

RESEARCH

Open Access



Role of shear wave elastography in characterization of hepatic focal lesions

Dena M. Serag¹, Eman A. Ebeid^{2*}, Basma A. Dessouky¹ and Hazem Omar³

Abstract

Background: Elastography is a recently developed diagnostic method that aims to evaluate tissue stiffness. Its utility is based on the fact that pathological tissues are generally stiffer than surrounding healthy tissues which often show up as a hard lesion. Shear wave elastography (SWE) is a new technique based on shear waves that has been implemented in diagnostic ultrasound (US) systems. The aim of this study is to study the role of shear wave elastography in differentiation between benign and malignant hepatic focal lesions.

Results: The study was conducted on 110 patients (92 males, 18 females) with a mean age of 51.7 years. Age range was from 30 to 70 years; 28 patients were diagnosed with benign lesions, and 82 with malignant lesions. SWE shows that there is a significant difference in stiffness between malignant and benign lesions with p value = 0.002 and with mean \pm SD of 10.3 ± 6.31 kPa for the benign lesions and 16.2 ± 9.32 kPa for the malignant group. A cutoff value of 13.24 was selected to differentiate between benign and malignant lesions using the SWE mean providing sensitivity 78.04%, specificity 71.42%, and accuracy 64.2%.

Conclusion: SWE is a good tool in the differentiation of benign and malignant hepatic focal lesions.

Keywords: Shear wave elastography, Elastography, SWE, Hepatic focal lesions

Background

Liver tumors are tumors or growths on or in the liver. Several distinct types of tumors can develop in the liver because the liver is made up of various cell types. These growths can be benign or malignant. They may be discovered on medical imaging (even for a different reason than the cancer itself) or may be present in patients as an abdominal mass, hepatomegaly, abdominal pain, jaundice, or some other liver dysfunction [1]. Because of its advantageous cost/benefit ratio, widespread availability, and easy execution, ultrasound (US) is the first-line imaging modality in most countries for the initial liver survey and represents the imaging technique that usually detects complex liver lesions [2]. It is generally agreed that no other physical parameter of tissue is changed by pathological or physiological process to a remarkable extent as the tissue elasticity [3]. SWE estimates the speed

of shear waves to provide a quantitative estimate of tissue stiffness [4]. SWE has the advantage of being able to image liver tissue stiffness in real time because the shear waves are generated by US impulses [5]. Several features can be described with this technique, including the quantitative evaluation of the lesion elasticity in kilopascals or meters/second and the spatial heterogeneity of stiffness, and moreover, SWE imaging is guided using B-mode images with a higher frame rate. This method can provide more accurate assessment of liver tissue stiffness due to the advantages of SWE and B-mode image guidance [6, 7].

The purpose of this study was to evaluate the role of SWE in characterization of hepatic focal lesions.

Methods

This was a prospective study conducted from December 2017 to March 2019 after the approval of protocol from faculty of medicine ethical committee for human research; fully informed written consent was taken from

* Correspondence: monna.22222@gmail.com

²Department of Radiodiagnosis, Birket Elsaba Hospital, Menoufia, Egypt
Full list of author information is available at the end of the article

Table 1 Age and sex distribution among the studied patients

Age	Benign (28) (25.5%)		Malignant (82) (74.5%)	
	Male (18) (16.4%)	Female (10) (9.1%)	Male (74) (67.3%)	Female (8) (7.3%)
30 to > 40 years (17) (15.5%)	4 (3.6%)	5 (5.5%)	6 (5.5%)	2 (1.8%)
40 to > 50 years (33) (30%)	4 (3.6%)	3 (2.7%)	22 (20%)	4 (3.6%)
50 to > 60 years (36) (32.7%)	6 (5.5%)	1 (0.9%)	28 (25.5%)	1 (0.9%)
60 to > 70 years (24) (21.8%)	4 (3.6%)	1 (0.9%)	18 (16.4%)	1 (0.9%)

each patient after given an explanation of the procedures and the importance of the study; the confidentiality of the patient's data was guaranteed, and the patients had the right to refuse participation in this study without giving any reason.

The study enrolled 110 patients: 92 male and 18 females with a mean age 51.7 years after fulfillment of inclusion and exclusion criteria. Inclusion criteria were patient presented with at least one hepatic focal lesion greater than 1 cm in diameter and not more than 5 cm deep from the capsule. Exclusion criteria were focal lesion previously managed by intervention radiology, patient with perihepatic ascites, and uncooperative patients.

