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ROLE OF ULTRASOUND ELASTOGRAPHY IN EVALUATION OF FOCAL LIVER LESIONS

Radiology

Dr Himanshu Soni* MD, DMRE, Associate Proff Radiology Depratment *Corresponding Author

Dr Jitendra Rathava 3rd Year Resident Radiology

Dr. Rupal Vadhiya 2nd Year Resident Doctor

Dr. Bhavya Chauhan 2nd Year Resident Doctor

ABSTRACT

Introduction:
Ultrasonographic elastography is a new noninvasive imaging technique that can be used to depict relative tissue stiffness or displacement (strain) in response to an imparted force. Stiff tissues deform less and exhibit less strain than compliant tissues in response to the same applied force. Acoustic Radiation Force Impulse (ARFI) imaging is an ultrasound elastography technique where a short, high intensity focused ultrasound beam is introduced for target tissue displacement. This technique has enabled liver elastography by transmission of the acoustic wave between the ribs or from the sub-costal area. Different features can be shown on ARFI elastography according to the type of liver tumor and that quantification of tumor stiffness may be helpful in the diagnosis.

Aim and objectives:
The aim of our study is to evaluate the role of ultrasound elastography in differentiating benign and malignant focal liver lesions.

Materials and Methods:
After ethical clearance, a prospective study was carried out in the Gujarat Cancer and Research In statute, Ahmedabad, from May 2016 to October 2018. After obtaining consent, 50 patients with focal liver lesions were studied. USG and elastography of focal liver lesions performed and ARFI value of lesions measured. The final diagnosis was confirmed by CT and/or trucut biopsy in selected patients for histopathological confirmation. The diagnosis on the basis of contrast enhanced CT and histopathology was considered to be the gold standard.

Results:
Sensitivity and specificity of the USG for the diagnosis of the Malignancy is 96.67% and 70% while the accuracy is the 86 % in this study.Maximum observation of the benign lesion shear wave value is fall within the range of the 1.3 to 1.9 m/s density in elastography and for malignant lesions 2.70 to 3.10 m/s.

Conclusion:
ARFI elastography is more sensitive and specific than USG in discriminating between benign and malignant lesions at 2.0 m/s with sensitivity and specificity of 96% and 95% respectively. ARFI elastography has also higher accuracy of 96%. ARFI elastography is very useful in differentiating benign from malignant focal liver lesions.

KEYWORDS

Ultrasonography, Elastography, Benign, Malignant, Focal liver lesions.

INTRODUCTION

Focal liver lesions are a common occurrence during imaging evaluation of the liver. They include a wide variety of benign and malignant lesions. With advancement in technology, ultrasound (US) can detect small lesions at an earlier stage. Lesions can be characterized by their grey scale appearance and on the basis of vascular information obtained using color, spectral and power Doppler.

B Mode ultrasound (US) of the liver provides good spatial resolution and inherent soft-tissue contrast, which alone may allow the characterization of many liver lesions. Though color Doppler US and power Doppler US provide good depiction of large-vessel flow, they fail to yield the information that is provided with contrast enhanced CT and MR imaging about parenchymal vascularity of the lesion.

Ultrasonographic (US) elastography (sono-elastography) is a new noninvasive imaging technique that can be used to depict relative tissue stiffness or displacement (strain) in response to an imparted force [1, 2]. Stiff tissues deform less and exhibit less strain than compliant tissues in response to the same applied force. Thus, the basis of elastography is analogous to manual palpation [2]. The application of US elastography for imaging tissues is relatively novel, first described in 1987 by Krouskop et al [3]. Since its inception, sono-elastography has been used to evaluate numerous types of tissues, including breast, prostate, liver, blood vessels, thyroid, and musculoskeletal structures. Sono-elastography is based on the comparison of signals acquired before and after tissue displacement. Several sono-elastography techniques have been devised, including compression strain imaging [4], vibration sono-elastography [5], acoustic radiation force generated by the ultrasound pulse [6], and real-time shear velocity [7].

