Original Research Article

Determining the accuracy of elastography in differentiating benign from malignant nodules with fine needle aspiration cytology/ histopathological examination as the gold standard

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Abstract
Background: Thyroid nodules are very common and are found in 4% to 8% of adults by palpation, 41% by ultrasound, particularly among iodine-deficient individuals. Most nodules are benign, with less than 5% of them being malignant. **Aims and Objectives:** To determine the accuracy of elastography in differentiating benign from malignant nodules with Fine Needle Aspiration Cytology/ Histopathological examination as the gold standard. To determine the strain ratio of benign and malignant thyroid nodules. **Material and Methods:** The study was done at the Batra hospital & medical research centre (BMHRC), New Delhi. In this study 37 patients of thyroid swelling with total 43 nodules were evaluated finally during the study period. A prospective observational study of patient population who undergo grey-scale ultrasound (US) and real time ultrasound elastography (USE) for thyroid nodules and subsequently go for fine needle aspiration cytology/ histopathological examination for same. **Results:** The study comprises of 37 patients having 43 thyroid nodules. All patients underwent gray scale USG and ultrasound elastography followed by FNAC/histopathology examination. **Conclusion:** This prospective observational study shows that ultrasound elastography is a promising imaging technique and that in expert hands, it is a useful complement to US, enhancing its accuracy for thyroid malignancy detection and risk stratification. Elastography may be used to guide the follow up of lesions negative for malignancy at cytology or histopathology. Given the high prevalence of thyroid nodules and the substantial costs related to their workup and management, the use of USE could be a valuable tool for a better selection of nodules that need cytological evaluation. Large multicenter studies and periodic evaluation by international experts consensus panels are necessary to establish the role of USE in the diagnostic workup of thyroid nodules.

Keywords:accuracy,elastography

Introduction

Thyroid nodules are very common and are found in 4% to 8% of adults by palpation, 41% by ultrasound, particularly among iodine-deficient individuals. Most nodules are benign, with less than 5% of them being malignant[1]. The challenge of managing thyroid nodules is to reassure the majority of patients who have benign disease and to diagnose the minority of patients who will prove to have malignant disease. Conventional ultrasound provides information regarding characteristics correlated with the risk of cancer, such as hypoechogenicity, blurred or spiculated margins, microcalcifications, an anteroposterior/transverse diameter ratio (A/T) of 1 cm or greater, and intranodular vascularity. However, the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for these criteria are extremely variable from study to study. No ultrasound feature has both high sensitivity and high specificity[2-4]. The diagnosis for nodule malignancy is currently made via a fine needle aspiration (FNA) biopsy, which draws cytological samples from the nodule using a 25-gauge needle. A large percentage of these biopsies turn out to be benign.

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Thus, considering the increasing number of thyroid nodules being detected and the vast number of benign nodules undergoing FNA biopsies, the challenge lies in judiciously deciding which nodules should be aspirated[5]. The diagnostic advantages of high-frequency US examination and accuracy of thyroid cancer diagnosis based on stiffness are combined in US elastography. Although, US elastography is not yet used in routine clinical practice, it has shown to be useful in the differential diagnosis of breast cancer[6-17]. The basic principle of ultrasound elastography (US-E) is that the compression of the examined tissue produces a strain, which is smaller in hard tissues than in soft tissues. The results of this technique are scored by measuring the degree of distortion of the ultrasound beam while an external force is applied. Malignant lesions are often characterized by greater stiffness than in normal tissues[18-30]. Of all the elastographic techniques, tissue strain imaging under a very slow compression load is the simplest to use and is very promising. Strain images are constructed by using measurements of the local displacements induced by a compressive force applied to the tissue surface. The displacement fields are estimated by using correlation techniques that track the echo delays in segmented waveforms that are recorded before and after very slow compression. The results of the tissue compression are displayed as an image called elastogram, on which hard areas appear dark (blue) and soft areas appear bright (red). Strain ratio is measured with respect to a reference normal adjacent tissue at the same depth as strain varies as function of depth[31-47]. Various sensitivities and specificities have been reported for this technique. There seems to be no general consensus about the most accurate sensitivities and specificities. This recent technique's (USE) accuracy have been reported by few centres in evaluation of thyroid diseases.

