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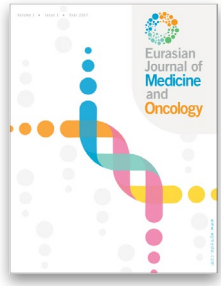

Research Article

Radio-Pathological Correlation of Suspected Malignant Thyroid Nodules using Elastography strain ratio and Bethesda Classification for Thyroid Cytopathology

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Abstract

Objectives: To determine the diagnostic performance of elastography strain ratio (SR) for the diagnosis of malignant thyroid nodules taking fine needle aspiration cytology (FNAC) as the gold standard at a tertiary care hospital in Pakistan.

Methods: This is a cross-sectional study. A total of 150 cases aged 20-60 years, of either gender, who presented with palpable/suspected malignant thyroid nodules of any size with Thyroid Imaging Reporting and Data System (TIRADS) category 3 or above on ultrasonography were included. These were further evaluated by elastography and ultrasound-guided fine needle aspiration cytology (FNAC). The elastography SR of the nodules was assessed. Final diagnosis was made using ultrasound-guided FNAC. Relevant clinical and demographic data were obtained from patient charts. The diagnostic sensitivity, specificity, negative predictive value, positive predictive value, and accuracy were calculated for elastography using FNAC as a gold standard.

Results: The mean age of all patients was 41.8±8.6 years (range: 20-60 years). There were 97 (64.67%) males and 53 (35.33%) females. The majority of patients, 50 (33.33%), belonged to age category of 41 to 50 years. Taking elastography SR of > 2.32 as the cut-off, 69 (46.0%) nodules were positive, and 81 (54.0%) were negative. The FNAC results showed that 72 (48.0%) were positive, and 78 (52.0%) were negative. The diagnostic sensitivity of SR was 92.31%, specificity, 87.50%, positive predictive value, 88.89% and negative predictive value was 91.30%. The overall diagnostic accuracy was estimated to be 87.5%.

Conclusion: The results from this study show that elastography and SR are highly valuable in discriminating benign from malignant thyroid nodules. These may serve as an affordable and reliable alternative diagnostic technique, particularly in the developing world.

Keywords: Bethesda system for thyroid cytopathology, elastography, strain ratio, thyroid incidentalomas, thyroid nodules

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Asymptomatic thyroid nodules are often detected incidently during diagnostic imaging procedures that are done for some other purpose.[1] These are known as thyroid incidentalomas (TIs).[1, 2] American Thyroid Association (ATA) has described thyroid nodules as lesions within the gland that are radiologically dissimilar from the surrounding parenchyma of

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the thyroid.[3] Thyroid nodular disease poses a diagnostic and therapeutic challenge, as there is a need to accurately identify malignant cases. The latter generally account for seven to 15% of all thyroid nodules. It has been noted that the incidence of thyroid cancer has significantly increased, and this has led to an increase in the demand for accurate diagnostic techniques.

Ultrasound (US) is an easily accessible, non-invasive procedure, and its affordability makes it a more desirable method of diagnosis in developing countries. These traits make US an essential investigation in the assessment of thyroid nodules.[4] However, US has demonstrated less value in being a consistent and reliable diagnostic tool for thyroid nodules. The sensitivity and specificity of US in detecting thyroid nodules tends to vary in literature between 52% to 97%, and 26% to 83%, respectively. As per the ATA guidelines, US lacks the required sensitivity and specificity that is needed to identify every type of malignant nodule. One reason for this could be that there is variation in the morphology, dimensions, and quantity of the thyroid nodules that can be observed among patients.[5,6] Thyroid Imaging Reporting and Data System (TIRADS) is used internationally for reporting the US characteristics of thyroid nodules and determining the risk of malignancy. There are five TIRADS categories and the risk of malignancy increases with each successive category. ATA guidelines state that FNAC is the diagnostic procedure of choice for the diagnosis of thyroid nodules.[3]