Compression elastography involves calculating a strain profile in a direction perpendicular to the tissue surface in response to an externally applied force. Specialized software is used to calculate the relative difference in tissue movement from one frame to another and then to estimate the tissue deformation. The deformation measurements are mapped onto an elastogram, on which stiffer areas are depicted as dark and more elastic areas are lighter, according to convention. This permits depiction of a lesion that is otherwise iso-echoic on gray-scale US images. Imaging software for compression elastography is currently available on some commercial US machines.

Acoustic Radiation Force Impulse (ARFI) imaging is an ultrasound elastography technique where a short, high intensity focused ultrasound beam is introduced for target tissue displacement [8, 9, 10, 11]. This technique has enabled liver elastography by transmission of the acoustic wave between the ribs or from the sub-costal area [12, 13]. The present study was performed to investigate the potential usefulness of ARFI elastography for evaluating focal solid hepatic lesions, assuming that different features can be shown on ARFI elastography according to the type of liver tumor and that quantification of tumor stiffness may be helpful in the diagnosis.

This quantitative technique provides a single uni-dimensional measurement of tissue elasticity, although the measurement area can be positioned on a two-dimensional B mode image. The region is a 1×0.5 cm rectangular, which can be freely moved in the two-dimensional B mode image to a maximum depth of 8 cm from the skin plane. The measurement is expressed in m/s, expressing shear wave speed, travelling perpendicular to the shear wave source.

We propose that by using ultrasound ARFI Elastography, we can make

a further attempt to evaluate the nature (Benign vs. Malignant) of hepatic lesions, thus improving diagnostic accuracy and reducing invasive procedures on these patients.

MATERIALS AND METHODS

This study was carried out in radiology department of The Gujarat cancer and research institute on 50 patients (30 males and 20 females) presenting with tumors affecting the liver between the period of May 2016 to November 2018. Lesions well visualized at conventional US, with a minimum diameter greater than or equal to 1.5 cm and absence of any previous local treatments (i.e. percutaneous ethanol injection, radiofrequency ablation, trans-arterial chemo embolization). A written informed consent was obtained from all patients prior to the ARFI examination. Brief relevant history and clinical examination findings were recorded

The study was carried out on Siemens Acuson S-3000 helix sonography machine by using convex probe (6C1) and linear probe (9L4). The liver was screened for focal lesions in B-mode and images were documented. On a B-mode US image the lesion was identified and interrogated for elastic properties by utilizing a Region of Interest (ROI), characterized by a box with fixed dimension of 1 cm × 0.5 cm. The target tissue is mechanically "pushed" by short-duration forces (less than 1 ms) that generate localized displacements. The shear waves produced propagate perpendicular to the acoustic pulse away from the target ROI. The ROI was entirely included into the lesion, in biggest ones changing the ROI location to cover the entire mass as much as possible, without including any vessels or biliary structures. The potentially presence of any degeneration (i.e. necrotic or cystic or hemorrhagic or calcified portion) or any other specific macroscopic finding, such as fibrotic scar, have not to be comprised into the ROI. In multiple lesions, largest or well visualized lesion was evaluated. Measures in the surrounding parenchyma were also performed, with the ROI within 2–3 cm from the focal lesion, taking care not to comprise any vascular or biliary structures. The calculation of the shear wave speed is expressed in meters per second.

All measurements were achieved after a short inspiration in order to improve the visualization of the lesion. We performed 4 measurements per lesion and 2 measurements in the surrounding liver. As reported above, the ROI was located in different portions of the lesions, in order to evaluate the entire mass. Since Virtual Touch tissue quantification expresses the shear wave speed in solid materials as numerical values, only numerical results were taken into consideration in this study. Thus, non-valid measurements due to an erroneous ROI positioning (i.e. necrotic or cystic portion of a lesion, vessels or biliary structures within the ROI) or patient motion, expressed by the system as "N/A" (not-available) or "XXXX" or "0", were excluded.

