



ROLE OF STRAIN ELASTOGRAPHY IN THE CHARACTERIZATION OF BENIGN AND MALIGNANT NATURE OF THE THYROID NODULES.

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ABSTRACT

Elastography is an imaging technique to measure the stiffness of tissues. Images are acquired before and after soft compression of tissues and the deformation is evaluated. Strain ratio -calculated as the ratio of stiffness between nodular tissue and surrounding normal thyroid tissue. With prior verbal and written consent patients were examined on gray-scale ultrasound on transverse images and then using elastographic ultrasonography technique. patients were followed up by fnac findings & postoperative histopathology report in cases of inconclusive FNAC reports. This is prospective study conducted on 200 subjects at Government Medical College, Department of RADIO-DIAGNOSIS, Nagpur from November 2016 to 2018. Regarding sonoelastograph, relation between elastograph scores and thyroid malignancies showing sensitivity, specificity and p value is calculated. The most accurate strain ratio cutoff value among studies calculated.

RESULTS: Ultrasound Strain elastography is a promising imaging technique that is useful in the differentiating between benign and malignant thyroid nodules. Further improvements in the technique and the diagnostic criteria are necessary for this examination to provide a useful contribution to diagnosis. The use of Real Time ultrasound strain elastography would lead to low thyroid FNAC's because of the high elasticity of being strongly associated with a benign cytology.

KEYWORDS : Elastography, Ultrasound elastography, Real time ultrasound elastography, Elastoscore, Strain ratio, Microcalcifications , Intranodular vascularity.

INTRODUCTION:

A thyroid nodule is an abnormal growth of cells within the thyroid gland and can be non-cancerous (benign) or cancerous (malignant). FNAC is still the most popular method of diagnosing thyroid nodules; it is not expected to be done for all patients. Some patients may be missed, others show insufficient specimen and others have very small nodules that are difficult to do FNAC.

This is prospective study conducted on 200 subjects at Government Medical College, Department of RADIO-DIAGNOSIS, Nagpur from November 2016 to 2018.

ELASTOGRAPHY [PRINCIPLE]- a) Active external displacement of tissue surface. b) Passive internal physiologically induced. Property displayed Strain ('ELASTOGRAM') Measurement Qualitative Imaging Full area image; colour image superimposed on a standard B-mode image (Real-time Tissue Elastography")

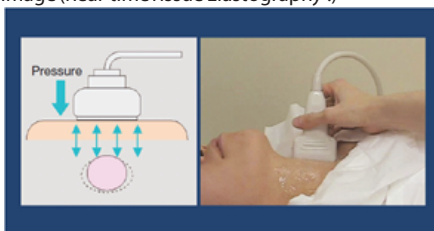


Figure 1: Operation of Elastography probe in thyroid.

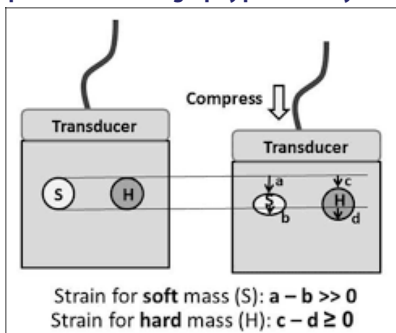


Figure 2: Calculating strain.

The effect of manual compression on soft (S) or hard lesions (H) within the soft tissue and how strain or elasticity is being calculated.

STRAIN RATIO -calculated as the ratio of stiffness between nodular tissue and surrounding normal thyroid tissue.

AIMS AND OBJECTIVES:

1. TO STUDY THE ROLE OF STRAIN ELASTOGRAPHY IN THE CHARACTERIZATION OF BENIGN AND MALIGNANT NATURE OF THE THYROID NODULES.
2. TO EVALUATE THE ELASTOGRAPHIC APPEARANCES OF THYROID NODULES.

- This is a prospective hospital-based study. We test the sensitivity and specificity of strain elastography in detection of malignant thyroid nodules, and compare its results with those of US & Doppler and the Fine Needle Aspiration Cytology results which is taken as the Gold Standard reference test in this study. Both results were correlated to the FNAC results as a gold standard test.

