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Diagnostic Accuracy of Sonoelastography in Differential Diagnosis of Benign and Malignant Thyroid Nodules Keeping FNAC as Gold Standard

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ABSTRACT

Background: Thyroid nodules are not uncommon with a minimal percentage of these nodules malignant. The gold standard in diagnosis is the fine-needle aspiration cytology (FNAC) which is invasive and resource-intensive in low-resourced settings. Strain sonoelastography is a non-invasive technique that can be used to evaluate the stiffness of nodules and distinguish between benign and malignant lesions. This study was done to establish the diagnostic accuracy of strain ultrasound elastography (Tsukuba scoring) in diagnosing benign and malignant thyroid nodules and using FNAC as the reference value. **Methodology:** This cross-sectional validation study was performed at Department of Radiology, PAF Hospital, Islamabad from 1st October 2023 to September 2024. A total of 258 patients were enrolled for this study using non-probability, consecutive sampling technique. Patients with thyroid nodules that were palpable were subject to strain elastography on a linear probe of 7.5 MHz; a Tsukuba score 1-2 was considered benign and 4-5 malignant. FNAC was done on the nodules which appeared suspicious and compared the results. The calculation of the diagnostic performance (sensitivity, specificity, PPV, NPV, accuracy) and ROC analysis was done with the help of SPSS 25. **Results:** In strain ultrasound elastography, 57.4% of nodules were benign and 42.6% were malignant; FNAC had 60.1% benign and 39.9% malignant. The percentages of sensitivity, specificity, PPV, NPV, and diagnostic accuracy were 75.7, 79.4, 70.9 and 83.1, respectively. The ROC analysis revealed that under the curve was 0.794 (95% CI). There was no gender difference in performance, but specificity was better in patients aged ≥40 years (84.0) and with nodules of longer duration (81.9). **Conclusion:** Strain ultrasound elastography effectively differentiated between benign and malignant thyroid nodules in our local population, utilizing FNAC as the gold standard. Its persistent efficacy with both genders, particularly among older persons and those with prolonged duration of nodules.

INTRODUCTION

Thyroid nodules are a common clinical finding, often discovered incidentally during imaging studies or routine physical examinations. Thyroid nodules, according to the American Thyroid Association (ATA) are "discrete lesions within the thyroid gland, radiologically distinct from surrounding thyroid parenchyma" [1]. Although most thyroid nodules are benign, a small percentage may represent thyroid cancer, necessitating a precise and early diagnosis to improve clinical outcomes. The prevalence of TNs ranging from 4–7% to 67% [2]. A recent study from Pakistan reported that 26% of patient had thyroid nodules [3].

Once a nodule is discovered, the primary goal of additional diagnostic examinations and follow up is to exclude thyroid malignancies. A comprehensive diagnostic approach involves a combination of physical examination, imaging studies, and cytological evaluation through fine-needle aspiration cytology (FNAC) [4]. FNAC is considered the gold standard for diagnosing thyroid malignancies due to its high sensitivity and specificity. However, its invasive nature, coupled with the fact that many nodules turn out to be benign, raises concerns about overutilization in low-resource settings [5,6]. Ultrasound (US) is the primary imaging modality for evaluating thyroid nodules due to its high sensitivity, non-invasive nature, and real-time imaging capabilities. Ultrasound-based elastography has emerged as a potential tool to bridge this diagnostic gap. Sonoelastography measures tissue stiffness, with malignant lesions typically being stiffer than benign ones and few studies have demonstrated a respectable diagnostic efficiency of sonoelastography for differentiating benign from malignant thyroid nodules [7,8].

In low-resource settings, where access to FNAC may be limited, ultrasound elastography can serve as a valuable

triage tool. Despite few available local and global studies that have examined the diagnostic accuracy of ultrasound elastography for thyroid nodules, there remains a need to evaluate its effectiveness in our local population. This study is distinct from previous local studies due to its focus on addressing geographical and operator-dependent variations in the diagnostic accuracy of sonoelastography in our local population. This study will also contribute to the growing body of literature by providing data specific to the Pakistani population. By identifying nodules that are likely benign, ultrasound elastography can reduce the number of unnecessary FNACs, thereby conserving resources and minimizing patient discomfort. This is particularly important from Pakistan point of view, where healthcare resources are often stretched, and access to specialized procedures like FNAC may be limited. So, this study will provide valuable insights into the feasibility of implementing sonoelastography technique in low-resource settings, ultimately benefiting patients by reducing invasive procedures and optimizing healthcare resources.