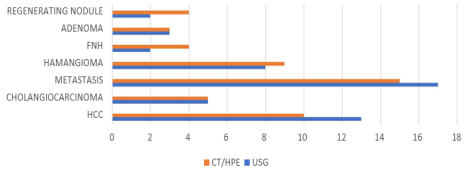
A subjective evaluation of the lesions was done on grey scale taking into consideration the history, number of lesions, echogenicity, margins, posterior acoustic enhancement, color Doppler (CD) findings. In the presence of cirrhosis, the differential diagnosis was narrowed down to either hepatocellular carcinoma (HCC) or regenerating nodules in suspect hypoechoic lesions. Focal nodular hyperplasia (FNH) or hepatic adenoma were considered as possibilities in female patients taking oral contraceptive pills.

The final diagnosis was confirmed by CT and/or trucut biopsy in selected patients for histopathological confirmation. The diagnosis on the basis of contrast enhanced CT and histopathology was considered to be the gold standard.

There were 30 patients with malignant liver lesions and 20 with benign liver lesions. The malignant liver lesions were diagnosed as hepato-cellular carcinoma (n= 10), cholangio-carcinoma (n=5) and metastases (n=15). The benign liver lesions were diagnosed as haemangioma (n=9), hepatic adenoma (n=3), regenerating nodules (n=4) and focal nodular hyperplasia (n=4).
The characterization of the lesions by USG was compared to the final diagnosis and the sensitivity, specificity and diagnostic accuracy of USG was calculated. Similarly, the ARFI values of the lesions were taken and the sensitivity, specificity and diagnostic aaccuracy of USG was compared with that of ARFI.

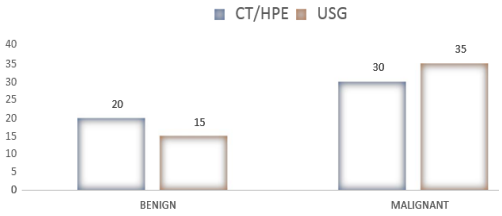
RESULTS

Figure 1: Distribution of lesions with diagnosis by USG and CT/HISTOPATHOLOGY



The above graph shows the distribution of the patient as per the two different diagnostic methods. Among them the diagnosis by the CT/Histopathology is considered as the final and USG is use for the screening of the patient. As per the two different methods, the representation of the distribution of the lesion is quite different except for the diagnosis of the Cholangiocarcinoma and adenoma.

Figure 2: Distribution with benignancy and malignancy of the liver lesions according to USG and CT/ HISTOPATHOLOGY



Above diagram shows the distribution of the carcinoma cases in benign and malignant as per the USG and final diagnostic methods CT/ Histopathology. The graph shows that the USG shows 15 benign and 35 malignant lesions respective to the finally diagnosed of the 20 benign and 30 malignant lesions.

As per this the sensitivity and specificity of the USG for the diagnosis of the Malignancy is 96.67% and 70% while the accuracy is the 86 % in this study.

There were 30 patients with malignant liver lesions. Out of these, 29 were accurately diagnosed as malignant lesions while 1 was classified as benign on USG.

This patient had homogeneously hyperechoic, well defined lesions on USG and hence he was diagnosed as haemangioma. Also there was no history of pre-existing malignancy. However CT revealed washout of contrast in late phase of enhancement, thus confirming the lesions to be malignant. Trucut biopsy was done in both instances and histopathology confirmed metastatic disease.

Six patients with benign lesions were diagnosed inaccurately as malignant by USG. One patient with FNH was diagnosed inaccurately as hepatic adenoma by USG. Thirteen patients with benign lesions were accurately diagnosed by USG.

