

Can Shearwave Elastography as an Adjunct Non-Invasive Technique to Ultrasound Help in Better Characterization of Focal Liver Lesions?

MARYSE AWADALLAH, M.D.*; RANIA R. EL-ZAKZUK, M.Sc.*; REDA S. ABD EL-LATIF, M.D.* and YAHIA LABIB MAHMOUD, M.D.**

The Department of Radiodiagnosis, Faculty of Medicine*, Cairo University and National Cancer Institute**, Cairo University

Abstract

Background: To characterise the elasticity properties of focal liver lesions (FLLs) using shear wave elastography (SWE) and to evaluate the clinical utility of SWE for lesion characterization.

Aim of Study: To determine the elasticity of the different focal hepatic lesions by shearwave elastography (SWE) and to assess the shearwave elastography (SWE) ability to characterise the different hepatic focal lesions.

Patients and Methods: This study used SWE in 26 patients with 30 FLLs for quantitative FLLs stiffness assessment. Stiffness was calculated for each lesion in (kPa). Histopathology or triphasic CT was used as reference standards for characterising the lesion. With the help of the statistical program SPSS version 22, data were coded and entered.

Results: SWE acquisitions failed in 5 nodules (17%) in 5 patients. For the 25 lesions successfully evaluated, There is a significant difference in stiffness values between malignant and benign groups with ($p < 0.001$), SWE values were (in kPa), for the 9 HCCs (20.67 ± 5.22), for the nine metastatic lesions was (35.89 ± 12.55), for the 4 Haemangiomas (7.50 ± 2.38), for the two focal fatty infiltration (8.50 ± 0.71 kPa), for one hepatic abscess (7 ± 2 kPa).

Conclusions: SWE is an adjunct to conventional ultrasound that can provide additional information with a more precise characterisation of focal liver lesions composition based on its tissue elasticity values, especially in cases where contrast imaging is contraindicated. However, the evaluation of the diagnostic accuracy of this technique needs a study with larger patient samples.

Key Words: Focal liver lesions – MRI – Acoustic radiation force impulse.

Introduction

ALL the available imaging modalities aim to satisfy the need for accurate characterisation and differentiation between different types of focal liver lesions (FLLs) [1].

Correspondence to: Dr. Maryse Awadallah,
E-Mail: Maryse.youssef@kasralainy.edu.eg
Maryseawadallah@gmail.com

The first imaging modality used to screen and study FLLs is conventional ultrasonography (US) because it is cheap and widely available. Recently microbubble contrast agents, together with Color-Doppler and Tissue Harmonic Imaging, have helped improve the characterisation of solid hepatic focal lesions. Cross-sectional imaging modalities such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are considered the second-line imaging modalities; despite being more expensive and less available, they can characterise previously detected hepatic lesions accurately. Contrast-enhanced imaging modalities added to the US, CT, and MRI can better help in the evaluation of the lesion's morphology and vascularisation; such specific features are well described in the literature and proved to have high diagnostic accuracy. Nevertheless, sometimes invasive studies such as tissue biopsies are required for reaching a definite diagnosis [1].

Cytological and histopathological diagnosis of the type of malignancy is the gold standard maneuver for a specific diagnosis. But liver biopsy has potential complications in a patient with decompensated liver cirrhosis, that is why the need for non-invasive criteria has been proposed for the diagnosis of HCC in patients with cirrhosis by the European Association for the Study of Liver Diseases (EASL) and the American Association for the Study of the Liver Diseases (AASLD) [2].

List of Abbreviations:

FLLs : Focal liver lesions
US : Ultrasonography.
CT : Computed Tomography.
MRI : Magnetic Resonance Imaging.
KPa : Kilo pascal.
TE : Transient elastography.
ARFI : Acoustic radiation force impulse .

The parenchymal stiffness of an organ is affected by its tissue composition and structure such as in neoplastic and inflammatory diseases [3].

Shear wave elastography (SWE) is a novel technology that involves the generation of transient mechanical forces remotely by a transducer into the tissue, then receives the resultant shear waves that are imaged with the same transducer at an ultra-fast imaging sequence to provide quantitative elasticity maps. Integration of SWE into ultrasound machines provides real-time two-dimensional B-mode images that help identify the area of interest [4].

Patients and Methods

Study design:

This is a prospective observational cross-sectional study.

Study population:

This study was done on 26 patients who were coming to the national cancer institute, with a provisional diagnosis of hepatic focal lesions. Ultrasound shear wave elastography was acquired in addition to the routine ultrasound scan.

A total of 30 hepatic focal lesions were evaluated in 26 patients. SWE acquisitions failed for 5 lesions (17%) in 5 patients, with a successful evaluation of 25 lesions in 21 patients.

Inclusion criteria:

This was a prospective study carried out on 26 patients referred to our Radiology department from December 2015 to April 2016. The study group's ages ranged from 33 to 66 years, with a mean age of 54.72 years, and every participant had at least one hepatic nodule that measured more than 1 cm in diameter and could be seen on B-mode ultrasonography.

Exclusion criteria:

Patients under 18 years or having hepatic nodules less than 1cm in diameter were excluded.

Patient's investigations:

All patients have been clinically assessed by; recording age, sex, and clinical presentation. Laboratory investigations such as liver biochemical profiles, renal function tests, and Alpha fetoprotein were done. All patients performed a triphasic CT scan followed by CT or ultrasound-guided biopsy if indicated.