MATERIAL AND METHODS

This cross-sectional validation study was performed at Department of Radiology, PAF Hospital, Islamabad from 1st October 2023 to September 2024. A total of 258 patients were enrolled for this study using non-probability, consecutive sampling technique and getting a formal approval from the CPSP. Sample size was calculated by sensitivity and specificity calculator came out to be 258 patients taking: sensitivity as 67.9%[12] and specificity as 75.9%[12], keeping confidence level as 95% and absolute precision as 10% for specificity and sensitivity, and frequency of malignant thyroid nodules as 32.6%[12]. Both male and female patients with age between 15-70 years who presented to the hospital with palpable thyroid nodule on physical examination and sent to radiology department for the ultrasound neck for the further evaluation of thyroid nodule status were selected for the study after signing a written informed consent. Patients diagnosed with purely cystic nodules, anechoic nodules without solid components, or with eggshell-calcified nodules and patients with positive history of radiotherapy, chemotherapy, or excision of thyroid tissue/ nodule in past were excluded from the study. Following a physical examination that confirms the distinct thyroid and a history of neck swelling, patients underwent ultrasonic elastography employing a linear high frequency probe (7.5 MHZ) by a specialist with consistent experience in the relevant field. The patients were positioned supine and lesion was centralized, and rhythmic compression-decompression manoeuvres were performed with the ultrasound probe perpendicular to the skin, lesion and neck. The colour scales visualized as a result of signals that were obtained before and after compression were evaluated by Tsukuba scoring and divided into five scores. Score 1 and 2 evaluated as soft nodules (benign), score 3, 4 and 5 as hard nodules (malignant) and patients with an elastography score of 4-5 were advised for FNAC. Using a biopsy needle and ultrasound guidance, the FNAC was performed by the histopathologist and the sample were preserved in an alcohol container. The sample then forwarded to the pathology department for a histopathological assessment. The histopathology reports were gathered and the findings were documented.

The SPSS 25.0 software was used to enter and evaluate the gathered data. The quantitative variables, were expressed as Mean ± S.D. While, qualitative variables displayed as frequencies and percentages. The 2x2 contingency table was utilised to assess the diagnostic accuracy and computed the ultrasound elastography for thyroid nodule's sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy. Study confounders like age, gender, duration of disease was stratified in order to measure the diagnosis accuracy. ROC curve analysis was performed to find out the AUC.

RESULTS

Among all the 258 enrolled patients mean age of the patient was 42.29 years (SD ±16.12), mean duration of the nodules was 12.48 months (SD ±6.95), while mean elastography score (Tsukuba score) found as 2.54 (SD±1.39). patients were further categorized into different groups on the basis of age and duration of disease which is illustrated in table 1. Study was female dominant with 156 (60.5%) of female patients.

Table 1

Frequency Distribution of Qualitative Variables (N=258)

Variable	Category	Frequency (n)	Percentage (%)
Age Group	< 40 years	112	43.4
	≥ 40 years	146	56.6
Gender	Female	156	60.5
	Male	102	39.5
Duration of Nodule	≤ 6 months	66	25.6
	> 6 months	192	74.4

We further noted that 148 (57.4%) of the nodules were benign, while, rest of the nodules were malignant. On the other hand, findings of the gold standard test (FNAC) classified 103 (39.9%) of the nodules as malignant, which established that prevalence of malignant thyroid disease in our population as 39.9% (table 2).

Table 2

Frequency of benign and malignant nodules on sonoelastography and FNAC (N=258)

Variable	Category	Frequency (n)	Percentage (%)
Strain Elastography Findings	Benign	148	57.4
	Malignant	110	42.6
FNAC Findings	Benign	155	60.1
	Malignant	103	39.9

Strain elastography showed good diagnostic performance in distinguishing benign from malignant thyroid nodules and the overall sensitivity, specificity, and diagnostic accuracy were 75.7%, 79.4%, and 77.9%, respectively (table 3). Stratified analysis showed that there was similar performance between genders, with sensitivity and specificity slightly higher among female subjects (76.1% and 79.8%). Patients 40 years and older had higher specificity (84.0%) than patients younger than 40 years (72.1%). Additionally, there was better diagnostic performance in nodules with a duration greater than 6 months (sensitivity 77.6%, specificity 81.9%) compared to other less than 6-month nodules (table 4).