The patients were subjected to full history taking and laboratory investigations. Real-time ultrasound and shear wave elastography (SWE) was performed using Philips iU22 × MATRIX ultrasound system with a curved array transducer 3–5 MH. The patients were examined in the supine or left lateral position with right arm elevated above the head to improve intercostal access. Gray scale abdominopelvic ultrasonography was initially performed to evaluate the liver size, echogenicity, texture, outline, and focal lesions. We identified hepatic focal lesions for number, site, size, margin, and echogenicity. Then, in SWE scanning, the patient was instructed to hold his or her breath for a few seconds. We located the segment of hepatic focal lesion, and a region of interest (ROI) was adjusted upon the targeted focal lesion; we took from 5 to 8 measurements for quantitative evaluation of stiffness. Then, the machine estimated the velocity of the propagated shear wave in the ROI and automatically

translates it to stiffness in kilopascals (KPs). In patient with more than one focal lesion, we ensured that all lesions have the same pathology guided by other modalities like CT and MRI, and then, we analyzed the most accessible one. Multiple successful measurements are obtained, and the results appear in the final report as the average of all measurements. Then, the data obtained by SWE scanning is compared with the results of triphasic CT and raised tumor markers in 92 patients (84%), dynamic MRI in 15 patients (13%), and 3 patients by histopathology to estimate the accuracy, sensitivity, and specificity of SWE in characterization of different hepatic focal lesions.

Statistical analysis

Data were collected, tabulated, and statistically analyzed using a personal computer with Statistical Package of Social Science (SPSS) version 20 [SPSS Inc., Chicago, IL, USA], where the two types of statistics were done.

Descriptive statistics

Quantitative data was expressed as mean ± standard deviation (SD). Qualitative data was expressed as frequency and percentage.

Table 2 The clinical presentation of the patients

Clinical presentation	No.	Percentage
Abdominal pain	40	36.4
Abdominal distention	45	40.9
Fever	3	2.7
Jaundice	10	9.1
Loss of appetite	15	13.6
Loss of weight	13	11.8
Asymptomatic (accidentally discovered)	17	15.5
Total	143	130

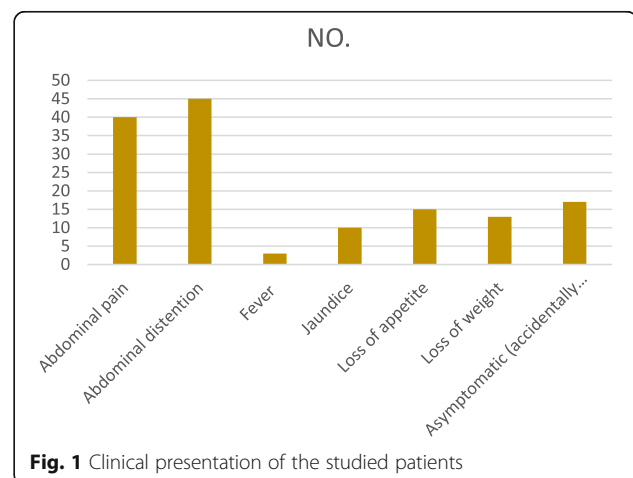
**Fig. 1** Clinical presentation of the studied patients

Table 3 Laboratory findings of the studied patients

Lab investigations		Benign lesions, N = 28 (25.45%)	Malignant lesions, N = 82 (74.54%)	χ^2	p value
CBC	RBCS (mean ± SD)	4.7 ± 0.23	4.5 ± 0.52	0.751	0.420
	WBCS (mean ± SD)	5876.2 ± 911.2	5395.1 ± 1037.1	1.56	0.120
	Platelets (mean ± SD)	250.3 ± 39.4	198.2 ± 67.23	2.745	0.009
Virology	Negative	10 (71.4%)	2 (4.9%)	27.65	0.001
	Hepatitis B	1 (7.1%)	11 (26.8%)		
	Hepatitis C	3 (21.4%)	28 (68.3%)		
Liver functions	Bilirubin (mean ± SD)	1.23 ± 1.67	2.06 ± 3.6	0.751	0.411
	Albumin (mean ± SD)	3.9 ± 0.2	3.52 ± 0.54	2.641	0.013
	SGOT (mean ± SD)	38.32 ± 12.35	57.32 ± 23.10	2.832	0.006
	SGPT (mean ± SD)	39.1 ± 14.20	56.32 ± 16.14	3.214	0.002
Renal functions	Creatinine (mean ± SD)	3.9 ± 1.20	1.2 ± 0.21	1.652	0.095
	Urea (mean ± SD)	32.1 ± 6.25	37.2 ± 5.64	2.741	0.008
INR	(mean ± SD)	0.91 ± 0.07	0.97 ± 0.17	0.851	0.376
PC	(mean ± SD)	75.2 ± 5.12	72.4 ± 8.32	0.941	0.351
Tumor markers	AFP (mean ± SD)	22.1 ± 14.32	504.32 ± 387.1	4.651	0.001