The results were compared to the laboratory, Triphasic CT scan findings for all patients, and the

available histopathology results of the US or CT-guided biopsy.

Methodology:

Real-time ultrasound and SWE were performed on the patients by Philips iU22 xMATRIX ultrasound system with liver scanning protocol using a curved array transducer (SC5-1) to acquire the baseline ultrasound B-mode images and to perform the elastography study. Identification of each hepatic lesion concerning its site, size, and echogenicity was recorded as baseline grey-scale ultrasound results. Patients were requested to breathe hold without deep inspiration, during the SWE acquisitions of each hepatic focal lesion, where a region of interest (ROI) was placed within each lesion for quantitative evaluation of stiffness. Less than 4 minutes per patient were spent on the SWE entire exam (including acquisitions and ROI placement). The mean depth of the lesions was 54 ± 22 mm.

Triphasic CT examination of the liver was performed in all cases using a 64-detector CT scanner (light speed VCT, GE Healthcare, Waukesha, WI), and a 16-row scanner (Aquilion, Toshiba Medical Systems). The scanning parameters used were 120kVp and 150-250mAs.

Reference standard:

Out of the total 21 patients, 11 cases (60%) reached the final diagnosis by Triphasic CT scans as they showed a typical pattern, and 10 (40%) cases needed an additional histopathological diagnosis of a guided biopsy. The biopsy was taken from only one lesion in patients with more than one lesion with similar ultrasound and CT features.

Statistical methods:

Quantitative evaluation of the stiffness value of each focal lesion was collected in (KPa), coded, and entered using the statistical package SPSS version 22. Quantitative data were summarised using minimum, maximum, mean, and standard deviation, while categorical data were summarised using frequency (count) and relative frequency (percentage). An unpaired *t*-test was used for comparison between SWE in benign and malignant lesions. *p*-values less than 0.05 were considered statistically significant.

Results

Demographic data:

In this study, 26 individuals with one or more hepatic focal lesions were examined.

26 patients and a total of 30 lesions were examined. Five patients and five lesions (17%) had unsuccessful SWE acquisitions.

Consequently, 21 patients in all were satisfactorily examined (11 males and 10 females). With a mean age of 54.72 years, the patient's ages ranged from 33 to 66. Table (1) displays the distribution of the 25 lesions that were satisfactorily examined by SWE.

Table (1): Number and Percentage of different pathological lesions in our study.

Final Diagnosis	Count
Abscess	1
Focal fatty infiltration	2
Hemangioma	4
HCC	9
Metastases	9
Total	25

Elastography:

The total elastographic exam duration for each patient was less than 4 minutes including the time consumed for the SWE acquisition and the ROI placement. The mean distance between the lesions and the surface of the skin was 54 ± 22 mm. The distribution of the stiffness values of the different lesions and their statistical analysis are summarised in Table (2) and Fig. (1).

*Analysis of the obtained data:
SWE quantitative analysis:*

In regards of stiffness, there was a significant difference between benign and malignant groups of lesions, with mean values of $(7.71 \pm 1.80$ kPa) for the former and $(28.28 \pm 12.18$ kPa) for the latter with ($p < 0.001$) (Table 3).

Table (2): Shearwave elastographyanalysis.

	Mean In KPa	Standard Deviation	Minimum	Maximum
Abscess	7.00	0	7.00	7.00
Focal Fatty Infiltration	8.50	.71	8.00	9.00
Hemangioma	7.50	2.38	5.00	10.00
HCC	20.67	5.22	13.00	28.00
Metastasis	35.89	12.55	20.00	57.00

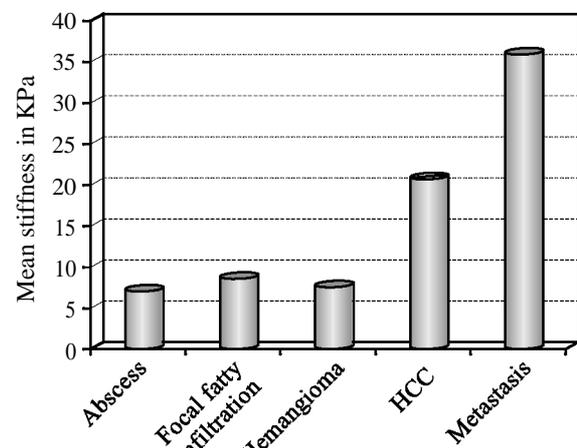


Fig. (1): Distribution of lesion stiffness.

Table (3): Analysis of stiffness values of benign and malignant groups by shear wave elastography.

	Malignant					Benign					p-value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
SWE	28.28	12.18	24.00	13.00	57.00	7.71	1.80	80.00	5.00	10.00	<0.001

The primary tumour type of metastatic lesions has affected the lesions' stiffness. The mean stiffness of the 9 metastatic lesions was $(35.89 \pm 12.55$ kPa) with minimum stiffness (20.00 kPa) and maximum

stiffness (57.00 kPa). Metastases from gastrointestinal origin showed lower mean elasticity values (28 ± 21) and (37 ± 11 KPa) than that of the breast (45 ± 22 kPa) and pancreas (57 ± 29 kPa) origin.