Table 3

Overall Diagnostic Accuracy of Strain Elastography in Differentiating Thyroid Nodules (N=258)

Sonoelastography Findings for Thyroid Nodules	FNAC Findings for Thyroid Nodules		Total
	Malignant (Positive)	Benign (Negative)	
Malignant (Positive)	78 (True Positives)	32 (False Positives)	110
Benign (Negative)	25 (False Negatives)	123 (True Negatives)	148
Total	103	155	208

Table 5

Sensitivity (%)	75.7
Specificity (%)	79.4
Positive Predictive Value (%)	70.9
Negative Predictive Value (%)	83.1
Diagnostic Accuracy (%)	77.9

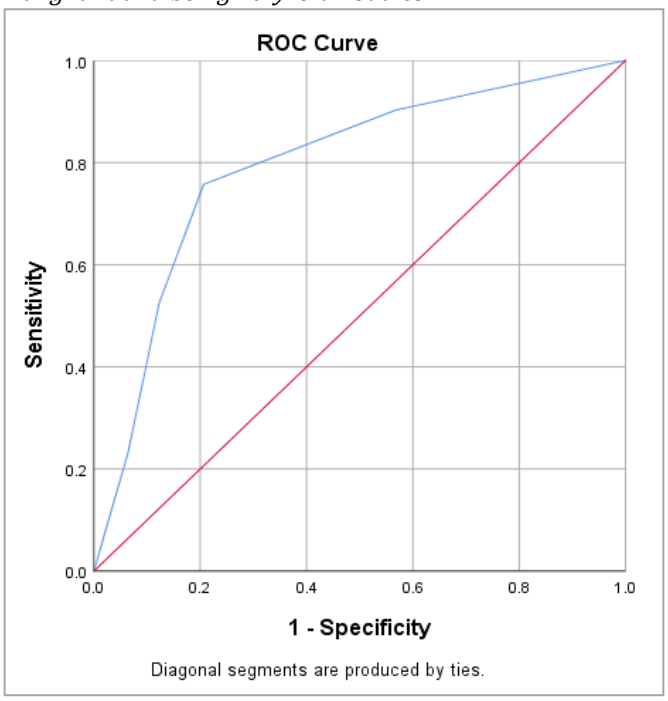
Table 4

Stratified Diagnostic Accuracy of Strain Elastography by Patient Subgroups

Subgroup		n	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Gender	**Female**	156	76.1	79.8	73.9	81.6	78.2
	Male	102	75.0	78.8	65.9	85.2	77.5
Age Group	**< 40 Years**	112	76.5	72.1	69.6	78.6	74.1
	≥ 40 Years	146	75.0	84.0	72.2	85.9	80.8
Duration of Disease	**> 6 Months**	192	77.6	81.9	73.8	84.8	80.2
	≤ 6 Months	66	70.4	71.8	63.3	77.8	71.2

Figure 1

ROC analysis of elastography score (Tsukuba score) for malignant and benign thyroid nodules



The AUC of 0.794 (95% CI) suggests the good diagnostic accuracy of strain elastography in distinguishing benign and malignant thyroid nodules. An AUC of 0.794 indicates that in almost 80% of the cases, a randomly chosen malignant nodule will have a higher elastography score (and hence greater stiffness) than a randomly chosen benign nodule (figure 1).

DISCUSSION

Thyroid nodules are a frequent clinical presentation and their incidence has been rising around the globe [9]. In the low-resource settings, such as Pakistan, the high volume of thyroid diseases, there is a great need for cost-effective, non-invasive diagnostic modalities that can reliably distinguish benign from malignant nodules and reduce unnecessary invasive procedures [10]. Sonoelastography, measuring tissue stiffness since it is related to malignancy, is particularly promising in such environments because of its accessibility, real-time nature, and ability to assist clinical decision-making without the need for specialized cytopathology services [11].

