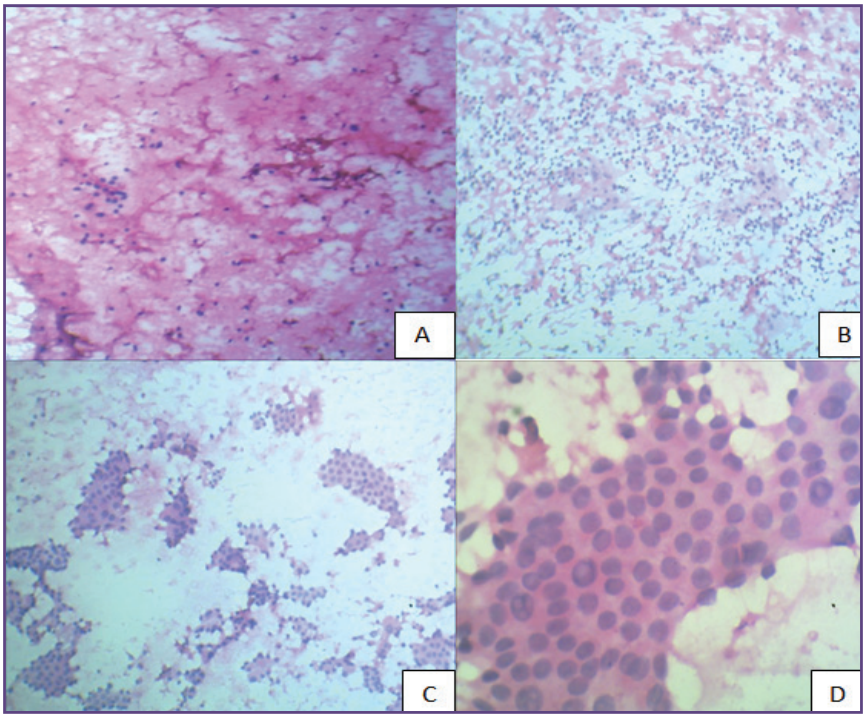

Fig. 1: A-Colloid Goitre-diffusely scattered follicular cells in background of thin colloid(H&E 10X),B- Lymphocytic thyoiditis-Follicular cells dispersed on background of denselymphocytes(H &E10X), C- Follicular Neoplasm-Repetitive microfollicular pattern of follicular cells (H &E 10X), D-Papillary thyroid carcinoma-showing overlapping,intranuclear inclusions(H&E 40X)

Discussion

Palpable Thyroid nodules are one of the main indications of thyroid FNACs. The prevalence of palpable thyroid nodules range from 4 to 7% for adults[16].In our study, thyroid FNACs accounted for 19.3% amongst all lesions subjected to FNACs. In present study, most common age group affected was 5thdecade with mean age of 41.8 years. Female preponderance was seen with Female :Male ratio of 6.09:1. Similar findings were noted in studies from different parts of India and Asian countries[4,7,17,18,19,20,21]

In present study, majority thyroid lesions on cytology were benign accounting for 75.6% and most common benign lesion found was colloid goitre (56.4%).Similar findings were noted in other Indian studies.[4,5,7,18,22] Frequency of Malignancy in our study on cytology was 7.7%.In other Indian studies it ranged from 1 to 16% [4,5,7,17,18,21,22]. [Table 5]

Cyto-histo Correlation: FNA has become a primary diagnostic tool for evaluating thyroid nodules and a correct cytologic diagnosis obviates unnecessary thyroid surgeries. Therefore incidence of benign cytological lesions subjected for surgical excision are less over the period of time due to efficacy of cytology. This was also observed in our study where histopathology was available in 36 cases (23.07%) out of 156 cytology cases. The overall cyto-histo concordance achieved in our study was 72.2%.In other Indian studies, it ranged from 50% to 95% [4,18,22,23,24].

In our study, out of twenty two cases of goitre on cytology, six showed papillary carcinoma on histology and accounted for false negative cases. Out of six, two were incidentally detected papillary micro-carcinomas in a colloid goitre specimen. This is a common pitfall of FNAC as lesion is too small which could have missed due to untargeted FNAC. Here, USG can help to detect smaller lesions like papillary micro-carcinoma with features such as solid nodule with microcalcification. In literature, it has been mentioned that papillary micro-carcinomas (smaller than 1 cm) incidentally found at the time of surgery are much more common (up to 36%) but it is controversial whether or not a survival benefit exists with the diagnosis and treatment of such entities, given their generally benign course[15,16,17,18].Another four case of papillary carcinoma on histology were follicular variant of PTC which was reported as adenomatoid goitre probably due to lack of high cellularity required for neoplastic lesions, follicular architecture, and inadequate or missed nuclear features lead to misdiagnosis. Strict criteria for nuclear features in lesion with follicular architecture should be followed to avoid misdiagnosis. Here also, imaging study findings can be correlated to come to conclusion.