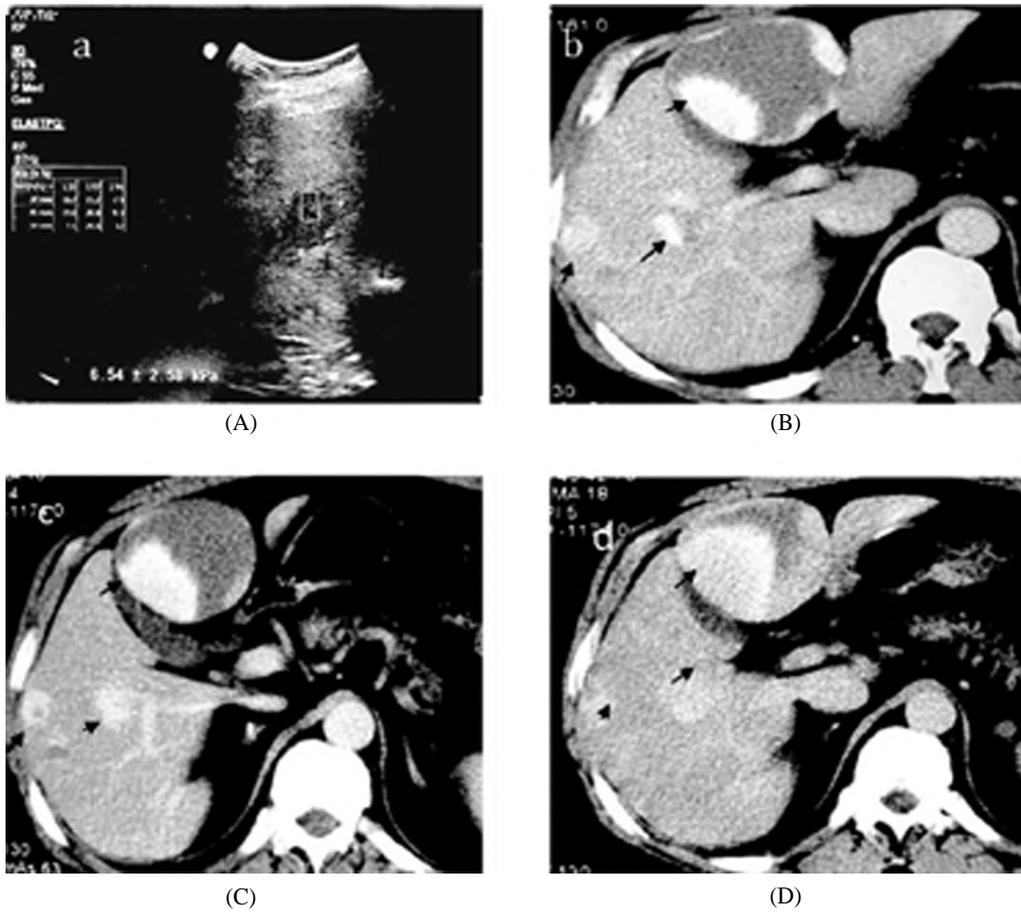


Fig. (2): Atypical hemangioma. 52 year old male, coming for follow-up of multiple variable sized hypoechoic focal lesion seen at segments IVa and V. (A) B-mode shows a well-defined hypoechoic focal lesion with SWE mean stiffness value (6 ± 2 kpa). (B-C-D) Axial Triphasic CT, in the arterial, portal and delayed phases, (B, C & D), respectively, showing multiple hepatic focal lesions at segments IVa (the largest) and V, the arterial phase (B), Displays peripheral nodular contrast uptake, while portal and delayed phases (C-D), Display progression of the contrast uptake.

NB: The large lesion in segment IV a couldn't be properly assessed by SWE due to transmitted cardiac pulsation.

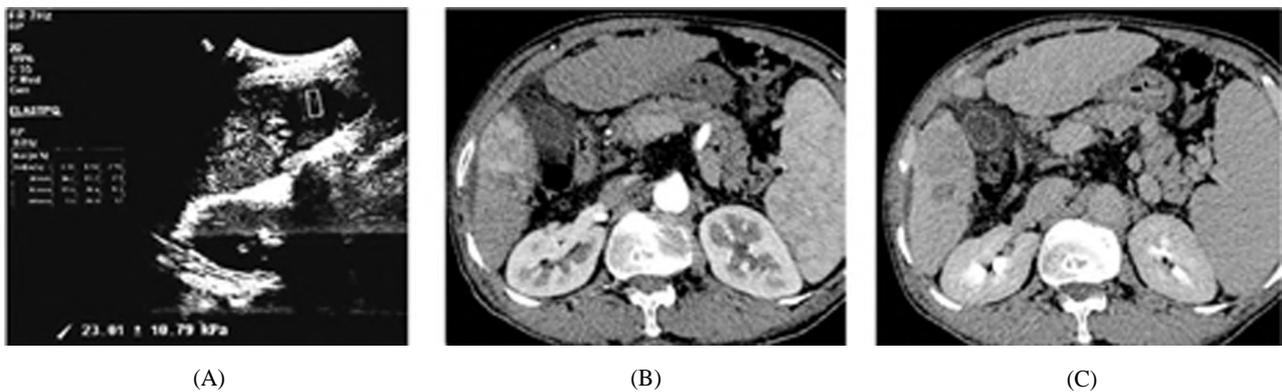


Fig. (3): Hepatocellular carcinoma on top of liver cirrhosis. 50 year old male presenting with past history of liver cirrhosis and elevated AFP (A) B-mode shows a well-defined hypoechoic focal lesion at segment V with SWE mean stiffness value (23 ± 10 kpa). (B-C) Axial Triphasic CT, arterial phase (B), delayed phase (C), which shows enhancement in the arterial phase and contrast washout in the delayed phases.