The present study results show that strain elastography shows the good diagnostic accuracy in differentiating benign and malignant thyroid nodules with overall sensitivity of 75.7%, specificity of 79.4% and diagnostic accuracy of 77.9% using FNAC as the gold standard. These results are consistent with the international literature. Kızılkaya MC and colleagues in a recent study from Turkey, reported overall sensitivity, specificity and diagnostic accuracy of strain ultrasound elastography in differentiation between benign and malignant thyroid nodules as 67.9%, 75.9%, and 73.3% respectively [12]. A study by Latia et al. who considered pathology results as the gold standard diagnosis and found that out of 97 nodules, 32 (33%) nodules were carcinomas, 65 nodules (67%) were benign nodules. At the final point, they compared the ultrasound data with the pathologies, which indicated that 19 of the 32 malignant nodules had increased stiffness on elastography (p=0.0002). [13]. Similarly, one systematic review and meta-analysis of 12 studies by the Tehran University of Medical Sciences found a sensitivity of 86.0% and specificity of 66.7% with a threshold elasticity score between 2 and 3 [14]. The slightly lower sensitivity in our study may be due to differences in the selection of patients, operators or the scoring system of elastography that was used. In a large multicenter randomized controlled trial, ultrasound alone was reported by Mehanna et al. to have a sensitivity of 91% but less specificity of 48% compared to US-FNAC, stressing that elastography should be considered a complementary, rather than replacement tool [15]. Khan et al in a comparative analysis of 360 patients had ultrasound elastography accuracy of 81.94% with sensitivity of 87.25% and specificity of 78.40% at an optimal cutoff value of 4.2 that are very similar to our results [16]. Regarding the studies from local Pakistan, Saleem et al. from Rawalpindi achieved higher sensitivity i.e. 93.4% and specificity i.e. 91% with overall accuracy 92.3% in 207 patients [17]. Idrees et al from INMOL

Lahore showed even better performance of the diagnostic test with sensitivity and specificity both at 90.0% and accuracy of 90.0% in 110 patients with an optimal cutoff of 2.57 and AUC of 0.933 [18]. Sohail and Zaman of Dow University of Health Sciences Karachi by using shear wave elastography in 157 patients with sub-centimeter nodules showed sensitivity of 81.5%, specificity of 92.3%, and accuracy of 90.5% [19]. Jesrani et al of Bahria University reported 85.3% diagnostic accuracy of the elastography in differentiating thyroid nodules, further supporting utility of this modality in the Pakistani population [20]. The differences in local reported accuracy between studies may be due to variation in the number of patients, nodule properties, elastography method and reference standards used.

The high negative predictive value of 83.1% observed in our study is of particular importance and is in line with the results of a meta-analysis of literature by Nell et al. who concluded that qualitative elastography can replace FNAC in patients with soft thyroid nodules [21]. This has implications that in our environment, if the elastography finding is benign, then the patient may be reliably reassured that there is no malignancy and may avoid unnecessary FNAC procedures. The positive predictive value of 70.9% is encouraging, in the sense that although malignant findings on elastography are worrisome, they must be confirmed with FNAC and definitive management decisions made. Our results of ROC analysis resulted in an AUC value of 0.794, indicating the good discriminatory power in this study, which is comparable to the range of 0.81-0.93 reported in the different studies [13,18,22]. The stratified analysis brought up some interesting patterns. Gender-based stratification demonstrated balanced performance with females (n=156) showing sensitivity of 76.1% and specificity of 79.8% compared to males (n=102) with sensitivity of 75.0% and specificity of 78.8% suggesting the performance of elastography shows no gender-based discrepancy. This differs from that reported by Sohail and Zaman who found greater diagnostic accuracy in females [19], although the latter study did use shear wave elastography which may have different gender-based performance characteristics. Age-based stratification showed higher specificity (84.0%) and NPV (85.9%) for the patients aged 40 years or older than younger patients (specificity 72.1%, NPV 78.6%). This finding is consistent with Sohail and Zaman who reported better diagnostic performance in patients over 40 years [19], and may reflect age-related changes in the composition of thyroid tissue or differences in tumor biology. Duration based stratification was superior for nodules present more than 6 months (sensitivity 77.6%, specificity 81.9%, accuracy 80.2%) as compared to nodules present less than 6 months (sensitivity 70.4%, specificity 71.8%, accuracy 71.2%). This is in line with the finding by Sohail and Zaman that diagnostic accuracy was higher for nodules with a known duration longer than 10 months [19], and probably reflects the biological behaviour of thyroid malignancies that are slower growing and may take time to develop the desmoplastic reaction and tissue stiffness that elastography detects [23]. The reduced performance in shorter duration nodules may also be affected by inflammatory changes that may resemble malignancy or be due to the presence of more aggressive tumor subtypes that may show differently [24].