- **STUDY SETTING** --- INDOOR AND OUTDOOR PATIENTS AT GMCH, NAGPUR REFERRED TO THE DEPARTMENT OF RADIOLOGY.

- **NO. OF PATIENTS** --- 200

- **PLACE OF STUDY** --- DEPARTMENT OF RADIO-DIAGNOSIS, GOVERNMENT MEDICAL COLLEGE AND HOSPITAL NAGPUR (M.S.).

- **DURATION OF STUDY** --- 2 YEARS. [FROM 2016 TO 2018].

- **MACHINE** --- PHILIPS IU 22 ULTRASOUND MACHINE.

THYROID ULTRASOUND SCANNING PROTOCOL:

Ultrasound examination was done on PHILIPS IU 22 ULTRASOUND MACHINE Fig. (3) by using high-frequency linear array transducer (5 to 12 MHz) Fig. (4), with spatial digital iU22 Philips compounded B-mode, color Doppler US (CDUS) and real time elastography. The subjects were examined in supine position, with pillow placed under their shoulders to hyperextend the neck. US gel was applied over the thyroid area Fig. (5). The elasticity score measurements Fig.(6) and ratios between nodules and adjacent parenchyma were calculated. Thyroid nodules were classified into benign or malignant

based on and elastography results which were correlated to FNAC results after FNAC.



Figure 3: Shows Ultrasound equipment u/s machine, IU 22 (Philips medical system).



Figure 4: Shows ultrasound transducer used is Broadband Linear Array Transducer 5 to 12 MHz extended operating frequency range. (Philips medical system)



Figure 5: Shows protocol scan plane for axial view for thyroid nodule.

Score 1 [Benign]: Whole area is evenly coded green (soft), with similar surrounding tissue, Fig. (6).

Score 2 [Benign]: Area with non-homogeneous elasticity shows mixed color of green, blue, and red, Fig. (6).

Score 3 [Intermediate]: Area coded green (soft) at the periphery, blue (stiff) at the center, Fig. (6).

Score 4 [Malignant]: Most of the area is blue with peripheral green area (stiff), Fig. (6).

Score 5 [Malignant]: Entire area is blue (high stiffness), Fig. (6).

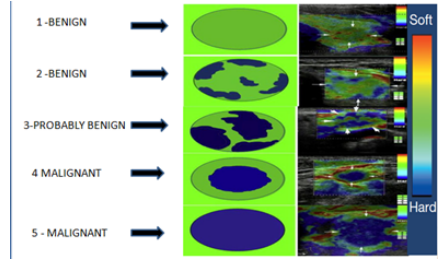


Figure 6 : NODULAR THYROID LESIONS WERE CATEGORISED ACCORDING TO THE SCORE GIVEN USING "RAGO SCORING SYSTEM"-

METHODOLOGY:

Study design: Prospective interventional study

MATERIALS AND METHODS:

The study is a prospective study conducted on convenience sample of 200 patients selected by simple random sampling who attended the Ultrasound section of department Radiodiagnosis at Government Medical College and Hospital Nagpur.

The selection of patients was done by the following criteria:

Inclusion Criteria:-

1. Patients with thyroid swellings referred for ultrasound evaluation.
2. Patients with ultrasound findings s/o thyroid nodule.

Exclusion criteria:

1. Patients not giving consent for procedure.
2. Patients having thyroid nodules with majority of the cystic component [$>30\%$].
3. Multifocal lesions of thyroid are excluded from the study.

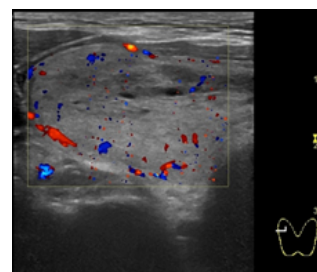
After history and clinical evaluation, the measurements taken by single examiner so as to avoid observers bias.