Aims and objectives

1. To determine the accuracy of elastography in differentiating benign from malignant nodules with Fine Needle Aspiration Cytology/ Histopathological examination as the gold standard.

2. To determine the strain ratio of benign and malignant thyroid nodules.

Methodology

The study was done at the Batra hospital & medical research centre (BMHRC), New Delhi. In this study 37 patients of thyroid swelling with total 43 nodules were evaluated finally during the study period. A prospective observational study of patient population who undergo grey-scale ultrasound (US) and real time ultrasound elastography (USE) for thyroid nodules and subsequently go for fine needle aspiration cytology/ histopathological examination for same. Prospective cases over a period of June 2015-May 2016 were included. All the patients with thyroid nodules will be included under the study. Patients who refused FNAC / histopathology or whom the final confirmatory diagnosis could not be established and purely cystic lesions without solid component were excluded.

After taking valid consent patient were then subjected to both conventional sonography and real-time USE using a Philips IU22 system equipped with a liner probe with a central frequency of 5 MHz to 17 MHz

The following parameters of the nodule were assessed by conventional grey scale US:-

Echogenicity: hyperechoic, isoechoic, hypoechoic

Margins: hypoechoic halo, regular margins, irregular margins, infiltrative growth

Calcifications: no calcifications, micro calcifications, coarse dense calcifications or peripheral rim like calcifications.

Conventional ultrasound provides information regarding characteristics correlated with the risk of cancer, such as hypoechogenicity, blurred or spiculated margins, microcalcifications, an anteroposterior/transverse diameter (A/T) of 1 cm or greater, and intranodular vascularity. By strain elastography, two kinds of elasticity assessments can be obtained. First, visual scoring of colors within and around the nodules can be assessed, using 4-scale scoring systems. Second, two regions of interest (ROIs) are drawn over the target region and the adjacent reference region, respectively. Then, a strain ratio is automatically calculated through the machine. The likelihood of malignancy increases with an increase in the strain ratio. Real-time elastography measurements will be performed after US examination using the same probe. Patients will be lying in the same position as for conventional US. A light external compression with the US probe will be applied to the anterior neck above the nodule to fix its position and to avoid lateral movement. The region of interest (ROI) will be set to include the evaluated nodule and the surrounding thyroid and subcutaneous tissue, as this technique of elastography measures relative stiffness. US elastogram will be superimposed over the B-mode image and the stiffness of the tissue will colour-coded from blue to red: red will be assigned to the softest tissue, blue to the hardest elements, and green expressed an intermediate degree of stiffness. The ES images were classified according to elasticity score also be used by Asteria et al (9). The ultrasound elastography score of 1-2 favours benign lesions while score 3-4 favours suspicious malignant lesions. The histologic diagnosis served as the reference standard for correlation of ultrasound elastography findings. After ultrasound scanning and real time elastography, all patient undergoes fine needle aspiration cytology (FNAC) or surgery for final confirmation of diagnosis. The SPSS version 17.0 software package (SPSS Inc, Chicago, IL) was used for statistical data analysis. Data were expressed as mean ± SD. The x^2 test was performed to determine whether the elasticity scores are different between two groups. To assess the diagnostic value of conventional ultrasound imaging and ultrasound elastography compared with the histological results, the diagnostic sensitivity, specificity, PPV, and NPV were calculated.

P< .05 with 90% confidence interval was considered statistically significant wherever applicable.

Results

The study comprises of 37 patients having 43 thyroid nodules. All patients underwent gray scale USG and ultrasound elastography followed by FNAC/histopathology examination. Among 37 patients, 30 were female patients (81%), majority in the age group of 26-35 (40.5%) and 7 males (19%) majority in 46-55 age group (8.1%). Size of nodule was unrelated to nature of nodule. Smallest nodule size was 8x8 mm and largest nodule size was 30x28 mm. Mean size of nodules was 26x22 mm. In benign nodules mean size was 28x26 mm and in malignant nodules mean size was 24x20 mm. Fine needle aspiration cytology (FNAC) was performed in all nodules (43) included in the study. Among the 13 malignant nodules (Figure 1), 8 were papillary thyroid carcinoma, one was follicular carcinoma, one was hurthle cell carcinoma, two were anaplastic carcinoma, and one was metastasis from breast carcinoma. The remaining 30 nodules were benign based on histological results. Of these, 14 were colloid nodules, 9 were adenomatous goiters, 4 were Hashimoto thyroiditis and 3 were lymphocytic thyroiditis (Figure 2).

