Journal of Clinical Gastroenterology and Hepatology
ISSN: 2575-7733

Open access Research Article

Elasticity Characterization of Malignant and Benign Liver Lesions by Two Dimensional Shear Wave Elastography

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ABSTRACT

Background: Detection and characterization of focal liver lesions (FLLs) poses a frequent challenge in clinical practice. 2D-Shear Wave elastography (2D-SWE) is a recent technique which uses acoustic radiation force to induce mechanical vibrations and assess tissue elasticity

Aims: To study the elasticity characteristics of focal liver lesions by 2D shear wave elastography and to determine whether it can be used to differentiate benign from malignant lesions

Materials and methods: All patients with FLL underwent 2D-SWE and elasticity quantification. Contrast enhanced CT or MRI findings were used as the reference method for the diagnosis of FLLs

Results: 216 patients with FLL were evaluated by the 2D-SWE. 130 patients had malignant FLLs of which 90 had Hepatocellular Carcinoma (HCC), 20 had Intrahepatic Cholangiocarcinoma (IHCC) and 20 had metastatic lesions. Of the 86 benign FLL, there were 36 Hemangiomas, 12 FNH, 24 simple cysts, 4 complex cysts, and 10 abscesses. Mean liver stiffness of various lesions by 2D-SWE was 65.7 (IHCC), 60.5 (HCC), 45.4 (Metastases), 7.6 (Hemangioma), 16.9 (FNH), 9.14 (abscess), 8.62 (simple cyst) and 2.95 (complex cyst). ROC analysis revealed that a SWE cut off of 40 kPa could distinguish between benign and malignant lesions with sensitivity of 100% and specificity of 80% (AU-ROC of 0.87). The lesion to background liver parenchyma stiffness ratio in cirrhotic patients was 4.81 for IHCC, 3.16 for metastasis and 1.93 For HCC. Therefore in cirrhotic patients, a lesion to liver stiffness ratio <2 along with SWE of lesion more than 40 kpa favors HCC. However in non-cirrhotic livers, there was no statistically significant difference between stiffness ratio of various malignant focal lesions.

Conclusion: 2D-SWE could be a useful non-invasive method for the differentiation of benign and malignant focal lesions of liver

Keywords: Shear wave; Elastography; Liver lesions; 2D; Elasticity

ABBREVIATIONS

(SWE) Shear Wave Elastography; (FLL) Focal Lesions Liver; (CECT) Contrast Enhanced Computerized Tomography; (CEMRI) Contrast Enhanced Magnetic Resonance Imaging; (US) Ultrasound; (CCC) Cholangiocarcinoma; (HCC) Hepatocellular Carcinoma; (IHCC) Intrahepatic Cholangiocarcinoma; (FNH) Focal Nodular Hyperplasia; (PSWE) Point Shear Wave Elastography; (ARFI) Acoustic Radiation Force Impulse; (ROI) Region Of Interest; (2DSWE) 2D-Shear Wave Elastography

INTRODUCTION

The introduction of contrast enhanced (CE) US significantly improved the overall sensitivity and specificity for the diagnosis of malignant liver lesions to 93% and 90 [1,2]. It is equivalent or even superior to other contrast based imaging techniques such as computed tomography (CT) or magnetic resonance imaging

Received:	01-June-2022	**Manuscript No:**	IPJCGH-22-13459
Editor assigned:	03-June-2022	**PreQC No:**	IPJCGH-22-13459 (PQ)
Reviewed:	17-June-2022	**QC No:**	IPJCGH-22-13459
Revised:	22-June-2022	**Manuscript No:**	IPJCGH-22-13459 (R)
Published:	29-June-2022	**DOI:**	10.36648/2575-7733.6.6.26

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Citation George B, George EE, Vijay NH, Varghese J, George A, et al. (2022) Elasticity Characterization of Malignant and Benign Liver Lesions by Two Dimensional Shear Wave Elastography. J Clin Gastroenterol Hepatol.6 No.6.26

(MRI) [1,2]. Nowadays, CEUS has become the standard method for characterization of liver nodules found on surveillance and routine US [3]. The drawbacks are the cost of contrast agents, availability, the rare side effects, and diagnostic uncertainty in some cases, as for instance, in the differentiation of cholangiocarcinoma (CCC) and hepatocellular carcinoma (HCC).