REPRESENTATIVE CASES:

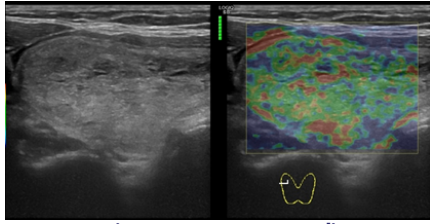
CASE 1: A 33 years old female patient presented with painless lump on right side of neck since one year.



CASE-1 : a) clinical photograph: lump in right side of neck.

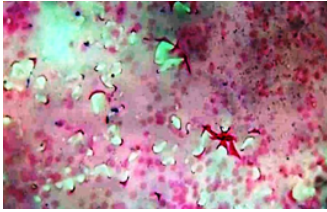


b) Colour Doppler: nodule showing predominantly peripheral vascularity.



c) Gray scale ultrasound: Hyperechoic, relatively well defined lesion (halo sign present), TR>AP[TR=transverse diameter, AP=anteroposterior diameter of the lesion] and without microcalcifications.

d)Elastogram:showing elastoscore of 2. Strain ratio was 1.5

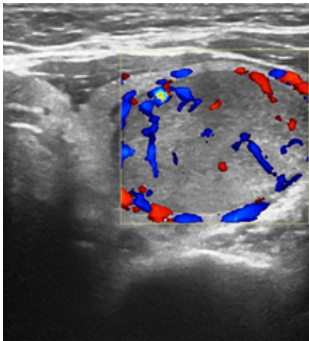


e):FNAC: showed features suggestive of COLLOID GOITRE.

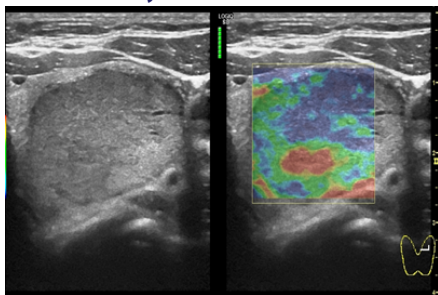
Case-2: A 45 years old female patient presented with painless lump in neck on left side since 1 year.



CASE 2- a) Clinical photograph: lump in left side of neck.

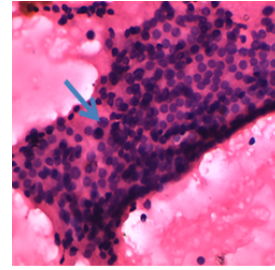


b) Colour Doppler: showing predominantly peripheral and mild intranodular vascularity.



c) Gray scale ultrasound: iso to hyperechoic, well defined(halo sign present), TR>AP, lesion without microcalcifications.

d) Elastogram: showing elastoscore of 3(i.e. probably benign). Strain ratio was 2.1

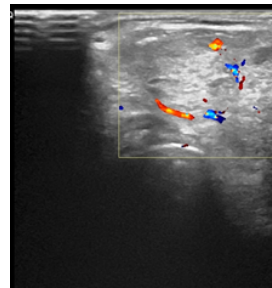


e) FNAC: showed features suggestive of Follicular Adenoma, which was also subsequently proven as follicular adenoma on postoperative specimen histopathology.

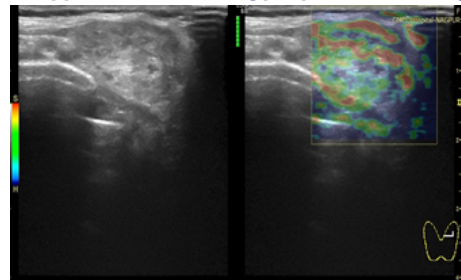
Case-3: A 40 years old female patient presented with painless lump in left side neck since two years



CASE-3 : a) clinical photograph: lump in left side of neck.