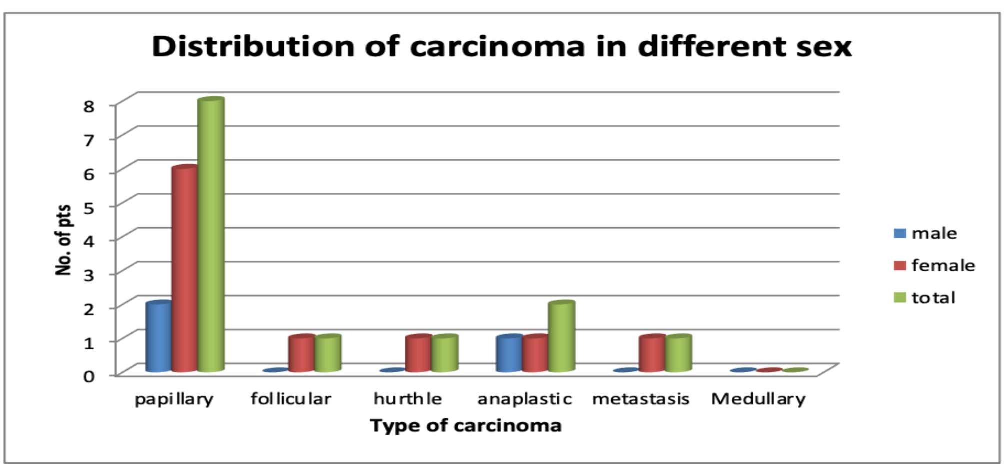

Fig 1: Distribution of different types of pathologically confirmed malignant nodules in correlation to the patients' gender