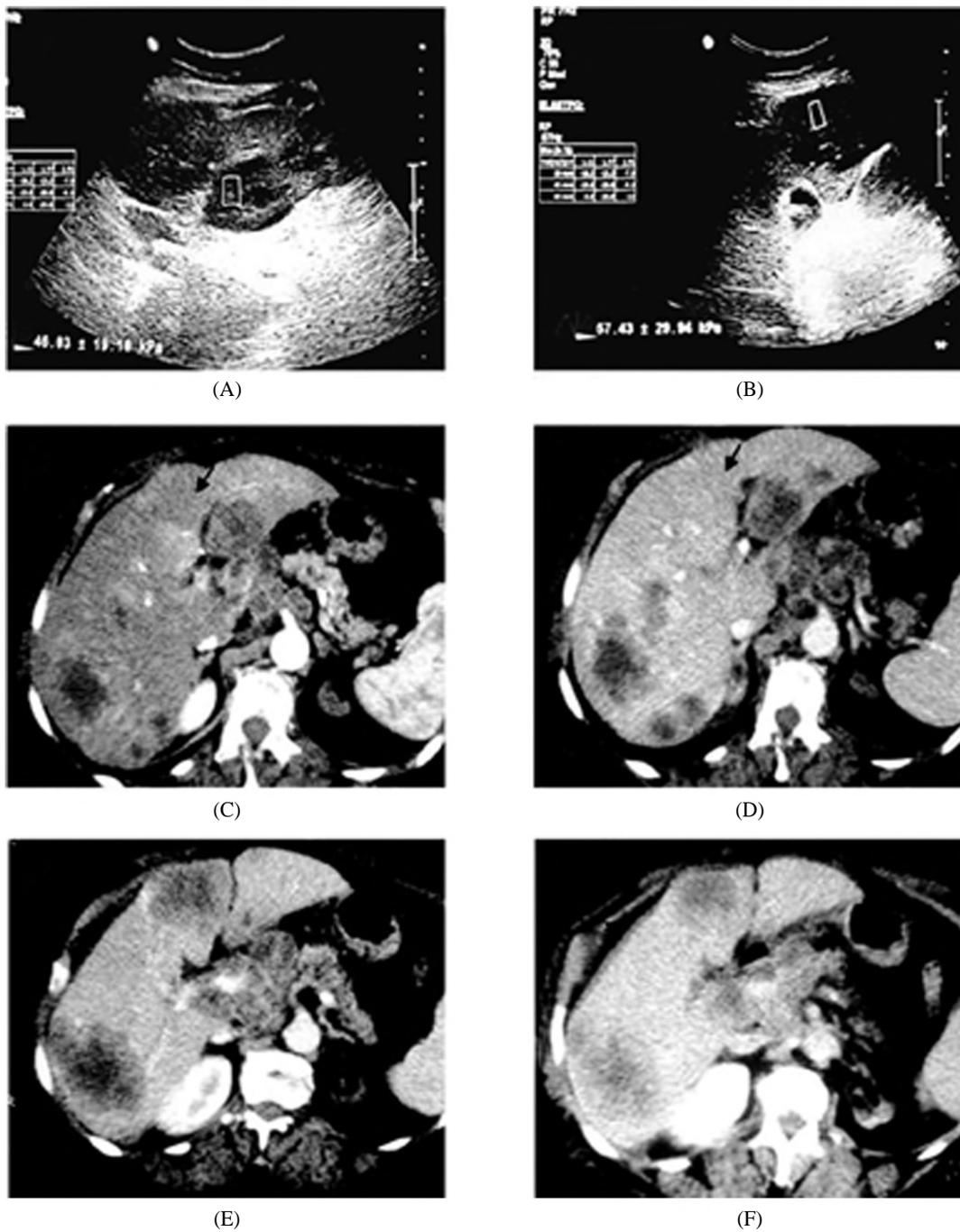


Fig. (4): Liver metastases from pancreatic head carcinoma. 61 year old female presenting with past history of cancer head of pancreas, with bilobar variable sized hepatic hypoechoic focal lesions. (A-B) B-mode shows two well-defined hypoechoic focal lesions at segments IVa and IVb respectively, with SWE mean stiffness values (46 ± 19 and 57 ± 29 Kpa) respectively. Axial triphasic CT, showing arterial and portal phases of segments IVa (C-D) and IVb (E-F), showing peripheral thick marginal arterial enhancement with progressive enhancement in the portal phase and central non enhancing areas of break down.

Fig. (5): Typical hemangioma. 33 year old female, coming for abdominal ultrasound (A) B-mode shows a well-defined hyperechoic focal lesion with SWE mean stiffness value (9+2 kpa). (B-C-D) Axial Triphasic CT, arterial phase (B) Portal and delayed phases (C-D) Displayed peripheral nodular contrast uptake in the arterial phase and centripetal progression of the contrast uptake in the portal and delayed phases.