Findings of our study have strong clinical implications in management of thyroid nodules in the Pakistani population and other resource-constrained populations. The high negative predictive value of 83.1% implies that strain elastography may be used as an effective triage tool, which could potentially be used to decrease the number of unnecessary FNAC procedures by reliably identifying benign nodules which can be treated in a conservative way. This is especially valuable in settings where cytopathology services are highly limited, patients are financially restricted in accessing healthcare and where follow-up is difficult [10]. The role of ultrasound features including the use of elastography in risk stratification and clinical decision-making is supported by British Thyroid Association guidelines and recent evidence from the ElaTION trial [15,25]. For nodules with non-specific cytology (Bethesda III and IV), which have significant problems, elastography information is helpful in providing more risk-stratification information to guide management decisions. The consistent performance in both sexes and the specificity enhancement in older patients support the applicability in various demographic groups of the clinical practice. Furthermore, the superior performance in the nodules of longer duration may help both to prioritize which nodules need urgent evaluation and which can be safely observed. However, it is important to emphasize that elastography should be a complementary, rather than a replacement, procedure to FNAC because the moderate positive predictive value (70.9%) means that a significant proportion of elastography-suspicious nodules will be pathologically proven to be benign on cytology [11,17]. A practical solution in low resource settings may be to perform elastography as the first line of diagnostic testing, with FNAC being the second line diagnostic test for nodules which have suspicious elastography features or those with discordant clinical, ultrasound and elastography results, which optimises use of resources while preserving good diagnostic accuracy.

The strengths of this study include an adequate sample size of 258 patients, use of FNAC as the gold standard reference, stratified analyses in a range of demographic and clinical subgroups, and inclusion of analysis of the ROC cure to evaluate the overall discriminatory power. The research was carried out in a real-world clinical setting, which adds to the generalisability of findings for routine practice. The detailed reporting of the true positives, true negatives, false positives and false negatives supports complete transparency in the assessment of diagnostic accuracy. However, a number of limitations need to be recognized. First, the study used FNAC rather than histopathology as the reference standard for the vast majority of patients, which, while practical and clinically relevant, has inherent limitations that include false negative rates as well as indeterminate results [26]. Second, the single center design may restrict the generalizability to other populations and healthcare settings. Third, inter-observer variability in elastography interpretation was not determined and elastography is known to be operator-dependent [16]. Fourth, the study did not assess inter-

nodule variability in patients with multinodular glands in which sampling error could affect results. Fifth, the potential confounding effect of nodule size on the accuracy of elastography was not analyzed, but evidence exists to suggest that elastography performs well in nodules less than a centimeter in size [19]. Sixth, the cross-sectional design excludes evaluation of long-term outcomes of patients with benign findings. Finally, the incremental value of combining elastography with conventional ultrasound features and the use of elastography strain ratios were not evaluated in this study which may have improved diagnostic performance [13,22]. Future multicenter studies using histopathological correlation, standardised elastography protocols, evaluation of inter-observer agreement and including cost-effectiveness analyses will further enhance the evidence for elastography implementation in low resourced settings.

CONCLUSION

Strain ultrasound elastography showed good diagnostic performance (77.9%), and the negative predictive value (83.1) in distinguishing between benign and malignant thyroid nodules in a Pakistani cohort that used FNAC as the reference standard. Its strong diagnostic consistency in both genders and increased specificity in the elderly patient population highlights its proficiency as a non-invasive triage tool in limited resource settings, which attempts to decrease the unnecessary invasive interventions and preserve diagnostic accuracy. Elastography must be used as a complement to FNAC rather than a replacement, which requires more multicenter clinical trials that can confirm generalizability and cost-effectiveness.

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