In case of malignancies, two follicular neoplasm on cytology turned out to be follicular carcinoma. This is one of the true pitfall of cytology were criteria to diagnose follicular carcinoma is capsular and vascular invasion which can be assessed only on histology and cannot be assessed on cytology.

Four cases of follicular lesions of undetermined significance (FLUS) cytology were diagnosed due to high cellularity which was more for colloid goitre but short of suspicious follicular neoplasm turned out to be adenomatoid colloid goitre on histology. Repeat aspirates can help to clinch a definitive diagnosis on cytology in these cases which are sitting on fence and comes under grey zone, thus helping clinicians for further definitive management [3].

In present study, unsatisfactory/ non-diagnostic cases accounted for 6.4%. Six cases were unsatisfactory due to haemorrhage and low cellularity inspite of repeat aspirates. Four cases showed poor compliance and lost in follow-up. Non-diagnostic rate approximately ranged from 0.7 to 10% in the studies from different parts of India [4,5,7,18,22].

In statistical analysis, sensitivity, specificity , diagnostic accuracy, negative predictive value and positive predictive value in our study was 40%, 100%, 81.3%, 78.6% and 100% respectively. Low sensitivity was due to low number of sample subjected to histopathology examination and as well as false negative cases missed on cytology,suspicious on radiology and subjected to surgical excision.Sensitivity, specificity, ,diagnostic accuracy, negative predictive value and positive predictive value in other studies ranged from 40-90%, 85-100%, 77-98%, 80-98% and 70-100% in Indian studies respectively[4,5,17,18,21,22,23]. Other Asian studies show higher sensitivity but low specificity as compared to Indian studies[19,20].[Table 6]

Cyto-Hormonal Correlation: Though FNACs are the mainstay investigation in the evaluation and diagnostication of thyroid masses, thyroid function tests and USG neck study are the next important investigations in further evaluation of thyroid nodules. In our study, majority (78%) cases were euthyroid and most of them were colloid goitre (60.8%) on cytology. Similar findings were noted in other studies were euthyroid cases ranged from 56 to 66% [18,7].Interestingly , in our study hypothyroidism was more common (18.6%) than hyperthyroidism(3.4%) in this southern coastal iodine sufficient belt .This is in contrast with the study from northern parts of iodine deficient sub-Himalayan belt of India where hyperthyroidism cases were more frequent[7]. Interestingly, study from western India showed near equal occurrence of hypo and hyperthyroidism [18].Majority of the cases of Hypothyroidism in our study showed thyroiditis (54.5%) on cytology. Thus, inflammation and goitrogens

may be the contributory factors for more hypothyroidism cases in this part of India.

Cyto-Radio correlation Thyroid USG is an important technique widely used in the detection and evaluation of thyroid nodules. It is a non-invasive, inexpensive procedure that provides information with regard to nodule dimensions, structure, and thyroid parenchymal changes. Thyroid USG allows targeting of nodules with suspicious appearance for cytology.

In our study, the overall cyto-radiological concordance was 81.03%.In two malignant cases and one cystic case, cyto-radio-histopathology concordance was 100%.Thus emphasising that instead of cytology alone, USG also can play pivotal role in establishing diagnosis in thyroid lesions and lead to avoidance of surgery in benign cases.

In present study ,radiological findings were useful in grey areas of cytology like false negative cytology, follicular neoplasm and non-diagnostic cases. In six false negative cytology cases, USG showed solid Hypoechoic nodule with micro-calcification which showed features PTC on histology. Two cases of follicular lesion on cytology showed follicular adenoma on USG but histology showed follicular carcinoma. This suggests further radiological studies like elastography may be helpful in establishing malignant features in these cases. Elastography is a recent advancement in the diagnosis of thyroid nodules and a promising tool for predicting the malignant potential of thyroid nodules as it assesses the hardness of the tissue as an indicator of malignancy[29]. This technique was demonstrated to be highly specific (96%–100%) and sensitive (82%–97%) in the diagnostic evaluation of thyroid nodules, independent of nodule size, or location within the thyroid gland[30].

Conclusion

FNAC is a simple, reliable cost-effective outpatient procedure for evaluating palpable thyroid masses. It is more specific than sensitive, thus underlining its role in diagnosing malignant lesions than benign lesions. Also, further evaluation of thyroid nodule for thyroid function status as hypo/hyper or normal helps the clinicians a step further in management of thyroid lesions. Radiology in support with cytology has a definitive role to play, as it helps to overcome grey zones of cytology.

Thus, multidisciplinary correlation of thyroid lesions gives us better understanding of lesions.

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