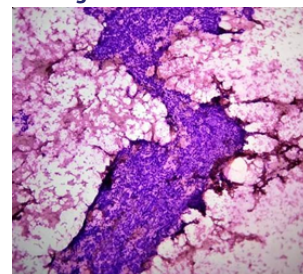


b) Colour Doppler: nodule showing peripheral vascularity.



c) Gray scale ultrasound : hyperechoic, relatively well defined(halo sign present), TR>AP, lesion without microcalcifications.

d) Elastogram: showing elastoscore of 2. Strain ratio was 1.8

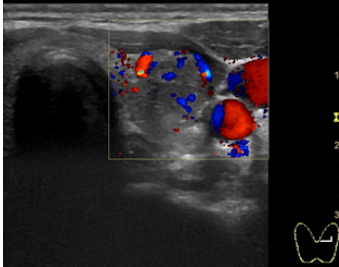


e) : FNAC: showing features suggestive of ADENOMATOUS GOITRE.

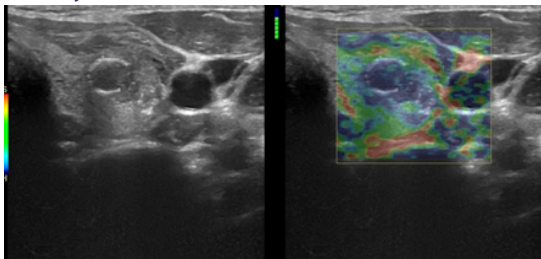
CASE-4 : A 32 years old female patient presented with painless lump on left side of neck since 6 months.



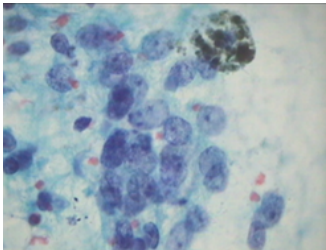
CASE-4: a) Clinical photograph, swelling in left side of neck.



b) colour Doppler: showing peripheral as well as intranodular vascularity.



c) gray scale ultrasound: hypoechoic, illdefined(absent halo), AP>TR, lesion with microcalcifications.
d) Elastogram: showing elastoscore 4. Strain ratio was 5.

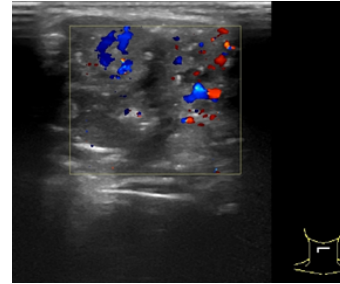


e) FNAC : revealed it to be a **PAPILLARY CA. THYROID** [Bethesda category-VI]- Cellular atypia with prominent nucleoli and intranuclear inclusions.

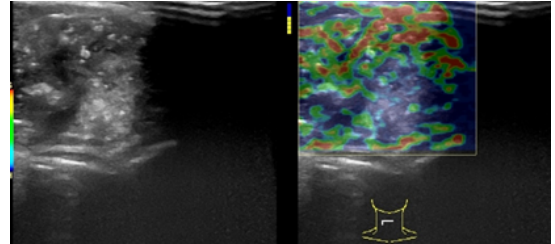
CASE-5: 53 years old female patient presented with painless lump on left side of neck since two years.



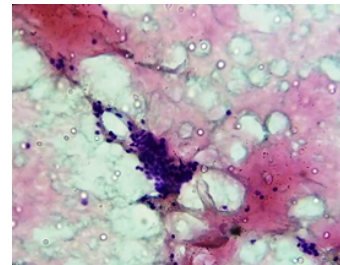
CASE-5: a) clinical photograph: swelling in right side of neck



b) colour doppler: showing mild intranodular vascularity.



c) Gray scale ultrasound : Hyperechoic, relatively well defined(halo sign present), TR>AP, lesion with coarse calcifications.
d) Elastogram: showing elastoscore of 3 (i.e. probably benign). Strain ratio was 2.3

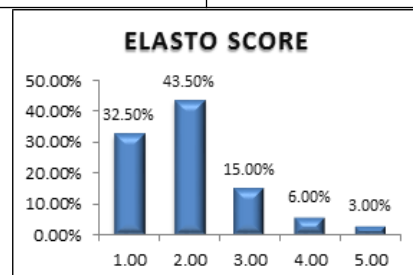


e) FNAC : showing features suggestive of **Multinodular goitre.**

OBSERVATIONS:
 This study included 200 patients who were referred to radiology department, ultrasound section. The majority of patients studied were females 180 (90%), while males present the percent of 20 (10%). The average age of the patients in present study was 39.0 years. The peak incidence was among the age between 31-40 years of age presenting the percent of (31.0%) of the total patients (200).