Elastography is a novel technique that assesses the level of rigidity of the parenchyma, as nodules which are hard, are more likely to be malignant. There is some evidence in literature that suggests that elastography significantly contributes to the detection of malignancy.[7, 8] Nonetheless, the value of elastography as a diagnostic tool for thyroid nodular lesions is not extensively studied in the field.[9] There are two kinds of elastography techniques which are being used in the field of medicine: strain and shear-wave elastography (SWE). Strain elastography (SE) is able to assess tissue elasticity by two techniques. In one technique, colors around and within the nodules are appraised qualitatively and visually scored as per a 4-5 scale scoring system. The other technique helps specify the target regions and the adjacent reference area. Subsequently, elastography computes a strain ratio (SR). There is a high probability of malignancy in cases where there is an increased SR. Overtime, there has been increased utilization of the technique of fine needle aspiration cytology (FNAC) guided by US. With an increased access to cytology analysis through FNAC guided by US and functional imaging modalities such as 18 FDG-PET, the related diagnoses of thyroid cancer has shown a rising trend.[10-12] Notwithstanding the fact that both US and FNAC are widely recommended procedures to study patients with thyroid nodules, the value of the exact concordance between the two methods has yet to be established.

In Pakistan, there is scarcity of data regarding the burden of TIs and their risk stratification. To the best of our knowledge, there is only one well-documented study on the prevalence of TIs conducted in Karachi, Pakistan.[5] Consequently, the purpose of this study was to assess the diagnostic performance of elastography SR for the diagnosis of malignant thyroid nodules taking FNAC as the gold standard at a tertiary care hospital in Karachi, Pakistan.

Methods

This is a cross sectional study which was conducted from July 2021 to July 2022 at the Radiology Department of Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan after approval from SIUT Ethical Research Committee (Approval no: SIUT-ERC-2021/A-307 dated 1st July 2021). A total of 150 cases aged 20-60 years, of either gender, who presented with palpable/suspected malignant thyroid nodules on US with TIRADS category 3 or above of any size, were included. Non-probability consecutive sampling was used for this study. US evaluation of thyroid with SE using SR technique was performed using Canon system Aplio i800 machine.

Written informed consent was obtained from all patients. Patients who had had a previous thyroid surgery, history of radiation to the neck area, were on thyroxin medication, or who had a confirmed histopathology record in their medical charts were excluded from this study. Patients with history of acute coronary syndrome, stroke, chronic renal failure, chronic obstructive pulmonary disease, and asthma were also excluded.

Malignant thyroid nodules were diagnosed using Bethesda classification for thyroid cytopathology. For the purpose of this study, categories V and VI were labelled as positive for malignancy (Fig. 1). In US elastography, a cut-off value of 2.32 was chosen, and SR values above 2.32 were labeled as "positive", and values below 2.32 were labeled as "negative" (Fig. 2). True positives were defined as those patients who had malignant thyroid nodule according to Bethesda Classification for FNAC and also on US elastography. True negatives were those patients who had no malignant thyroid nodule according to Bethesda Classification for FNAC and also no malignant nodule on US elastography. False positives were those patients who had no malignant thyroid nodule according to Bethesda Classification for FNAC; however they had a malignant thyroid nodule on US elastography. False negatives were those patients who had a malignant thyroid nodule according to Bethesda Classification for FNAC, but had no malignant thyroid nodule detected on US elastography.

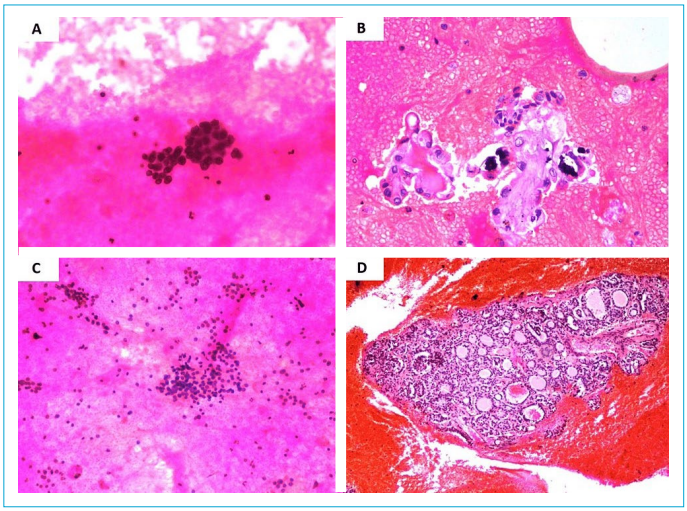

Figure 1. Cytological and histological features of thyroid lesions. **(a)** Medium-power view of a cytology smear showing papillary structures. (Hematoxylin and eosin, ×200). **(b)** High-power view showing a papillary process covered by epithelial cells with nuclear features suggestive of papillary carcinoma. (Hematoxylin and eosin, ×400). **(c)** Low-power view showing numerous clusters of follicular cells suggestive of a follicular lesion. (Hematoxylin and eosin, ×100). **(d)** Medium-power view showing a lesion composed of variable sized follicles suggestive of a follicular lesion. (Hematoxylin and eosin, ×200).