Table 4 Ultrasound criteria in the benign and malignant lesions

US criteria		Benign lesions, N = 28 (25.45%)	Malignant lesions, N = 82 (74.54%)	χ^2	p value
Liver	Size			0.895	0.596
	• Average	12 (42.9%)	36 (43.9%)		
	• Enlarged	16 (57.1)	46 (56.1%)		
	Echo pattern			8.564	0.004
	• Non-cirrhotic	22 (78.6%)	28 (34.1%)		
	• Cirrhotic	6 (21.4%)	54 (65.9%)		
Focal lesion	Number			1.657	0.643
	• One	18 (64.3%)	64 (78%)		
	• Two	6 (21.4%)	14 (17.1%)		
	• Three	2 (7.1%)	2 (2.4%)		
	• Multiple	2 (7.1%)	2 (2.4%)		
	Echogenicity			2.854	0.410
	• Echogenic	10 (35.7%)	14 (17.1%)		
	• Heterogenic	2 (7.1%)	16 (19.5%)		
	• Hypoechoic	14 (50%)	42 (51.2%)		
	• Isoechoic	2 (7.1%)	10 (12.2%)		
	Margin			0.323	0.124
	• Ill-defined	6 (21.4%)	24 (29.3%)		
	• Well-defined	22 (78.6%)	58 (70.7%)		
Spleen	• Normal	18 (64.3%)	24 (29.3%)	5.362	0.023
	• Enlarged	10 (35.7%)	58 (70.7%)		
Ascite	• No	28 (100%)	46 (56.1%)	9.824	0.019
	• minimal	0 (0)	36 (43.9%)		

Table 5 Pathological diagnosis among the studied patients

Benign lesions (28)	Malignant lesions (82)
Hemangioma (24) (21.8%)	HCC (70) (63.6%)
Focal fatty infiltration (4) (3.36%)	Cholangiocarcinoma (6) (5.4%)
	Metastasis (6) (5.4%)

Analytic statistics

Independent samples *t* test of significance will be used when comparing between two means. Chi-square (χ^2) test of significance will be used in order to compare proportions between two qualitative parameters. ROC curve is a graph called a receiver operating characteristic curve; it is a plot of the true positive rate against the false positive rate for different possible cutoffs of diagnostic test or marker. *p* value ≤ 0.05 was considered to be statistically significant. *p* value ≤ 0.001 was considered to be highly statistically significant.

Results

Our study was conducted on 110 patients (92 male (83%), 18 female (17%)). The patients' age ranged from 30 to 70 years with a mean age of 50.2 years for the benign lesions and 54.2 years for the malignant; Table 1 shows that the malignant lesions presented more among the male patients aged 50 to 60 years representing 25.5%. Clinical analysis of the clinical presentation of the studied patients revealed that 45 patients (40.9%) were presented by abdominal distention and 40 patients (36.4%) were presented by abdominal pain followed by loss of appetite (13.6%), loss of weight (11.8%), and jaundice (10%) (Table 2; Fig. 1).

The laboratory findings of the studied patients are summarized in (Table 3); the most significant lab investigations in patients with malignant lesions were alpha-feto proteins, hepatitis viral markers, and liver function tests (SGPT, SGOT, albumin) with *p* value of 0.001, 0.001, 0.002, 0.006, and 0.013, respectively. High-resolution ultrasound scanning of the 110 patients yielded the detection of 152 focal lesions. In patient with more than one focal lesion, we ensured that all lesions have the same imaging criteria by other modalities like CT and MRI, and then, we analyzed the most accessible

Table 6 SWE stiffness values in the studied patients with benign and malignant lesions

SWE criteria	Benign lesions	Malignant lesions	<i>t</i> test	<i>p</i> value
SWE mean (mean ± SD)	10.3 ± 6.31	16.2 ± 9.23	2.653	0.012
SWE standard (mean ± SD)	4.10 ± 2.35	6.2 ± 4.3	2.130	0.033
SWE median (mean ± SD)	10.32 ± 6.74	17.23 ± 8.25	3.320	0.002

one. Ultrasound imaging criteria for the liver parenchyma and hepatic focal lesions are listed in Table 4. The cirrhotic liver was significantly related to the presence of malignant lesions with p value < 0.004 , while the size of the liver had no statistically significant relationship to the pathology of the lesions with p value 0.6. Also, the presence of splenomegaly and ascites was significantly related to malignancy with p value < 0.02 and 0.019, respectively.