TABLE 1: Showing percentage of ELASTO SCORES found in the present study in 200 patients with thyroid nodules:

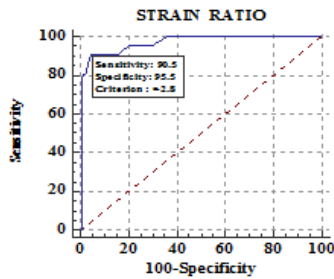
Score	Percentage
1.00	32.50%
2.00	43.50%
3.00	15.00%
4.00	6.00%
5.00	3.00%
Total	100.00%



GRAPH 1: Showing percentage of ELASTO SCORES found in the present study in 200 patients with thyroid nodules:

Table (2): Strain ratio obtained in 200 patients with thyroid nodules

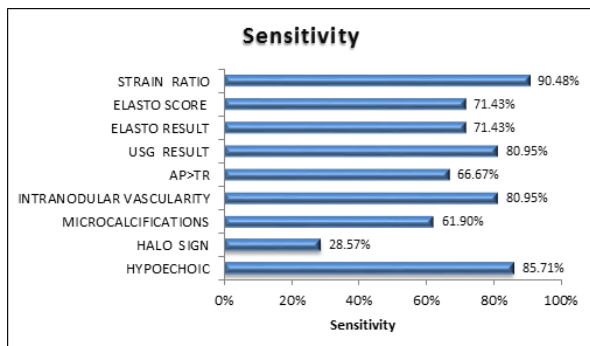
STRAIN RATIO	Frequency	Percentage
<=2.8	173	86.50%
>2.8	27	13.50%
Total	200	100.00%



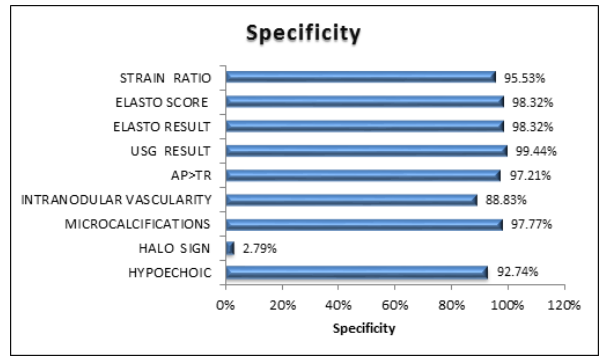
GRAPH 2: showing sensitivity and specificity of strain ratio.

Table (3): Showing predictivity of ultrasound features compared with gold standard test [FNAC]

Parameter Studied	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
HYPOECHOIC	85.71%	92.74%	58.06%	98.22%
95% CI	63.66% to 96.95%	87.90% to 96.08%	39.08% to 75.45%	94.90% to 99.63%
HALO SIGN	28.57%	2.79%	3.33%	25.00%
95% CI	11.28% to 52.18%	0.91% to 6.40%	1.23% to 7.11%	8.66% to 49.10%
MICROCALCIFICATIONS	61.90%	97.77%	76.47%	95.63%
95% CI	38.44% to 81.89%	94.38% to 99.39%	50.10% to 93.19%	91.57% to 98.09%
INTRANODULAR VASCULARITY	80.95%	88.83%	45.95%	97.55%
95% CI	58.09% to 94.55%	83.27% to 93.04%	29.49% to 63.08%	93.84% to 99.33%
AP>TR	66.67%	97.21%	73.68%	96.13%
95% CI	43.03% to 85.41%	93.60% to 99.09%	48.80% to 90.85%	92.19% to 98.43%
USG RESULT	80.95%	99.44%	94.44%	97.80%
95% CI	58.09% to 94.55%	96.93% to 99.99%	72.71% to 99.86%	94.47% to 99.40%
ELASTO RESULT	71.43%	98.32%	83.33%	96.70%
95% CI	47.82% to 88.72%	95.18% to 99.65%	58.58% to 96.42%	92.96% to 98.78%
ELASTO SCORE	71.43%	98.32%	83.33%	96.70%
95% CI	47.82% to 88.72%	95.18% to 99.65%	58.58% to 96.42%	92.96% to 98.78%
STRAIN RATIO	90.48%	95.53%	70.37%	98.84%
95% CI	69.62% to 98.83%	91.38% to 98.05%	49.82% to 86.25%	95.89% to 99.86%