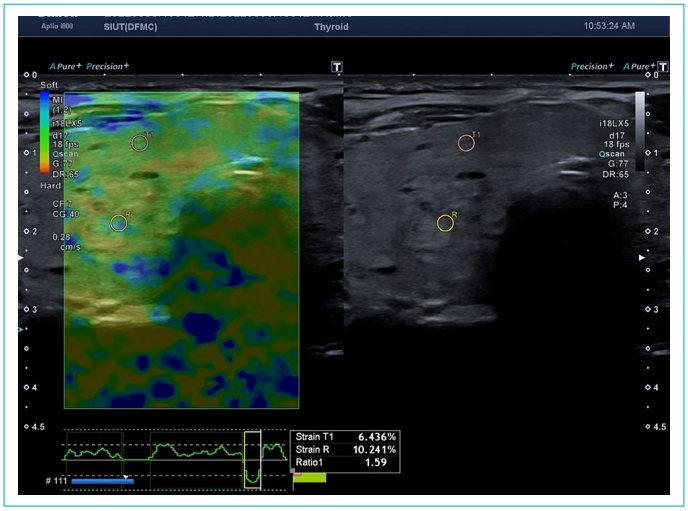

Figure 2. Ultrasound strain elastography image performed with superficial linear probe on thyroid nodule with heterogonous morphology texture and irregular margins having strain ratio of 1.59. According to the cut-off value of 2.32, this will qualify as negative for malignancy.

Data Analysis

Data analysis was done using SPSS® Version 22.0 (IBM Corp., Armonk, New York). Mean±SD, were calculated for the descriptive statistics of continuous variables like age. Frequency and percentages were calculated for categorical variables such as gender, and Bethesda categories. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were calculated using a two-by-two contingency table.

Results

There were 150 cases of palpable/suspected malignant thyroid nodules included in this study. The mean age of all patients was 41.8±8.6 years (range: 20-60 years). There were 97 (64.67%) males and 53 (35.33%) females. The majority of patients, 50 (33.33%), belonged to age category of 41 to 50 years, as shown in Table 1. Taking elastography SR of greater than 2.32 as cut-off for malignancy, 69 (46.0%) nodules were positive, and 81 (54.0%) were negative (Table 2). The FNAC results showed that 72 (48.0%) nodules were positive, and 78 (52.0%) were negative. On comparing the results of SR elastography with the gold standard of FNAC results, the diagnostic sensitivity of SR was 92.31%, specificity was 87.50%, PPV was 88.89% and NPV was 91.30%. The overall diagnostic accuracy was estimated to be 87.5%.

Table 1. Demographic characteristics of patients with suspected malignant thyroid nodules and the results of elastography and fine needle aspiration cytology

Variables	Number	Percentage
Age (years)		
20-30	41	27.33%
31-40	34	22.67%
41-50	50	33.33%
51-60	25	16.67%
Gender		
Males	97	64.67%
Females	53	35.33%
Malignant thyroid nodules on SR		
Positive	69	46.0%
Negative	81	54.0%
Malignant thyroid nodules on FNAC		
Positive	72	48.0%
Negative	78	52.0%

SR: strain ratio; FNAC: fine needle aspiration cytology.

Table 2. Results of elastography strain ratio (SR) taking fine needle aspiration cytology (FNAC) as the gold standard

	FNAC Result		
	Positive	Negative	Total
Strain ratio			
Positive	63 (TP)	06 (FP)	69
Negative	09 (FN)	72 (TN)	81
Total	72	78	150

TP: true positives; FP: false positives; FN: false negatives: TN; true negatives.

Discussion

The prevalence of thyroid nodules has been noted to demonstrate an increasing trend.[13] There are some commonly found risk factors that predispose a patient to high risk of developing thyroid nodules such as: being a female, increasing age, iodine deficiency, and any history of radiation to the patient's neck and head regions. Detection of thyroid nodules varies according to the method employed for the purpose of detection: 2-6% by palpation and about 19-35% by US evaluation.[14, 15]