In these uncertain cases, percutaneous biopsy is mandatory, which carries the risk of morbidity and mortality to the patient [4,5]. The knowledge that the mechanical properties of tissue are altered by fibrosis, inflammation, or tumor infiltration, has led to the development of elastography as a new imaging technique [6,7]. The first generation Elastography technique was Vibration controlled transient elastography (VCTE) (Fibroscan®, France), which was developed to measure liver tissue stiffness It represents the current standard for non-invasive methods in the staging of liver fibrosis and detection/exclusion of cirrhosis [8]. International guidelines have been established for VCTE. However, no B-mode visualisation is possible with the Fibroscan® and therefore focal liver lesions cannot be assessed. The second generation liver shear wave Elastography method (point shear wave Elastography, pSWE) is integrated into conventional ultrasound systems allowing the performance of surveillance ultrasound in addition to pSWE. pSWE uses push pulses of focused acoustic radiation force to deform the tissue and induce shear waves [9,10]. It shows comparable results to VCTE for the assessment of liver fibrosis In addition, it enables the evaluation of FLL with Elastography [11]. A meta-analysis of pSWE using acoustic radiation force impulse (ARFI) showed high sensitivity and specificity (86% and 89%, respectively) for the differentiation of benign and malignant FLLs [12]. Complementary effect of benign and malignant liver lesions [13]. The region of interest (ROI) size is 5 × 10 mm, hence spatial resolution is low [14]. 2D-shear wave Elastography (2D-SWE) using Supersonic shear imaging (Aixplorer®, France) is one of the most recent diagnostic liver Elastography imaging systems developed. Focused ultrasonic beams lead to a cylindrically shaped shear wave and enable the formation of real time shear wave images with a spatial resolution of one micrometer [7]. Feasibility has been proven for the assessment of liver fibrosis [15] characterization of breast masses [16], and prostate and thyroid nodules [17]. In addition, recently published pilot studies have revealed promising results for the evaluation of FLLs [14,18]. However, contradictory stiffness values and cut-offs between several lesions require further elucidation.

The purpose of this study was to evaluate 2D-Shear Wave Elastography (2D-SWE) (Aixplorer™) for the differentiation of benign und malignant liver lesions. We attempted to find out specific cut off values for easy differentiation of the malignant lesions of liver.

Aims and Objectives

- To study the elasticity characteristics of focal liver lesions by 2D shear wave elastography
- To determine whether 2D SWE can be used to differentiate benign from malignant focal lesions

MATERIALS AND METHODS

This was a prospective single center study done at a University hospital, Trivandrum, India. We included all patients with Focal lesion liver, diagnosed between January 2018 and January 2020 who came to the Department of Medical Gastroenterology. 2d Shear wave Elastography and elasticity quantification was performed along with conventional ultrasound of the liver in 216 patients having FLL. The diagnosis of FLL was obtained by typical imaging (CECT/CEMRI) findings. Radiologists specialized in liver imaging with at least 10 years of experience performed and interpreted the radiological examinations. Patient characteristics and epidemiological data were recorded.

All patients aged above 18 years of age, diagnosed with FLL by typical imaging findings were included in the study. Patients who were pregnant, those with contraindications for CE imaging techniques (CECT, CEMRI) and patients in whom a proper 2dSWE reading could not be obtained were excluded.

Baseline B-mode ultrasound of the liver was first performed to identify FLL. 2dSWE examination was performed using an Aixplorer system with a 3.5-MHz convex transducer. The operator was blinded to the clinical information and diagnosis of each patient. The patient was placed in the supine position with the right arm extended and placed over the head. In order to minimize the respiration related tissue motion in the Region of interest, the patients were asked to perform a brief period of breath hold and each measurement was performed during a separate breath hold. For the elasticity characterization of the FLL, a mean of 5 consecutive stiffness measurements was used as a representative value for each lesion. Background liver stiffness was measured at least 3 cm from the periphery of the lesion and the lesion-parenchyma stiffness ratio was calculated.