Out of the studied 110 patients, 82 patients (74.5%) were finally diagnosed with malignant lesions (70 of them (63.6%) had HCC, 6 patients (5.4%) with cholangiocarcinoma, 6 patients (5.4%) with metastasis) and 28 patients (25.5%) were finally diagnosed with benign lesions (hemangioma in 24 patients (21.8%) and focal fatty infiltration in 4 patients (3.36%)) as seen in Table 5.

All patients were subjected to shear wave elastography scanning. It showed that there was a significant difference in stiffness (p value < 0.002) between malignant and benign lesions with mean \pm SD of 10.3 ± 6.31 kPa for the benign lesions and 16.2 ± 9.23 kPa for the malignant group as listed in Table 6. Table 7 and Fig. 2 showed that a cutoff point of 13.24 was selected to differentiate between benign and malignant lesions using the SWE mean providing sensitivity 78.04%, specificity 71.42%, positive predictive value 88.8%, negative predictive value 52.6%, and accuracy 64.2%. We found that the 4 focal fatty infiltration were found to have stiffness

Table 7 Validity test of SWE mean regarding benign and malignant lesions

AUC	p value	Cutoff point	Sensitivity	Specificity	PPV	NPV	Accuracy
0.777	0.002	13.24	78.04%	71.42%	88.8%	52.6 %	64.2%

mean \pm SD values of 12.6 ± 8.8 kPa. The 24 hemangioma lesions were found to have stiffness mean \pm SD of 9.5 ± 4.2 kPa (Fig. 3). The stiffness mean \pm SD of the 70 HCCs was 15.4 ± 7.2 kPa, while the stiffness mean \pm SD of the 6 cholangiocarcinoma was 32.5 ± 8.25 kPa. The stiffness of the 6 metastatic lesion mean \pm SD was 22.1 ± 0.4 kPa as described in Table 8.

Discussion

The accurate characterization and the differential diagnosis between the different types of FLLs are important aims that all the imaging modalities available today should satisfy [8]. The aim of this study was to assess the accuracy and sensitivity of SWE in characterization of hepatic focal lesions. Shear wave elastography quantitative assessment of focal liver lesions stiffness was done and compared with the final diagnoses obtained by triphasic CT, dynamic MRI, and pathological results. In this work, we found that there was a significant difference in stiffness between benign and malignant groups