A lesion that was iso-echoic with intra-lesional vascularity was diagnosed to be a metastasis on USG. However, CT revealed peripheral nodular enhancement in

early phase followed by centripetal filling in which is diagnostic of haemangioma.

A Haemangioma in a cirrhotic liver was also misdiagnosed as HCC on USG as it was iso-echoic. However, CT confirmed the enhancement characteristics to be that of a haemangioma.

2 cases with regenerating nodules in a cirrhotic liver were misdiagnosed as HCC on USG which later on conformed by histopathology.

One patient with a hepatic adenoma was misdiagnosed as metastasis on USG. On CT scan it appeared as well defined iso attenuating to liver and showed transient relative arterial post contrast enhancement and wash out on delayed phase. The CT scan features suggested a benign lesion like hepatic adenoma, which was confirmed by histopathology.

One patient of FNH was diagnosed on USG as metastasis. On CT scan the lesion shows bright homogenous arterial enhancement except central scar. On delayed scan scar shows post contrast enhancement.

These findings were suggestive of FNH and histopathology was confirmatory.

One patient with FNH was diagnosed as Hepatic adenoma on USG. Lesion appeared heterogeneously hyper-echoic with intra-lesional vessels on color Doppler. Finding on CT scan suggestive of FNH and histopathology was confirmatory.

Table 1: Mean wave velocity values derived from all measurements performed according to the definitive diagnosis for the benign lesions

Diagnosis on CT/Histopathological	Elastography (ARFI) value Mean	Elastography (ARFI) value SD
Adenoma	1.23	0.01
Hemangioma	1.48	0.36
FNH	1.88	0.04
Regenerating nodule	1.66	0.07

The above table shows the final diagnosis and the shear wave value for that diagnosis in case of the benign lesion. For the Adenoma the mean value of the lesion in ARFI elastography is 1.23 m/s. Similarly for the Haemangioma, FNH and Regenerating nodule the mean shear wave value are 1.48, 1.88 and 1.66 m/s respectively.

Table 2: Mean wave velocity values derived from all measurements performed according to the definitive diagnosis for the malignant lesions

Diagnosis on CT/Histopathological	Elastography (ARFI) value Mean	Elastography (ARFI) value SD
HCC	2.26	0.25
Metastasis	2.99	0.11
Cholangiocarcinoma	3.1	0.16

The above table shows the final diagnosis and the shear wave value for that diagnosis in case of the malignant lesion. For the HCC the mean shear wave value of the lesion in ARFI is 2.26 m/s. Similarly for the Metastasis and the Cholangiocarcinoma the mean shear wave value of the lesion are the 2.99 and 3.1 m/s respectively.

Table 3: Mean ARFI value for Benign and Malignant lesions

Diagnosis on CT/Histopathological	Elastography (ARFI) value Mean	Elastography (ARFI) value SD
Benign	1.56	0.27
malignant	2.78	0.45

*Benign= Adenoma, FNH, Haemangioma, Regenerating nodule
**Malignant = Cholangiocarcinoma, Metastasis and HCC

The above table shows the mean shear wave value for the Benign and Malignant lesion on ARFI elastography. The mean shear wave value for the benign lesion is 1.56 m/s. And for the malignant lesion the mean shear wave value is the 2.78 m/s.

Table 4: Distribution of the patient according to total mean shear wave velocity (m/s) values for each type of lesion and of their surrounding parenchyma.

Final diagnosis	Mean of Parenchyma	SD	Mean of Lesion	SD
Adenoma	1.32	0.06	1.23	0.01
Haemangioma	1.5	0.39	1.48	0.36
Regenerating nodule	2.91	0.1	1.66	0.07
HCC	2.87	0.14	2.26	0.25
Metastasis	1.4	0.2	2.99	0.11
Cholangiocarcinoma	1.59	0.12	3.1	0.16

Table 5: Distribution of the patient according to the ARFI value of the parenchyma in the cirrhotic and non-cirrhotic liver

	Count	Mean	SD
Cirrhotic liver	14	2.87	0.15
Normal liver	36	1.43	0.10

The above tables show mean ARFI value of the parenchyma in the cirrhotic liver is 2.87 m/s and non-cirrhotic/normal liver is 1.43 m/s. HCC and Regenerating nodules are seen in cirrhotic liver and the mean shear wave value of the lesions are the 2.26 and 1.66 m/s respectively.