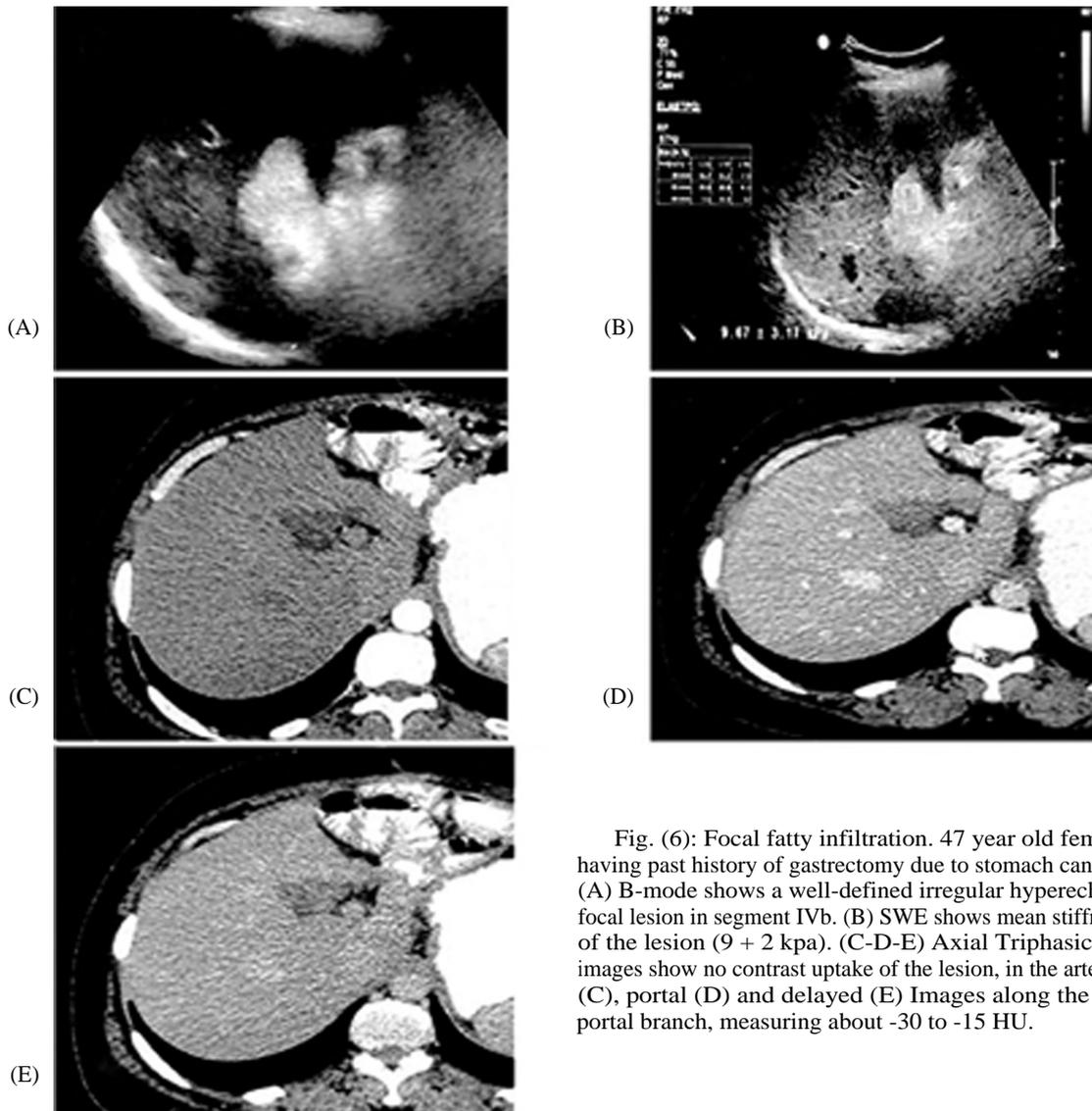
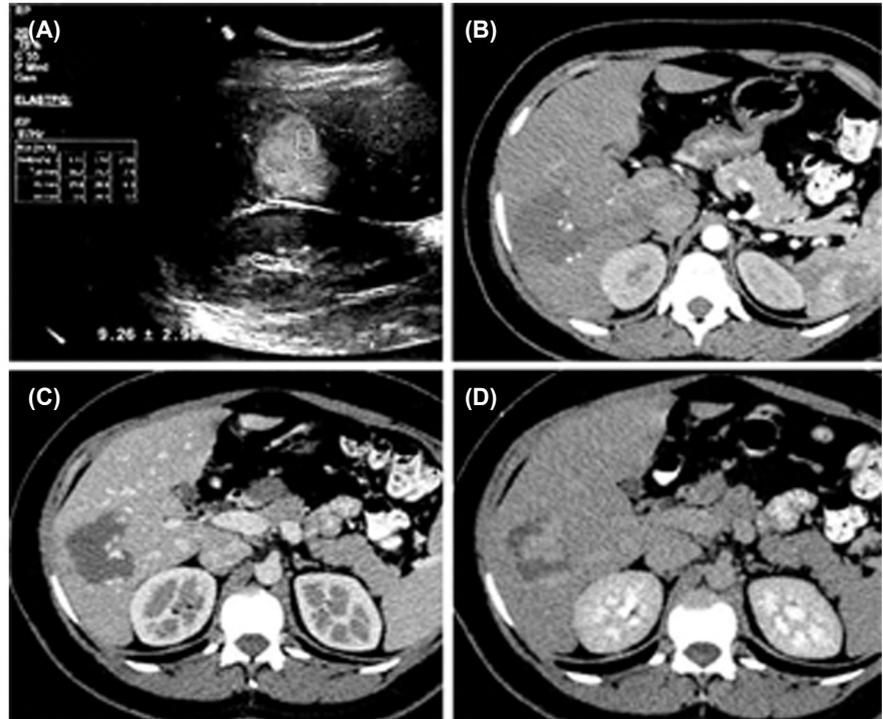