RESULTS

Patients

A total of 232 focal lesions were evaluated in 232 patients during the recruitment period. 16 patients were excluded from the statistical analysis due to 2D–SWE measurement failure. Failure was mainly due to anatomic features-FLL location close to the capsule or to the great vessels and those that were deep seated >8 cm. Excessive tissue movement due to respiratory or cardiac motion, obesity and severe steatosis were other causes of failure.

216 patients with FLL who were, successfully evaluated by the 2D-SWE were included (**Figure 1**).

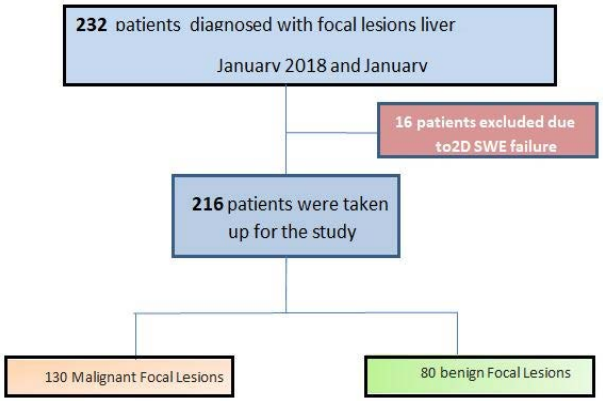


Figure 1: Consort Diagram

Baseline Characteristics

The age ranged from 19 to 87 years (mean age of 56.2 years). There were 164 males (75.9%) and 52 females (24.1%).

Distribution of Focal Lesions

There were 130 malignant FLLs. 90 patients had Hepatocellular Carcinoma (HCC), 20 had Intrahepatic Cholangiocarcinoma (IHCC) and 20 patients had metastatic lesions.

Of the 86 benign FLL, 36 were Hemangioma, 12 were FNH, 24 were simple cysts, 4 were complex cysts, and 10 were abscesses.

The metastatic lesions originated from the following primary tumour types: 14 colorectal adenocarcinomas, 1 gastric adenocarcinoma, 3 pancreatic adenocarcinomas, and 2 from unknown primaries. Of the 90 patients with HCC, 82 occurred in cirrhotic patients and 8 in non-cirrhotic patients. The aetiology of the cirrhosis was not evaluated in the current study (**Table 1**).

Table 1: Distribution of various etiologies of focal lesion

Lesion	Frequency	Percent
IHCC	20	9.3
HCC	90	41.7
HEMANGIOMA	36	16.7
FNH	12	5.6
METASTASIS	20	9.3
CYST	24	11.1
COMPLEX CYST	4	1.9
ABSCESS	10	4.6
Total	216	100.2

Tissue Elasticity of Various Focal Lesions

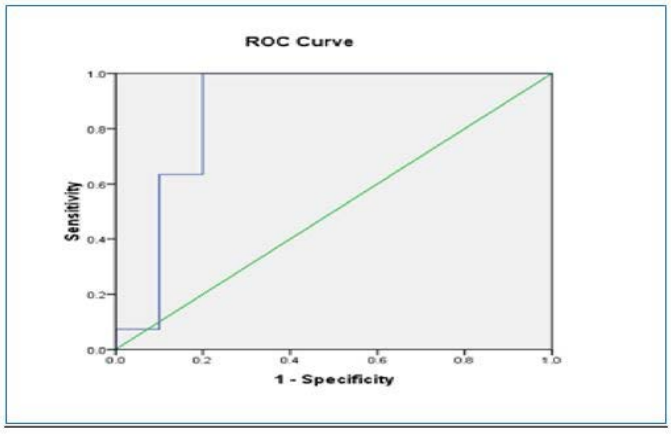
- IHCC were having a mean liver stiffness of 65.7, HCC of 60.5, Hemangioma of 17.6, FNH of 16.9, Metastasis of 45.4, simple cyst of 8.62, complex cyst of 2.95 and abscess of 9.14 kPa.
- Among malignant FLL, IHCC was the stiffest entity with significantly higher stiffness as compared to HCCs (p=0.033) and metastases (p=0.0079)
- No significant difference in elasticity was observed between HCCs and metastases.
- Typical imaging (CECT/CEMRI) findings were used as the reference method for the diagnosis of focal lesions (**Table2**).