Figure 3: Frequency distribution of the lesion density for benign lesions.

The above frequency distribution shows that the maximum observation of the benign lesion shear wave value is fall within the range of the 1.3 to 1.9 m/s density in elastography.

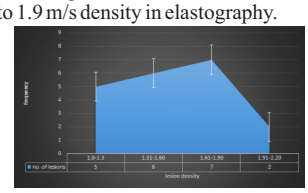


Figure 4: Frequency distribution of the lesion density for malignant lesion

The above frequency distribution shows that the maximum observation of the lesion shear wave value is fall within the range of the 2.70 to 3.10 m/s for the malignant lesion.

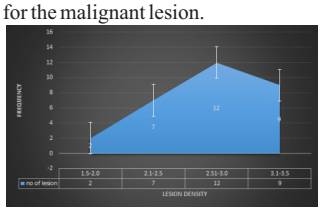


Table 6: Different cut-off value of the lesion density in Elastography for the differentiation of the Malignant and Benign lesion with the accuracy.

Cut off for the Malignant Lesion	Sensitivity	Specificity	Positive Predictive Value	Accuracy
1.5	100	40	71.43	76
1.7	100	70	83.33	88
2	96	95	96.67	96
2.3	70	100	100	82

The above table shows the different cut-off value of the lesion density considering the higher values represent the malignant lesion and lower values represent the benign lesion. Considering the maximum sensitivity if we put our cut off at a lower value so that we don't miss any malignant case as false negative as the cut off is set at 1.5 or 1.7 m/s. But the accuracy of the test will be compromised and we can have false positive cases as Malignant. On the contrary if we want to more specific, than we have to set cut off value at higher values so that we don't have any false positive cases but the sensitivity will be compromised and we could miss many cases as False Negative. So considering the above if we would set our cut off point at the maximum accuracy as in above table at 95%, the cut off shear wave value is 2 m/s for the Malignant and Benign Lesion.

IMAGE GALLERY

Figure 5: Ultrasound ARFI technique with Virtual Touch tissue quantification in a HCC.

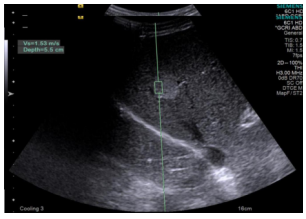


Figure 6: Ultrasound ARFI technique with Virtual Touch tissue quantification in a haemangioma.

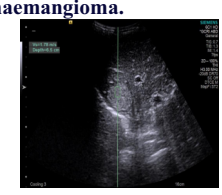


Figure 7: Ultrasound ARFI technique with Virtual Touch tissue quantification in a focal nodular hyperplasia

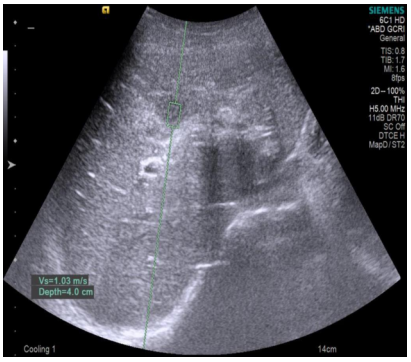


Figure 8: Ultrasound ARFI technique with Virtual Touch tissue quantification in a hepatic adenoma

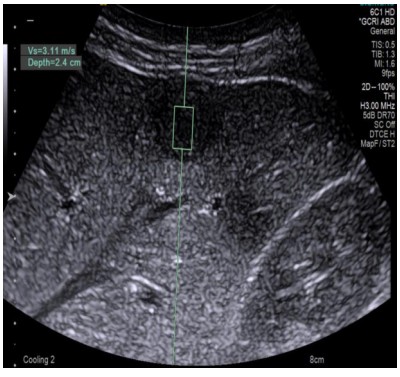


Figure 9: ARFI technique with Virtual Touch tissue quantification in a metastasis.