Fig. (6): Focal fatty infiltration. 47 year old female having past history of gastrectomy due to stomach cancer. (A) B-mode shows a well-defined irregular hyperechoic focal lesion in segment IVb. (B) SWE shows mean stiffness of the lesion (9 + 2 kpa). (C-D-E) Axial Triphasic CT images show no contrast uptake of the lesion, in the arterial (C), portal (D) and delayed (E) Images along the left portal branch, measuring about -30 to -15 HU.

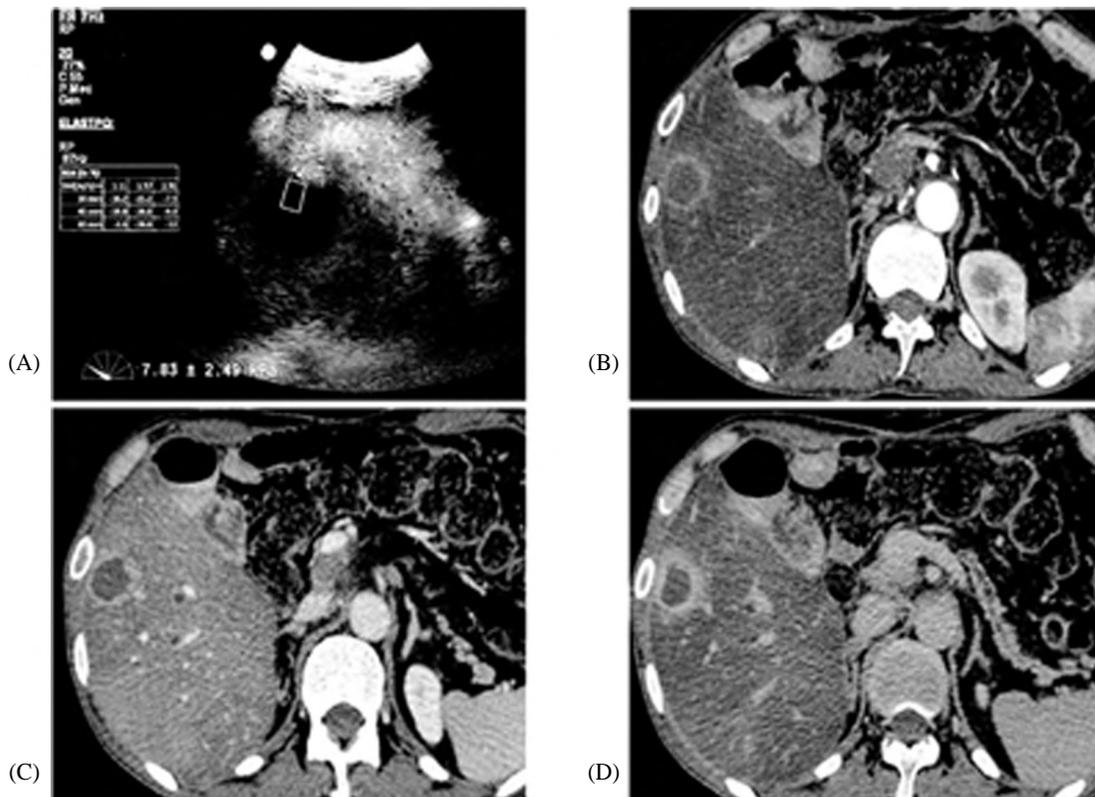


Fig: (7): Cytologically proven liver abscess with suppurative inflammation. A 57 year old male with history of Whipple operation 7 months ago due to cancer head of pancreas, under chemotherapy, now presents with multiple hepatic focal lesions, likely metastatic deposits. (A) B-mode shows a well-defined hypoechoic focal lesion with SWE mean stiffness value (7 ± 2 kpa). (B-C-D) Axial Triphasic CT arterial (B), Portal (C) and delayed phases (D) Display ring enhancement in all phases.

Discussion

Elastography is an imaging method used for the estimation of tissue elasticity. A large number of researches have been published in the literature, which proves the efficiency of real-time elastography in differentiating the stiffness of many neoplasms such as prostatic, thyroid, pancreatic, and breast tumors [5]. Only a few research have investigated quantitatively the stiffness of focal liver lesions [6].

Tissue stiffness was estimated clinically by two different mechanisms. The first mechanism is widely implemented in ultrasound machines, it depends on the manual compression with the ultrasound transducer that causes a sort of tissue deformity. The resultant displacement of the tissues is estimated and displayed as strain maps. However, this approach is limited by the lack of reproducibility and its failure in the examination of lesions within the deep organs [7].

The second mechanism depends on shear wave generation at a predetermined focus in the tissue, where the tissue stiffness is estimated according

to the wave velocity. Shear wave approach has been implemented on the liver clinically in three different techniques.