Table 2: 2D-SWE of various focal lesions

DIAGNOSIS	MEAN	N	STD. DEVIATION
IHCC	65.64	20	9.118
HCC	60.54	90	10.883
METASTASIS	45.44	20	8.315
FNH	16.92	12	6.931
HEMANGIOMA	17.6	36	7.703
CYST	8.62	24	0.739
COMPLEX CYST	2.95	4	0.289
ABSCESS	9.14	10	1.301

SWE Cut Off for Differentiating Benign and Malignant FOL

- ROC analysis revealed that a SWE cut off of 40 kPa could distinguish between benign and malignant lesions with sensitivity of 100% and specificity of 80% (AUROC of 0.871) (**Figure 2**).



Area	Std. Error	Asymptotic Sig.
.871	.065	.000

Figure 2: ROC Curve

Lesion to Background Liver Stiffness Ratio

- Background liver stiffness by 2D-SWE was measured at least 3 cm from the periphery of the lesion and the lesion-parenchyma stiffness ratio was calculated
- The average duration of 2D-SWE (acquisitions and placement of ROI) was approximately 4 min per patient. All the malignant FLL were found to have significantly higher stiffness value than the surrounding liver stiffness.
- Mean lesion to liver, stiffness ratio was 7.49 for IHCC, 7.33 for metastasis and 2.79 for HCC.
- Among malignant FLL, Intrahepatic Cholangiocarcinoma was the stiffest entity with significantly higher stiffness as compared to HCCs (p=0.033) (**Table 3**).

Table 3: Focal lesion to liver, SWE ratio

DIAGNOSIS	MEAN	N	STD. DEVIATION
IHCC	7.49	20	1.752
HCC	2.79	90	2.819
METASTASIS	7.33	20	1.909
HEMANGIOMA	2.69	36	1.406
FNH	2.48	12	0.582
CYST	2.17	24	0.69
COMPLEX CYST	0.13	4	0.104
ABSCESS	2	10	0.274

Subgroup Analysis of Stiffness Ratio of HCC in Cirrhotics vs Non-Cirrhotic Livers

- Subgroup analysis of lesion to liver stiffness ratio was calculated separately for patients with HCC with background cirrhotic and non-cirrhotic livers
- In patients with cirrhosis, the lesion to liver, stiffness ratio for HCC was 1.93 and in patients without cirrhosis the ratio was 11.65
- Therefore in cirrhotics, a lesion to liver stiffness ratio <2 with SWE of lesion more than 40 kpa suggests HCC.
- Because of the small volume of subgroups among other metastatic FLLs, we did not do further statistical sub analysis.
- Among the benign lesions there was no staitistically significant different stiffness ratios in patients with cirrhosis as compared to patients without cirrhosis

DISCUSSION

Numerous studies have addressed the diagnostic benefit of the pSWE using ARFI [7,14,15]. Subsequently, a meta-analysis showed significant differences in tissue stiffness between benign and malignant FLLs [19]. However, the ROI of ARFI covers a fixed area of 5 × 10 mm. As a result, the spatial resolution is low. The potential inhomogeneity of FLL is neglected and inter examiner reliability of its placement within a lesion may be affected.

Very few pilot studies have evaluated the most recent diagnostic elastography imaging system 2D-SWE for stiffness investigation of FLLs. It provides quantitative elasticity maps in real time with a spatial resolution of one micrometer [20]. The circular ROI is operator adjustable. However, most studies did not give precise information on the choice of ROI placement. Recent studies done by Gerber et al. [14], Guibal et al. [21] showed similar findings in our study. In all these studies malignant FLLs have higher stiffness compared to the benign FLLs.