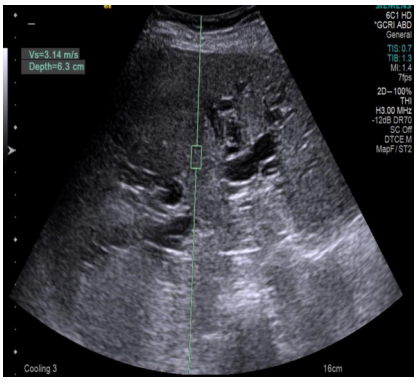


Figure 10: ARFI technique with Virtual Touch tissue quantification in a cholangio-carcinoma.

DISCUSSION

US has excellent spatial and contrast resolution. It provides useful information about the liver and its masses. However there is also extreme reliance on clinical information. Without knowledge of the patient's history and demographics, therefore, different interpretations may result from an identical ultrasonographic appearance. For example, a well-defined hyper-echoic lesion showing posterior acoustic enhancement is most likely to be a benign haemangioma. However in a cirrhotic patient at risk for HCC, a hyper-echoic lesion may very well be malignant. Similarly, multiple hypo-echoic lesions are most likely to be metastases. Recognition of a hypo-echoic halo or rim surrounding an echogenic or isoechoic liver mass suggests probable malignancy [14, 15, 16, 17, 18]. In most cases, a mass seen on ultrasonography has to be referred for contrast enhanced CT scan, MRI and FNAC for a confident diagnosis.

ARFI technology represents a relatively new imaging method able to non-invasively assess the elastic properties of target tissues. This technology differs from other previous elastographic techniques, since it allows the evaluation of deep tissues without the need for an external compression. [19]

Its quantitative implementation called Virtual Touch tissue quantification gives an objective numerical evaluation of the tissue stiffness [20, 21]. Integrated intoa conventional US system, it provides real-time additional information to the examination [22].

The calculation of the shear wave speed mainly reflects the elasticity and viscosity of the targettissue [23, 24]. Soft materials allow for large displacement amplitudeswhereas hard materials typically lead to low displacementamplitudes.

Fahey et al. in 2007 analyzed seven lesions, including HCCs, which resulted softer and metastases, which resulted stiffer than the regional liver parenchyma [23]. Cho et al. in 2009 studied the shear wave velocity in 36 focal solid liver lesions, including metastases and cholangio-carcinomas (grouped together), HCCs and hemangiomas [25].A. Gallotti et al. in 2012, evaluated the application of ARFI ultrasound imaging and its potential value for characterizing 40 focal solid liver lesions including FNH and Hepatic adenoma [26].

According to Cho, most metastases and cholangio-carcinomas were stiffer than the surrounding liver, but only 24% of the HCCs were softer than the surrounding cirrhotic liver, being the 76% characterized by equal or greater stiffness [25]. According to A. Gallotti and in our study, all metastatic lesions were stiffer than the surrounding liver [26]. This is probably due to the presence of fibrous content potentially found in many of the metastatic lesions. The eventually presence of necrotic degeneration, mainly in the biggest masses, does not influence the results. Since the aim of our study was to assess the stiffness of solid portion
of the focal liver lesions included, the ROI was in fact accurately located out of the necrotic central portion.