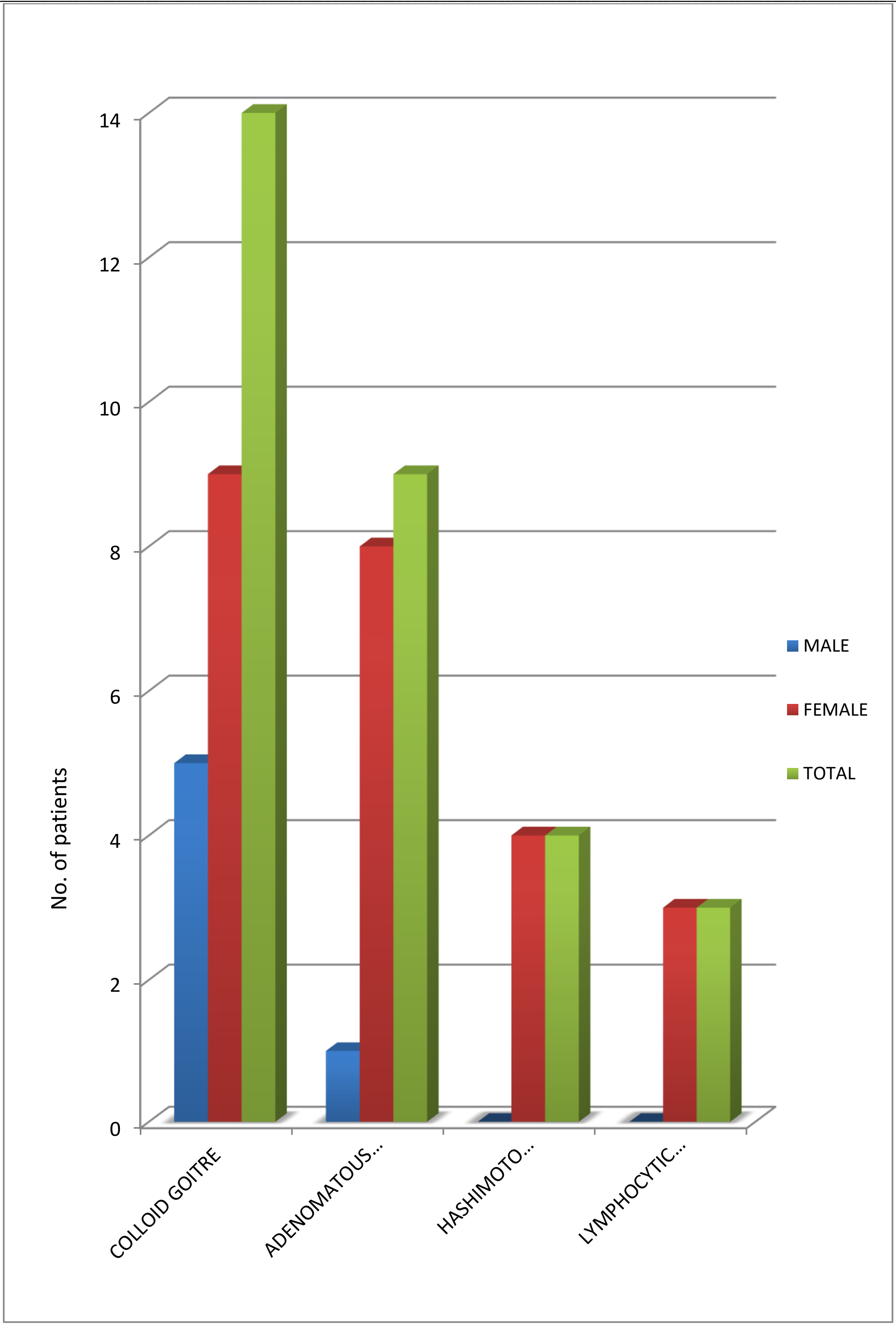

Fig 2: Sex distribution among benign nodule

Features associated with malignancy in thyroid nodules on ultrasound are microcalcifications, hypoechogenicity, solid aspect, and shape ratio (A/T ≥ 1). Lymph Nodal Enlargement was observed in – 3/43 X 100= 4.61%. Lymph node enlargement of the neck was seen in 3(6.9%) of the total cases. In one case jugulodiagastric and in the two other cases, left supraclavicular lymph nodes were enlarged. All the cases were diagnosed as malignant thyroid nodules. 29 of the 43 nodule had score 1 and 2 and 27 of these nodule were diagnosed as benign.14 of the 43 nodule had score 3 and 4 and 11 nodules were diagnosed malignant on histopathology. Score 1 and 2 were seen mainly in benign nodule while score 3 and 4 were seen mainly in malignant nodule with sensitivity 84%,specificity 90% and 88% accuracy (Table 1).

Table 1: Results of FNAC in correlation to USE scoring system

USE score	NO. of Benign	No of Malignant	Total
Score 1	9	0	9
Score 2	18	2	20
Score 3	3	4	7
Score 4	0	7	7
total	30	13	43

29 out of 30 benign nodules had Strain Ratio (SR) **,** SR <2.9 and 12 of 13 malignant nodules had strain ratio >2.9. SR -2.9 was taken as cut off value to differentiate benign and malignant (Table 2) . The mean strain ratio for benign nodule was 1.40 ± 0.50 and for malignant nodule mean strain ratio was 6.64 ± 3.8. The SR was 1.51 ± 0.69 for colloid nodule, 1.82 ± 0.33 for adenoma, 1.62 ± 0.65 for hashimoto thyroiditis and 0.67 ± 0.3 was for lymphocytic thyroiditis. In malignant nodules mean SR was 7.9±4.3 for PCT, 5.21±1.7 for anaplastic carcinoma, 3.21 for follicular carcinoma and 3.3 for metastatic nodule. SR for benign and malignant nodules were significant different (p<0.001) with 95% of confidence interval of this difference from 6.53 to 3.68.

Table 2: Distribution of Strain Ratio Among Nodule

	Benign	Malignant	Total
SR<2.9	29	1	30
SR>2.9	1	12	13
Total	30	13	43

(p< 0.05,Chi-Square test)

Also Out of 30 nodules, 23 nodules appeared benign on both gray scale USG and elastography that turned out benign on histopathology. In these 23 nodules, 14 were colloid nodules and 9 were adenomatous goiter.7 nodule appear malignant on USG, however on subsequent elastography pattern 1 and 2 were seen on ES and mean SR 0.65 ± 0.3 favouring benign soft nodule. All were turned out benign on histopathology. In 13 malignant nodules, 9 were malignant on USG and elastography, 1 was benign on both gray scale usg and elastography and 3 were benign on gray scale, however on elastography they were consisting with malignant histology.