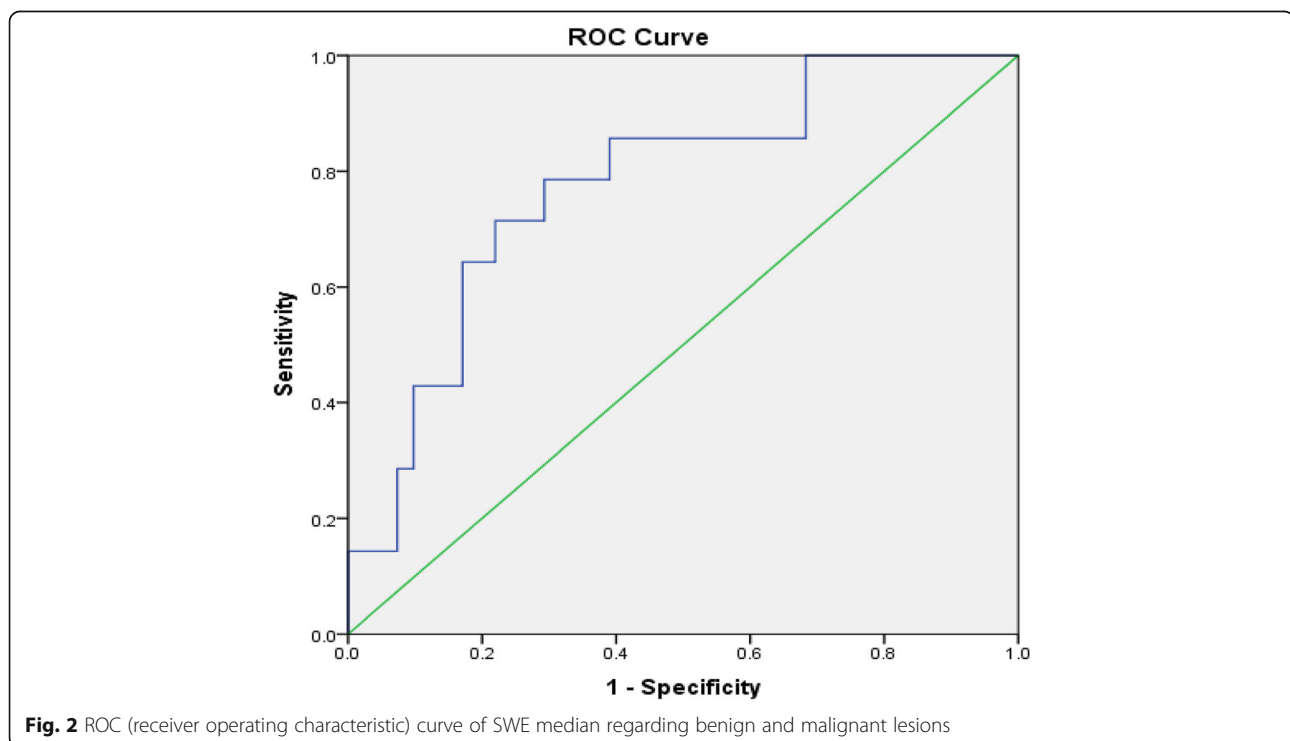


Fig. 2 ROC (receiver operating characteristic) curve of SWE median regarding benign and malignant lesions

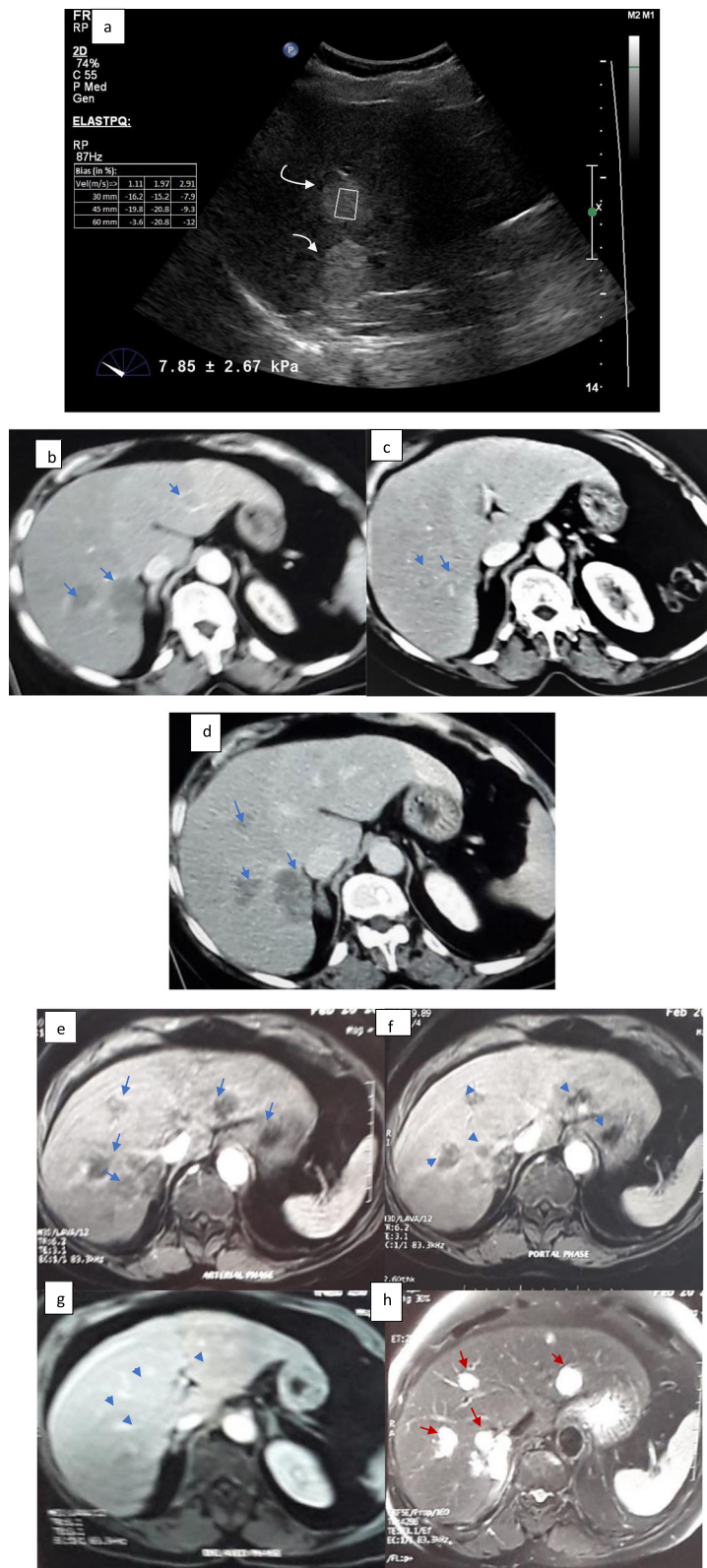


Fig. 3 A case of hemangioma. **a** US image. **b–d** Triphasic CT. **e–h** Dynamic MRI