GRAPH 3: Showing Sensitivity of each parameter in the study.



GRAPH 4: Showing Specificity of each parameter in the study.

DISCUSSION:

There are many US criteria for differentiating benign from malignant thyroid nodules. Such differentiation is important for selecting patients for further FNAC in cases with suspicious of malignancy, or to avoid unnecessary FNAC's for those with benign criteria. There are multiple US features that are highly suggestive of malignancy in a thyroid nodule including presence of microcalcifications, hypoechogenicity, irregular margins, absence of a halo sign, predominantly solid composition, and intranodular abnormal vascularity.

In this study we have taken FNAC as the Gold standard [Reference] test. The aims of our prospective study were to evaluate the elastographic appearances of thyroid nodules and to determine whether ultrasound elastography (USE) may assist in differentiating benign from malignant thyroid nodules and results in reducing of thyroid FNAC'S.

The sample of this study consisted of **200** patients all had U/S scan and 200 patients had U/S, real time ultrasound elastography and FNAC examination.

The majority of the sample study were females; **180** patients with percentage of **(90%)**, while males were **20** with percentage of **(10%)**. Females to Males ratio was approx **(9:1)**, and from **21** patients had malignant nodules there were **18** female had malignant nodules with percentage of **(85.71%)** and **3** males **(14.28%)**, with females: males ratio of **(6:1)**, and this is true since **Elgizouli et al** reported the predominance of thyroid malignancy in females, with a female: male ratio of (10:1).

In our study, tissue stiffness on ultrasound elastography was scored from 1 (greatest elastic strain) to 5 (no strain) based on subjective analysis of the elastogram image. The scoring was classified to differentiate benign and malignant lesions and is based on color pattern with elastography image. Score 1, and 2 included nodules with high elasticity, score 3 was maintained as an intermediate score; and scores 4 and 5 included nodules with low elasticity. Using this score classification, the predictivity of US elastography was highly rewarding. Scores 4 and 5 were associated with malignancy.

In our study, by combining the ultrasound parameters such as presence of microcalcifications, hypoechogenicity, absence of a halo sign, antero-posterior diameter of the lesion more than tranverse diameter (AP>TR) and intranodule abnormal vascularity had a sensitivity of 80.95%, a specificity of 99.44%, a positive predictive value of 94.44%, a negative predictive value of 97.80% in the prediction of malignancy.

In our study, by combining the scores 1, 2, 3, 4, and 5, **ULTRASOUND ELASTO SCORE** had a sensitivity of 71.43%, a specificity of 98.32%, a positive predictive value of 83.33%, a negative predictive value of

96.70% in the prediction of malignancy. This study confirmed by study of Rago et al.^[3] (Our results are very close to the findings reported by previous studies^[8], showing **REAL TIME ELASTOGRAPHY (RTE)** sensitivity of 82% and specificity of 93.7% considering Elastography Score 1 and 2 as benign and Elastography Score 4 and 5 as malignant).