The first technique assesses liver fibrosis using transient elastography (TE) [8]. TE has also been used for the estimation of the stiffness of hepatic focal lesions [9]. However, the predicted elasticity is assumed to be at a constant acquisition line over a 4cm distance because TE does not produce a guiding image.

The second technique is the acoustic radiation force impulse (ARFI) this shear wave-based technique provides an estimation of the elasticity in a more local quantitative way. It is integrated into a diagnostic ultrasound system, that provides imaging guidance for the radiologist to select the region of interest within the desired tissue for stiffness estimation. However, the estimated stiffness is limited to a single point and single acquisition. Both of the aforementioned methods-TE and ARFI-have been used to treat focal hepatic lesions [1,10], but they share the same drawback in that they can only quantify the average stiffness of a fixed, narrow region of interest, 0.4×0.5 cm.

A third newer technique is shear wave elastography (SWE), which is also integrated into a diagnostic ultrasound system, and in addition, it allows a real-time 2D image that can measure tissue stiffness quantitatively. This technique allows the visualisation and registration of the spatial variation of elasticity to a B-mode image. These values of elasticity are mapped and represented in a colour display within the region of interest.

This shear wave elastography method is able to characterise elasticity by a number of novel properties, including the quantitative assessment of the lesion elasticity in kPa or m/s, the spatial heterogeneity of stiffness, and the estimation of the stiffness ratio between the lesion and the liver. SWE has demonstrated that it can enhance ultrasound's capability to characterise lesions in surface-level applications, such as the breast [11].

In the current study, SWE was successfully used to assess a total of 25 lesions in 21 patients. All lesions were subjected to 2-D ultrasound studies, followed by Shearwave elastography quantitative assessment of focal liver lesions stiffness, and compared with the Triphasic CT and pathological results. The distribution of the 25 lesions that SWE successfully assessed is displayed in (Table 1).

Table (2) summarises the results of the stiffness analysis; Fig. (1) shows the distribution of the stiffness values for the different lesions.

SWE acquisitions failed for 5 lesions (17%) in 5 patients. Therefore, a total of 21 patient with 25 lesions were successfully evaluated (11 males and 10 females). These numbers of acquisition failure are slightly higher but consistent with those published by Guibal et al. [6] who had SWE (failure in 14 % of the lesions) and with other researchers using ARFI such as (Park et al.) [12]. This failure was mostly caused by patients' inability to hold their breath long enough, which results in excessive tissue movement during respiratory motion. Other causes of failure were transmitted cardiac pulsations (Fig. 2) and lesions deeper than 8cm.

Ronot et al. [13] have reported that the mean stiffness for HCC is (19.6 kPa), which corresponds to the current study (20.67±5.22 kPa) (Fig. 3); however, Guibal et al. [6] reported a mean stiffness of (14.86±10 KPa) for HCC which is slightly lower than the current study.

It is worth mentioning that Masuzaki et al., and Heide et al. [9,10], who have used TE and ARFI techniques, respectively reported that Cholangiocarcinoma had the highest stiffness value of all

lesion types. This was matching with Guibal et al. [6], who have used the SWE technique, also found a significant difference ($p=0.0004$) between the elasticity of hepatocellular carcinoma and cholangiocarcinoma, these distinct differences in SWE could aid in the differentiation of HCCs and cholangiocarcinomas. The authors suggested that the elevated stiffness value of cholangiocarcinomas is due to their highfibrotic component. Unfortunately, the current study couldn't include cases of cholangiocarcinoma.

According to Guibal et al. [6], the stiffness values of metastases varied depending on the primary malignant tumour. Metastatic lesions from gastrointestinal adenocarcinomas had mean elasticity values of 21.814.6 KPa, but metastases from carcinoids had stiffer values of 30.716.6 KPa. However, this difference was not statistically significant ($p=0.1116$). Hoyt and Warram [14], also reported similar observation stiffness of metastases varied according to their primary tumour with mean stiffness (35.89±12.55 kPa).

In the current study, the stiffness values of metastatic lesions varied according to the primary malignant tumour type. The mean stiffness of the nine metastatic lesions was (35.89±12.55 kPa) with minimum stiffness (20.00 kPa) and maximum stiffness (57.00 kPa) of pancreatic metastasis. Metastases from gastrointestinal origin showed lower mean elasticity values (28±21) and (37±11 KPa) than that of breast and pancreatic origin with stiffness values of (45±22 KPa) and (57±29 KPa) respectively (Fig. 4).

In this study, we had four cases of hemangiomas, two of them were typical in appearance and the other two had an atypical appearance, with a mean stiffness value of (7.50±2.38 kPa). (Figs. 2, 5) This value is lower than that of Guibal et al. [6] (13.8±5.5 kPa). Heide et al, Ronot et al., as well as Davies and Koenen [10,13,15], also described similar observations. However, all studies observed that hemangiomas have slightly higher stiffness values as compared with the surrounding liver. Guibal et al. [6] explained that this could be due to the presence of fibrous septae separating the blood-filled spaces and hence elevating the stiffness value.