In the study we have evaluated the different FLLs with different etiology to get a proper differentiation cut off between benign and malignant lesion specifically, mean of 5 consecutive stiffness measurements was used as a representative value for each lesion. Background liver stiffness was measured at 3 cm from the lesion periphery, within the lesion and lesion-parenchyma stiffness ratio was calculated for each lesion separately.

Among malignant FLL, IHCC was the stiffest entity with significantly higher stiffness as compared to HCCs (p=0.033) and metastases (p=0.0079). As described by Xing Hu et al. [19], Gerber et al. [14], choangiocarcinoma was the stiffest FLL among the ones studied, it can be explained by the pronounced desmoplastic stroma reaction, but internal haemorrhage or necrosis in malignant lesions would decrease stiffness. No significant difference in elasticity was observed between HCCs and metastases.

The value of stiffness for metastases vary widely depending on the type of primary tumor they have. Most patients with metastases were on treatment with chemotherapy and anti angiogenic therapy which may be affecting their stiffness values.

In view of this assumption comparison of stiffness between different primaries of metastasis not attempted in the present study Among the benign lesions studied maximum number of lesion in this study we studied were hemangioma (41.86%), simple cysts (23.2%) and FNH (13.9%). Out of the lesions studied Hemangiomas were almost homogenous lesions with slightly elevated stiffness value (17.6 ± 7.7 kPa) compared with the surrounding liver. Cho et al. [22], Davies and Koenen [23] and Heide et al. [24] have also described similar observations. This is probably because histologically, haemangiomas consist of large blood filled endothelial lined spaces separated by fibrous septa, likely accounting for the elevations in stiffness.

The median stiffness value of FNH was (16.92 ± 6.92). This result is almost similar in agreement but having a lower value with Guibal et al. [21] who reported SWE mean stiffness of FNH 33 kpa ± 14 kpa and also having similar results with the previous studies by Gallotti et al. [24] and Heide et al. [25]. The higher stiffness may be because of the lesions which are composed of enlarged hepatocytes which are supported by weak framework of collagen and they lack biliary canaliculi. But in contrary to the results of precious studies mentioned FNH in our studies have lesser stiffness compared to hemangioma. It may be because of lesser number of FNH lesions compared to hemangioma evaluated in this study and we may extend the study further to see this finding is repeating in larger numbers.

In our study ROC analysis revealed that a SWE cut off of 40 kPa could distinguish between benign and malignant lesions with sensitivity of 100% and specificity of 80% (AUROC of 0.871). Literature search did not reveal any other studies which were able to arrive at a specific cut off with greater sensitivity and specificity. The current study also had a much larger sample size than previous studies.

Sub group analysis of malignant FLL in cirrhotics and non cirrhotics done in the study to find out any specific shear wave limit and ratio between focal lesion SWE to surrounding SWE liver to differentiate at least between the cholangiocarcinoma and HCC. The study was able to find out by using lesion to liver stiffness ratio particularly in cirrhotics with SWE cut off >40 and if the ratio is lower than 2 we may be able to differentiate HCC non-invasively. This cut off needs to be validated in further larger studies and in different populations

CONCLUSIONS

- Tissue elasticity value of more than 40 kPa determined by 2D-SWE suggests malignant focal lesion liver with sensitivity of 100% and specificity of 80%
- In cirrhotic livers, a lesion to liver stiffness ratio less than 2 with SWE >40 kPa in cirrhotic livers is more in favour of HCC.
- If validated in larger samples, tissue elasticity measured by 2D-SWEcan be useful for the non-invasive characterization of focal liver lesions

LIMITATIONS IN OUR STUDY

- The reference method was diagnosis of focal lesion was CECT or CE-MRI performed by expert radiologist rather than liver biopsy which is the gold standard

- The study has to be validated in larger samples and different geographical settings

AKNOWLEDGEMENT

None

DISCLOSURE OF FUNDING

None

CONFLICT OF INTEREST

The authors declare no conflict of interest

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