FNAC is the technique of choice for differentiating malignant from benign thyroid nodules. In cases where the cytology is not confirmatory, then real-time elastography is a useful method that helps in deciding whether the patient should get the surgery done or not.[13] Elastography is a novel technique being increasingly used in the assessment of thyroid nodules by comparing tissue elasticity.[15] SE and SWE are two distinct types of elastography that are utilized in medical practice.[16] Among these, SE is most commonly used in the assessment of thyroid pathology. Two techniques are employed: one option is the appraisal of colors within and around the nodules and their visual scoring according to the 4-5 scale scoring systems. The other one identifies areas of interest and the adjoining reference area. After the qualitative assessment, elastography estimates SR spontaneously. A greater SR suggests an increased probability of malignancy.[16]

In this study, all patients underwent strain US elastography by the SR technique. It assisted in the diagnosis of malignant thyroid nodules among a significant number of patients, as subsequently confirmed by FNAC results. The overall diagnostic sensitivity, specificity, PPV, NPV and diagnostic accuracy of SR elastography in differentiating between benign and malignant thyroid nodules, taking FNAC as gold standard was 94.0%, 90.20%, 90.38%, 93.88% and 92.08%, respectively. In a study, the prevalence of malignant thyroid nodules was found to be 40.65% and the sensitivity and specificity of strain ultrasound elastography as 88.0% and 93.0%, respectively in differentiating benign from malignant thyroid nodules. [10] A different group of researchers observed that SE had the highest sensitivity of 100.0% and specificity of 80.2% in differentiating between benign and malignant thyroid nodules.[11]

Elastography is increasingly being used in the assessment of thyroid nodules by comparing tissue elasticity.[17] However, the initial encouraging results were challenged by a large retrospective study of Moon et al with 703 nodules (217 malignant).[18] SE was assessed with both Asteria and Rago scoring criteria, but the results displayed mediocre performance of elastography; sensitivity was noted to be 65.4% and NPV was at 79.1%. However when the gray-scale US features were used in combination with elastography, then sensitivity was observed to be 91.7% and NPV was at 94.7%. They concluded that SE on its own was not valuable in predicting whether FNAC was required or not. Another study also showed that there is a benefit of using the gray-scale US.[19] One research study found the NPV of elasticity score to be 97.2%. Ko et al.[20] assessed the effect of physician's experience in differentiating malignant thyroid nodules from benign nodules using elastography and concluded that skilled doctors had greater specificity in comparison to inexperienced doctors. Cantisani et al.[19] described the interobserver agreement using Cohen's kappa coefficient for the SR measurements. It was noted to be 0.95 for SR, and 0.83 for the echogenicity score. Agreement was noted to be excellent in two other studies.[20, 21]

Ragazzoni et al.[21] carried out a study using elastography and noted that 77 out of 92 benign nodules were classified as score 1 or 2, and 34 out of 40 malignant nodules were categorized as score 3 or 4 (specificity 83.7%, sensitivity 85%, NPV 92.7%, and PPV 69.3%). Asteria et al.[22] assessed 17 malignant and 69 benign lesions and determined the sensitivity, specificity, PPV, NPV, and accuracy of elastography to be 94.1%, 81%, 55.2%, 98.2%, and 83.7%, respectively. In a study done by Ferrari et al., there were 23 thyroid nodules. They had shown that 88% of malignant nodules were patterns 3-4. They observed the specificity, sensitivity, NPV, PPV, and diagnostic accuracy of elastography to be 78%, 88%, 91%, 72%, and 82%, respectively.[23] Additionally, Cantisani et al.[24] prospectively calculated the specificity and sensitivity of elastography to be 91.7% and 97.3%, respectively, and concluded that the thyroid lesions with SR of more than 2 were often malignant.

Limitations

There are certain limitations to this study. This is a single center based cross-sectional study. Hence, follow-up and treatment data is not available. Histopathology was not used as the definitive test for the diagnosis of thyroid malignancy. Instead, FNAC was used as the gold standard, which is not perfect.

Conclusion

Our study shows that elastography in general and SR technique in particular are useful in the detection of malignant thyroid nodules. In combination with grey-scale US, it can be useful in selecting patients for FNAC testing of the thyroid nodules.

Disclosures

Ethics Committee Approval: Karachi, Pakistan after approval from SIUT Ethical Research Committee (Approval no: SIUT-ERC-2021/A-307 dated 1st July 2021).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.L.; Design – A.L.; Supervision – S.M.F., M.M.; Materials – M.F.; Data collection &/or processing – A.L., S.Q.; Analysis and/or interpretation – M.M.; Literature search – A.L., A.J.; Writing – A.L., M.M.; Critical review – S.M.F.

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