According to Fahey and Gallotti but inconsistent with Cho's results despite the similar diameter of the lesions, in our study almost all the HCCs evaluated resulted in softer lesions compared to the surrounding cirrhotic liver, and the mean value was lower than that of the surrounding parenchyma. On diffuse hepatic fibrosis, cirrhotic liver shows a wave velocity value higher than that of the normal liver, depending on the amount of fibrotic tissue [21] however, a significant difference in wave velocity values between different degree of fibrosis is not still clearly demonstrated for US application of ARFI technology. Some papers showed that ARFI imaging could be able to differentiate between cirrhotic and non-cirrhotic liver, but the potential differentiation between different degrees of liver fibrosis is still under discussion [22] Thus, the lower wave velocity valueobserved in HCCs than the surrounding liver parenchyma could bedue to the presence of multiple cells in cord and few connective tissuein HCCs and the great abundance of fibrosis in the surroundingliver, almost always a cirrhotic parenchyma.

Cho et al. showed that the 78% of soft lesions depicted on ARFI images were haemangioma and reported a mean value of 1.51 ± 0.71 m/s and it is consistent with our results but according to the Virtual Touch tissue imaging analysis, this type of focal lesions had a similar number of stiffer tumors and softer tumors relative to the background liver [25]. Thus, our result are not so inconsistent with Gallotti's, because almost always they observed higher values in hemangiomas than in the surrounding parenchyma. However, we agree withGallotti et al., regarding the potential great variability of this type of lesion, depending on the amount of fibrotic septa which divide the dilated vascular spaces.

Adenomas showed wave velocity values similar to those observed in the surrounding liver: this is a softer focal liver lesion, the most soft analyzed. The absence of portal spaces and biliary ducts, the presence of cells similar to normal hepatocytes and few stroma, explain the low mean wave velocity value calculated in adenomas compared to other focal lesions. These results are consistent with Gallotti et al.

FNH showed wave velocity values always higher then surrounding liver. The result is explained with the well-known high fibrotic content of this type of liver lesion, but our results are inconsistent with Gallotti et al. in which FNHs resulted stiffer lesions after metastases.

For the first time, in our study also regenerating nodules were studied. Regenerating nodules showed shear wave velocity values(1.66 ± 0.07

m/s) always lower then surrounding cirrhotic liver and it is softer than HCC (2.26 ± 0.25 m/s). So we can easily diagnose between them in a cirrhotic patient by ARFI.Limitations or pitfalls of ARFI elastography are:

- Sometimes, we cannot assess deep lesions by ARFI.
- We have assessed ARFI in 50 patients. Larger study may be required for more accurate results.
- Non-valid measurements like N/A (not-available) or XXX or O were found in very hard lesion, necrotic or cystic portion of a lesion, vessels or biliary structures within the ROI) or in patient motion. So we had to exclude these non-valid measurements from our study.
- In large lesions, we have to take multiple ARFI values and calculate mean of these multiple values.

The present study seems to confirm the potential application of elastography technology for characterizing focal solid liver lesions. According to the results, significant differences between the total mean wave velocity values typical for each type of lesions have been achieved. In the clinical setting, ARFI technique seems to be a useful tool in US liver imaging.

CONCLUSION

ARFI elastography is more sensitive and specific than USG in discriminating between benign and malignant lesions at 2.0 m/s with sensitivity and specificity of 96% and 95% respectively. ARFI elastography has also higher accuracy of 96%.

ARFI elastography gives a differential diagnostic possibility between adenomas and FNHs. ARFI imaging with Virtual Touch tissue quantification could supply significant complementary information to the US examination, providing high mean velocity values in FNHs and low values in adenomas.

ARFI elastography also gives the differential diagnosis between adenomas and metastases, both of which can be multiple, but at Virtual Touch tissue quantification, higher mean velocity values are found in metastases as compared to adenomas.

ARFI elastography also gives the differential diagnosis between regenerating nodules and HCC, both of which can be present in cirrhosis of liver, but at Virtual Touch tissue quantification, higher mean velocity values are found in HCC as compared to regenerating nodules.

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