Table 8 Comparison between different types of benign and malignant lesions regarding SWE parameters

Lesions	SWE parameter			
	N = 110	SWE average (mean ± SD)	SWE standard (mean ± SD)	SWE median (mean ± SD)
Hemangioma	24 (21.8%)	9.5 ± 4.2	4.2 ± 2.3	9.32 ± 5.37
Focal fatty infiltration	4 (3.63%)	11.2 ± 5.8	10.1 ± 6.8	12.4 ± 7.23
HCC	70 (63.63%)	15.4 ± 7.2	6.3 ± 4.6	16.30 ± 7.54
Cholangiocarcinoma	6 (5.45%)	32.5 ± 8.25	9.3 ± 3.2	22.23 ± 9.4
Metastasis	6 (5.45%)	22.1 ± 0.4	6.3 ± 1.02	23.6 ± 2.64

with a mean value of 10.32 ± 6.74 for benign lesions and 17.23 ± 8.25 for malignant lesions with a statistically significant difference of $p < 0.002$. This was consistent with Guibal et al. [8] who reported that there was a significant difference in the stiffness between benign and malignant lesions with means of 18.53 ± 13.5 kPa and 26.9 ± 18.8 kPa for benign and malignant lesions, respectively (with high significant difference $p > 0.01$). Also, Park et al. [9] reported that the stiffness values of malignant lesions were significantly higher than those of benign lesions ($p < 0.0001$), while other studies have not demonstrated any differences (Ronot et al. [10], Frulio et al. [11], Gallotti et al. [12], and Heide et al. [13]).

In this current study, we had 24 cases of hemangiomas which were found to have a mean stiffness of 9.5 ± 4.2 kPa. This was close to the results reported by Guibal et al. [8] who reported a mean stiffness of 13.8 ± 5.5 kPa for the 22 hemangiomas. Guibal et al. explained this elevation in stiffness due to the presence of fibrous septa separating the blood-filled spaces. Ronot et al., Heide et al., Cho et al., and Davies and Koenen [10, 13–15] also described similar observations. In our study, we have 4 focal fatty infiltrations (FFI) which were found to have a mean stiffness of 10.2 ± 5.8 kPa. These results were higher than the values reported by Virchenko et al. [16]. They studied the stiffness values of diffuse hepatic steatosis in 130 patients and reported a mean SWE value of 8.4 kPa for severe steatosis. The difference may be attributed to larger sample size in their study. Ronot et al. [10] also reported similar results regarding diffuse hepatic steatosis with a mean SWE value of 9.6 ± 4.7 kPa.

In the current study, the mean stiffness for 70 hepatocellular carcinomas (HCCs) was 15.4 ± 7.2 kPa. These results are matching with a study carried out by Guibal et al. [8]. They reported a mean stiffness of 14.86 ± 10 kPa for 26 hepatocellular carcinoma which is similar to our study (Fig. 4). Also, our finding was close to those reported by Ronot et al. [10] who reported a mean stiffness value of 19.6 kPa. We also found that cholangiocarcinoma and metastasis were the stiffest of all lesion types. SWE value was 32.5 ± 8.25 kPa for the 6 cholangiocarcinoma. This result was close to Ronot et al. [10]

who reported 34.1 ± 7.3 kPa for the two cholangiocarcinoma.

Our result was lower than that reported by Guibal et al. [8] who reported that cholangiocarcinoma were the stiffest of all lesion types with a mean stiffness value of 56.9 ± 25.6 kPa. The difference in both observations may be due to the small sample size in our study. Guibal et al. [8] explained the elevation of the stiffness value of cholangiocarcinoma to their significant fibrotic component. Also, Masuzaki et al. [17] and Heide et al. [13] reported similar observations about the stiffness value. Also, in this current study, a mean stiffness value of 22.1 ± 0.4 kPa was reported for the 6 metastasis cases. This was consistent with Guibal et al. [8]; they studied 53 metastases with mean elasticity values of 21.8 ± 14.6 . Guibal et al. [8] reported that the elevation in elasticity values found with SWE likely originates from several factors, including changes in vascular and lymphatic permeability, along with changes in collagen deposition and cellular architecture. Malignant lesions grow in an environment restrained by the surrounding tissue, and this can result in an increase in interstitial pressure [8].