Two cases were diagnosed as focal fatty infiltrations with stiffness values (9±3 kPa) and (8±0 kPa) and mean stiffness (8.50±.71 kPa) which is higher than normal liver parenchyma (Fig. 6). Although we didn't find any studies that included focal fatty infiltration, these results are matching

with that of diffuse liver steatosis as in Ronot et al. [13] who reported mean stiffness values of diffuse liver steatosis 9.6 ± 4.7 kPa, and Virchenko et al. [16] who reported 8.4 kPa for severe steatosis.

The current study included one hepatic abscess that showed mean stiffness (7 ± 2 kPa), but we didn't find any similar study that included a hepatic abscess (Fig. 7).

In this work, we found that there is a significant difference in stiffness between malignant and benign groups of lesions with means of (7.71 ± 1.80 kPa) for the benign group and (28.28 ± 12.18 kPa) for the malignant group and with ($p < 0.001$) (Table 3) which is consistent with Park et al. [17], who used SWE and reported that malignant lesions were significantly higher in their stiffness values than those of benign lesions ($p < 0.0001$), (Guibal et al., Davies and Koenen, Park et al., Zhang et al. and Tian et al.) [6,15,17,18,19] also reported a significant difference between malignant and benign groups, while others such as (Gallotti et al., Heide et al., Ronot et al., Yu and Wilson, Frulio et al.) [1,10,13,20,21] had not demonstrated any differences.

Ronot et al. [13] reported that real-time elastography failed to differentiate the stiffness of hepatic tumours; they explained this discrepancy by the fact that the studies that have addressed this issue were discordant and the prevalence of malignant and benign tumours varied widely. For instance, Davies and Koenen [15] study measured metastases and haemangiomas only, while hepatic haemangiomas are known to be considered one of the soft liver lesions. Hence, Ronot et al., [13] believed that the different thresholds of stiffness values that are published in the literature to be used to distinguish benign and malignant lesions should be considered with great caution.

There are observable and measurably different tissue stiffness values between malignant and benign lesions, according to Guibal et al. [6]. However, a straight forward diagnostic threshold is not clinically effective because of the variability of stiffness values within benign and malignant lesion types. For instance, compared to FNHs, which are firmer benign lesions, HCCs were generally softer.

In the current study, there is an overlap in the stiffness values within the malignant group (HCC & metastasis) i.e. the largest HCC stiffness value was 28 kPa while the lowest metastasis stiffness value was 20 Kpa, as well as within the benign group (hemangioma ranged between 5 and 10 Kpa, the abscess was 7 Kpa and focal fatty infiltrations were 8 and 9 Kpa) that's why it is not specific.

Results of the current study agreed with Tian et al., [19] and Guibal et al., [6]. They have agreed that SWE, used in conjunction with normal ultrasound and contrast imaging, may be able to answer more precise clinical queries. As in the atypical hemangioma case (Fig. 2), the multiplicity and the hypoechoic pattern of the lesions raised the suspicion of metastasis; however, the low stiffness value favoured the diagnosis of multiple hemangiomas rather than metastasis, which was proved by the triphasic CT scan which showed peripheral nodular enhancement in the arterial phase and progressive fill in in the portal and delayed phases.

Also, it was of great help in the benign inflammatory lesion (abscess) (Fig. 7), SWE helped to exclude the diagnosis of metastases from the cancer head of the pancreas, the lesion had a stiffness value of 7 ± 2 kPa, which is much less than expected in metastasis, refer to Fig. (4) (liver metastasis from pancreatic head carcinoma) which had stiffness values 46 ± 19 & 57 ± 29 kPa.

Conclusion:

Finally, we concluded that; SWE, is an adjunct to conventional ultrasound that can provide additional information with a more precise characterization of focal liver lesions composition, based on its tissue elasticity values, especially in cases where contrast imaging is contraindicated. However, the evaluation of the diagnostic accuracy of this technique needs a study with larger patient samples.

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هل لإضافة قياس مرونة الكبد كتقنية غير تداخلية لفحص الموجات فوق الصوتية دور مساعد في تقييم البؤر الكبدية

قد تكون البؤر الكبدية حميدة أو خبيثة، ويتطلب العلاج تشخيص دقيق والذي يعتمد بدوره في المقام الأول على طريقة التصوير المناسبة وأخذ عينة منها باستخدام تقنيات الأشعة التداخلية.

وغالباً ما تكون الموجات فوق الصوتية هي طريقة التصوير الأولى في الكشف عن البؤر الكبدية ودراستها وذلك لانخفاض تكلفتها مع توافرها. إن قياس المرونة باستخدام الشير ويف الستوجرافي وهي تقنية جديدة تم دمجها في أجهزة الموجات فوق الصوتية الحديثة والتي تعتمد على بث موجات ميكانيكية مؤقتة خلال الأنسجة باستخدام نفس محول الموجات فوق الصوتية ومن ثم تصويرها بتسلسل فائق السرعة من أجل الحصول على خرائط كمية لمرونة الأنسجة.

بالنسبة للبؤر الكبدية الأكثر شيوعاً وجدنا أن البؤر الكبدية الخبيثة سواء كانت أولية أو ثانوية تعرض قيم صلابة أعلى من الأورام الوبائية الحميدة.

وأخيراً استنتجت الدراسة أن الشير ويف الستوجرافي كتقنية مساعدة للموجات فوق الصوتية التقليدية. يمكنها توفير معلومات إضافية عن خصائص البؤر الكبدية استناداً إلى مرونة هذه البؤر.