Discussion

In our study, it was found that, most of the patients were in the age group of 26-35 years at presentation, which were 16 (40.5% of the total cases). The youngest and oldest age at presentation was 20 and 72 years respectively. The mean age at presentation was 34 years+/- 13.69 (standard deviation). Lyshchiket al [42] reported in their study that the mean age of the patient was 49.7 years +/-14.7.Rago et al [8] found that the youngest patient with the symptom related to thyroid was 8 years old, and the oldest was 70 years old. In this study, most of the patient's i.e, 30 out of 37 were females (81.08%). Only 7 (18.91 %) patients were male. The female to male ratio was 4.2:1.Similar results were obtained by Tranquart et al[15] where males constituted 11.46% and females constituted 88.54% of the total patients and the female to male ratio was 7.7:1[13]. It is seen that, in almost all of the cases the symptom which brings patient to the doctor was neck swelling. In this study, all the patients (100%) presented with neck swelling. Capelli et al[2] reported that 98% of the patient presented with neck swelling in their study.Thyroid ultrasound (US) features associated with malignancy in thyroid nodules are microcalcifications, hypoechogenicity, irregular margins or absent halo sign, solid aspect, intranodular vascularisation & shape ratio (A/T >1).These ultrasound appearances when taken singly are poor in differentiation of benign and malignant nodules[2,3,38,39]**.** Microcalcifications are seen sonographically as multiple punctate bright echoes that are less than 2 mm in size, with or without acoustic shadowing. It is seen that most malignancies demonstrate hypoechoic pattern, yet most hypoechoic nodules are benign in view of the high prevalence of benign lesions. Koike et al[39] defined a markedly hypoechoic nodule as one that is hypoechoic to the strap muscles anterior to the thyroid gland. Our study showed sensitivity (76%) and specificity (23%) of hypoechogenicity for malignant thyroid nodules. The USG feature of marked hypoechogenicity has a high negative predictive value of 90.9% indicating that nodules that are not markedly hypoechoic are likely to be malignant in only about 9% of cases. Accuracy of hypoechogenicity was 76.9%.The shape of the nodule has also been studied as a marker of malignancy. The width of the nodule on a transverse scan corresponds to the natural growth planes. Malignant tumors have a tendency for centrifugal growth and show expansion perpendicular to the natural growth plane and on USG it appears as a taller than wide (i.e., anteroposterior diameter > transverse diameter on transverse scan). Cappelli et al[2] in their series concluded that a taller-than-wide shape was a useful criterion for identifying a malignant lesion.In the present study, we measured the anteroposterior (AP) and transverse (T) diameters and found AP≥T to have a specificity of 73% and sensitivity of 53 % respectively. In conclusion, gray-scale USG features of thyroid nodules are useful to identify patients with clinically significant thyroid nodules from those with innocuous nodules. In this study, the USG features marked hypoechogenicity, micro calcification and taller-than-wide shape were found to have relatively high diagnostic accuracy for identifying malignant thyroid nodules. For the differentiation of malignant and benign thyroid nodules, a number of literature reports show encouraging results for USE. In 2010 a meta-analysis of 8 studies by Bojunga et al[21] including a total of 639 thyroid nodules resulted in encouraging results. An overall mean sensitivity of 92% and mean specificity of 90% were shown with a significant heterogeneity found for specificity in the different studies. Moreover, Rago et al[20] confirmed the effectiveness of USE also in the pre-surgical selection of thyroid nodules with indeterminate or non diagnostic cytology. Indeed, USE evaluation displayed effective PPV and NPV (76.9% and 99.0%, respectively) with excellent accuracy (92.9%). In 2013 the study group of Azizi et al[30] in a prospective study using four-grade elasticity score in the evaluation of 912 nodules resulted in positive predictive value (PPV) of 36.1%, which was slightly higher than that of microcalcifications (35.9%) and significantly greater compared with hypoechogenicity (13.6%). The negative predictive value(NPV) of elasticity score was 97.2%, which was better than any other predictor for malignancy. This study involved large number of nodules systematically studied with USE and it had no patient selection bias.In the study of Asteria et al[9] US-elastography scores were based on four classes of tissue stiffness (class 1 for soft nodules; class 2 and 3 for