There are several limitations encountered with the use of SWE:

1. The primary cause of failure was the lesion location beyond the penetration limits of SWE generally (> 5 cm), major steatosis, and the proximity to vessels.
2. Other failures were attributed to poor intercostal windows and patient inability to hold their breath long enough to acquire a stable SWE acquisition.
3. Another limitation is that the radiologist who acquired the elastography images was not blinded for the diagnosis, and this could introduce bias.

Conclusion

SWE is a good tool for differentiating between different benign and malignant hepatic focal lesions with high sensitivity, specificity, and accuracy. It shows that there is a significant difference in stiffness between malignant and benign lesions.

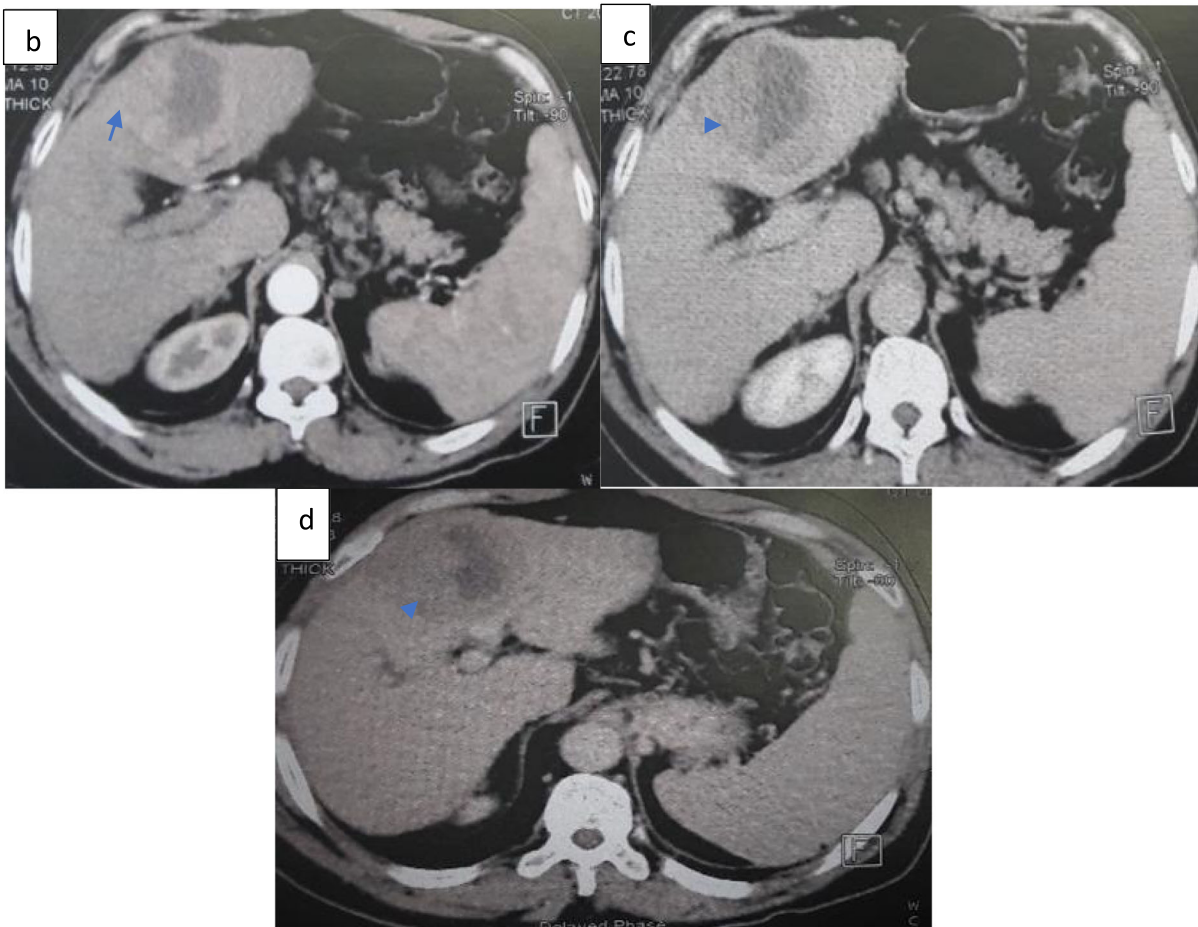


Fig. 4 A case of hepatocellular carcinoma. **a** US image. **b-d** Triphasic CT

Abbreviations

SWE: Shear wave elastography; US: Ultrasound; SD: Standard deviation; MH: Megahertz; ROI: Region of interest; kps: Kilopascals; CT: Computed tomography; MRI: Magnetic resonance imaging; FLLs: Focal liver lesions; HCC: Hepatocellular carcinoma; FFI: Focal fatty infiltration

Acknowledgements

There is no acknowledgement.