Intermediate score; and scores 4 and 5 included nodules with low elasticity. Using this score classification, the predictivity of US elastography was highly rewarding. Much more rewarding were the negative predictive values of the pattern of high elasticity scores to exclude malignancy. **In the current study**, scores of **1 or 2** were found in **47** cases, all benign lesions diagnosis at cytology. This means that nodules with high elasticity, which represent the largest proportion of nodules with indeterminate cytology, have no probability to bear malignancy according to our study result. The low number of false-negative results at USE, together with the low progression rate of differentiated thyroid cancer, would allow most patients to be placed in follow-up without significant costs in terms of prognosis. A **score 3 (intermediate score)** was found in **12** cases with two cases of carcinomas, and 10 cases benign lesions. In score 3 according to our result, all patients with score 3 must be sent to fine needle aspiration cytology (FNAC) for confirmation. **Our results** are very close to the findings reported by **previous studies of RAGO et al and NYEKOE and GLADYS, 2011**, showing RTE (Real Time Elastography) sensitivity of 92% and specificity of 93.7% (considering Elastography Score 1 and 2 as benign and Elastography Score 4 and 5 as malignant).

In our study, **STRAIN RATIO** had a sensitivity of **90.48%**, a specificity of **95.53%**, a positive predictive value of **70.37%**, a negative predictive value of **98.84%** in the prediction of malignancy. The **cut off** value of strain ratio for benign and malignant nodules **in present study** found to be **2.8**.

OUR STUDY LIMITATIONS:

Firstly, this type of elastography procedure [STRAIN ELASTOGRAPHY] which is dependent on personal colour scale to be replaced by the other elastography techniques, also it appears more operator dependent, to improve the real time elastography.

Second, **the previous study reported** that, the major limitation of FNA cytology is that 10% to 15% of specimens are not diagnostic^[7,8].

In present study percentage of nodule specimens with insufficient or inadequate for diagnosis at US (Ultrasound Guided)-FNAC was **8.5%**. In this study thyroid nodules with inconclusive reports by FNAC were followed up by histopathological report

SUMMARY:

In summary, we found that **REAL TIME ULTRASOUND STRAIN ELASTOGRAPHY (RTUSE)** is an easy, non-invasive and rapid technique that can be used routinely in thyroid US scans to select cases for FNAC, and decrease the number of unnecessary biopsies, and consequently decrease its hazards and costs. Cases that show score 1 or 2 are not in need for further investigation, and only follow up should be recommended.

Cases with score 4 or 5 are considered to be highly malignant and other US criteria of malignancy should be looked for to support the diagnosis e.g. pattern of vascularity and cervical lymph nodes infiltration. FNAC should be recommended in all cases of score 3 where malignancy can't be excluded using USE criteria only.

In the current study, all the 200 nodules selected for FNAC by the real-time ultrasound, the cytology results showed the incidence of malignancy was **(10.50%)**. This study shows more or less similar prevalence of malignancy compared with previous report of **RAGO et al**, 2010. **In the current study** Malignant nodules showed predominantly AP>TR in diameter than benign lesions, presence of microcalcifications and intranodular vascularity in apparent agreement with previous studies^[7,9].

CONCLUSION:

In conclusion, US is the modality of choice in evaluation of thyroid nodules. Ultrasound Strain elastography is a promising imaging technique that is useful in the differentiating between benign and malignant thyroid nodules. Further improvements in the technique and the diagnostic criteria are necessary for this examination to provide a useful contribution to diagnosis. No single criteria are sure of malignancy, however, combination of some criteria- in particular- Hypoechoogenicity, Microcalcification and Intranodular vascularity increases the likelihood of malignancy that warrants FNAC.

The use of Real Time ultrasound strain elastography would lead to low thyroid FNAC's because of the high elasticity being strongly associated with a benign cytology.

RECOMMENDATIONS:

- We recommend to utilize the REAL TIME ULTRASOUND STRAIN ELASTOGRAPHY as the protocol with the combination of the conventional ultrasound so as to reduce the thyroid FNAC's.
- Although ULTRASOUND STRAIN ELASTOGRAPHY still remains a promising non-invasive procedure for discriminating malignant from benign lesions and it is an operator-dependent procedure, therefore sonographers and sonologists should be well trained to improve the results.

FUNDING : No funding source.

CONFLICT OF INTEREST: None declared.

ETHICAL APPROVAL : The study was approved by the institutional Ethics committee.

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