nodules with an intermediate degree of stiffness; class 4 for lesions having no elasticity).In our study, tissue stiffness on ultrasound elastography was scored same as that of Asteria et al[9] from 1 (greatest elastic strain) to 4 (no strain) based on subjective analysis of the elastogram image. The scoring was done to differentiate benign and malignant lesions and is based on color pattern with elastography image with low elasticity suspicious for malignancy[7,13]. In the study of Asteria et al[9] they reported that the sensitivity (94.1%), specificity (81%),PPV (55.2%) and NPV (98.2%) of the ultrasound elastography for thyroid cancer diagnosis using this scoring. In our study 29 of the 43 nodules had score 1 and 2 and 27 of these nodule were diagnosed as benign. 14 of the 43 nodules had score 3 and 4 out of which 11 nodules were diagnosed malignant on histopathology. The score 1 and 2 were seen mainly in benign nodule while score 3 and 4 were seen mainly in malignant nodule. Thus, by combining the scores 1, 2, 3 & 4, ultrasound elastography (USE) had a with sensitivity 84%, specificity 90%, PPV 78.5%, NPV 93.1% and 88% accuracy. Three benign nodules had score 3. This false positive result can be explained by calcification, found in one nodule, causing decrease in elasticity of colloid nodule and proximity to carotid might have caused false positive results. The negative predictive values were much more rewarding of the pattern of high elasticity scores 1 and 2 to exclude malignancy. The current study shows that scores of 1 or 2 were found in 29 cases, 27 of which were benign lesions at cytology. This means that nodules with high elasticity have lower 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, can allow most patients to be placed in follow-up without significant costs in terms of prognosis[21,30]**.** Cases showing score 1 are not in need for further investigation and only follow up can be recommended. Cases with score 4 are considered to be highly suspicious for malignancy and other US criteria of malignancy (pattern of calcification and cervical lymph nodes infiltration) are correlated. FNAC should be recommended in all cases showing score of 2 and above where the suspicion of malignancy is high with USE criteria. In the present study, the thyroid tissue in the same depth as that of target nodule was taken as the reference. The longitudinal view of the thyroid was recommended because it could provide enough reference tissues at the same depth with the lesions. Depth of nodule can also influence elasticity score as deeper nodule will receive less pressure and less tissue distortion will be achieved[31]. A study carried out by Wang et al[31] which showed that the mean strain ratio for benign (1.64 ± 1.37) is significantly lower than that of malignant nodules (4.96 ± 2.13). This 20 year old male patient had ill defined 30x25 mm in size located in right lobe, hypoechoic in echotexture, without any intralesional calcification or peripheral halo. On color Doppler intralesional vascularity was found, but on basis of overall imaging findings it categorized as benign nodule, on subsequent elastography pattern 2 and SR 1.46 was observed favoring benign nature. It is not possible to differentiate follicular adenoma and carcinoma on basis of ultrasound. In a prospective study[31], the mean SR for follicular carcinomas was 4.95 ± 2.12. We would like to recommend that cases that showed elastography score 1 and with strain ratio< 2.9 are not in need for further investigation, and only follow up should be recommended. Cases with elastography score 4 and strain ration > 2.9 are considered to be highly suspicious to be malignant and other US criteria of malignancy should be looked for to support the diagnosis e.g. cervical lymph nodes infiltration. FNAC should be recommended in all cases of score above 2 where malignancy can't be excluded using USE criteria only.

Conclusion

This prospective observational study shows that ultrasound elastography is a promising imaging technique and that in expert hands, it is a useful complement to US, enhancing its accuracy for thyroid malignancy detection and risk stratification. Elastography may be used to guide the followup of lesions negative for malignancy at cytology or histopathology.Given the high prevalence of thyroid nodules and the substantial costs related to their workup and management, the use of USE could be a valuable tool for a better selection of nodules that need cytological evaluation. Large multicenter studies and periodic evaluation by international experts consensus panels are necessary to establish the role of USE in the diagnostic workup of thyroid nodules.

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