Authors' contributions

DS, EA, BD, and HO contributed equally to the study design, data collection, analysis, and interpretation of results. All authors have read and approved the manuscript.

Funding

There is no funding.

Availability of data and materials

Data will be available upon request via contacting the corresponding author.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Faculty of Medicine at Menoufia University in Egypt on 13 March 2016; reference number of approval: 32016-RAD. All patients included in this study gave written informed consent to participate in this research.

Consent for publication

All patients included in this study gave written informed consent to publish the data contained within this study.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Radiodiagnosis, Faculty of Medicine, Menoufia University, Menoufia, Egypt. ²Department of Radiodiagnosis, Birket Elsaba Hospital, Menoufia, Egypt. ³Diagnostic and Intervention Medical Imaging Department, National Liver Institute, Menoufia University, Menoufia, Egypt.

Received: 13 February 2020 Accepted: 30 March 2020

Published online: 20 April 2020

References

1. Bartolozzi C, Cioni D, Donati FC et al (2001) Focal liver lesions: MR imaging–pathologic correlation. *European radiology* 11(8):1374–1388
2. Corvino A, Sandomenico FS et al (2019) Morphological and dynamic evaluation of complex cystic focal liver lesions by contrast-enhanced ultrasound: current state of the art. *J Ultrasound* 11:1–9
3. Bamber J, Cosgrove D, Dietrich CF et al (2013) EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography: basic principles and technology. *Ultraschall Med* 34:169–184
4. Honjo M, Moriyasu F, Sugimoto K et al (2014) Relationship between the liver tissue shear modulus and histopathologic findings analyzed by intraoperative shear wave elastography and digital microscopically assisted morphometry in patients with hepatocellular carcinoma. *J Ultrasound Med.* 33:61–71
5. Herrmann E, de Lédinghen V, Cassinotto C et al (2018) Assessment of biopsy-proven liver fibrosis by two-dimensional shear wave elastography: an individual patient data-based meta-analysis. *Hepatology* 67(1):260–272
6. Ferraioli G, Tinelli C, Bello D et al (2012) Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C. *Hepatology* 56:2125–2133
7. Moustafa E, Makhlof F et al (2017) Non-invasive assessment of liver fibrosis in patients with hepatitis C: shear wave elastography and color doppler velocity profile technique versus liver biopsy. *Arab journal of gastroenterology* 18(1):6–12
8. Guibal A, Boularan C, Bruce M et al (2013) Evaluation of shear wave elastography for the characterization of focal liver lesions on ultrasound. *Eur Radiol* 23(4):1138–1149
9. Park, H. S., Kim, et al (2015). Shear wave elastography of focal liver lesion: intra-observer reproducibility and elasticity characterization. *Ultrasound Quarterly*; 31(4): 262-271.
10. Ronot M, Renzo SD, Gregoli B et al (2015) Characterization of fortuitously discovered focal liver lesions: additional information provided by shearwave elastography. *Eur Radiol* 25(2):346–358
11. Frulio N, Laumonier H, Carteret T et al (2013) Evaluation of liver tumors using acoustic radiation force impulse elastography and correlation with histologic data. *J Ultrasound Med* 32:121–130
12. Gallotti A, D'Onofrio M, Romanini L et al (2012) Acoustic Radiation Force Impulse (ARFI) ultrasound imaging of solid focal liver lesions. *Eur J Radiol* 81:451–455
13. Heide R, Strobel D, Bernatik T et al (2010) Characterization of focal liver lesions (FLL) with acoustic radiation force impulse (ARFI) elastometry. *Ultraschall Med* 31:405–409
14. Cho SH, Lee JY, Han JK et al (2010) Acoustic radiation force impulse elastography for the evaluation of focal solid hepatic lesions: preliminary findings. *Ultrasound Med Biol* 36:202–208
15. Davies G, Koenen M (2011) Acoustic radiation force impulse elastography in distinguishing hepatic hemangiomas from metastases: preliminary observations. *Br J Radiol* 84:939–943
16. Virchenko, O. V., Bodnar, et al (2013). 1329 diagnostic accuracy of a new elastographic method (shear wave™ elastography imaging) in the noninvasive assessment of non-alcoholic steatosis in patients with type 2 diabetes. *J Hepatol*; 58: S536.
17. Masuzaki R, Tateishi R, Yoshida H et al (2007) Assessing liver tumor stiffness by transient elastography. *Hepatology international* 1(3):394–397

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Submit your manuscript to a SpringerOpen® journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► [springeropen.com](https://www.springeropen.com)