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Role of sono-elastography in determination of solid hepatic lesions

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ABSTRACT

Background: Focal Liver Lesions (FLLs) are considered a major problem during abdominal examinations. Liver cancer represents the second leading cause of mortality in men and the sixth cause in women worldwide.

Objective: To identify the role of sono-elastography in solid hepatic lesion to differentiate benign from malignant.

Data sources: Medline databases (PubMed, Medscape, Science Direct. EMF-Portal) and all materials available in the Internet till 2023.

Conclusion: Significant differences in elastographic parameters among various benign and malignant liver lesions were apparent. The mean values of elastographic parameters were significantly higher in malignant liver lesions compared to benign liver lesions. Among the elastographic parameters, Strain ratio was found to be a better parameter to differentiate between focal liver lesions. These data may justify the more routine use of this technique in the characterization and assessment of focal liver lesions. The technique shows promising results in individual characterization of some malignant Hepatocellular Carcinoma and Cholangiocarcinoma (HCC and CCC) and benign hepatic focal lesion (FNH (Focal Nodular Hyperplasia) from other benign lesions).

Keywords: Sono-elastography; Solid hepatic lesions; Focal nodular hyperplasia; Malignant hepatocellular carcinoma; Cholangiocarcinoma

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INTRODUCTION

The liver is a rather unique organ as far as concerning imaging studies, since it can present many different types of masses. It is one of the most common target organs for many tumors in the metastatic stage and, therefore, secondary involvement is likely to be found upon pathologic examination in up to 30% to 40% of patients dying from an extra-hepatic primary cancer [1]. Focal liver lesions are defined as solid or cystic containing masses, foreign to the normal anatomy of the liver. Focal Liver Lesions (FLLs) are considered a major problem during abdominal examinations. Liver cancer represents the second leading cause of mortality in men and the sixth cause in women worldwide. FLLs are classified as benign or malignant. Benign hepatic lesions can be either solid or cystic, within these types; the subtypes include heamangioma (the most common), hepatic adenoma, focal nodular hyperplasia, focal fatty change, bile duct cysts, and hydatid cysts [2].

Malignant hepatic focal lesions can be either primary or secondary (metastases). The commonest primary malignant liver neoplasm is Hepatocellular Carcinoma (HCC) and the second most common neoplasm is cholangiocarcinoma. There are other rare liver neoplasms as angiosarcomas and hepatoblastomas. The widespread use of imaging modalities such as Ultrasonography (US), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI), particularly Ultrasonography (US), has led to the detection of a large number of small focal liver lesions in both screened and unscreened populations. However, differential diagnosis between benign and malignant liver lesions may be uncertain. Ultrasound is a first-line modality for examination of the liver because it is low in cost, convenient to use, and does not expose the patient to radiation [3].

Sonoelastography is a novel technique that uses ultrasound waves to allows a noninvasive estimation and imaging of tissue elasticity distribution within biological tissues to detect and display the relative stiffness of tissue by using real-time ultrasound Doppler techniques to image the vibration pattern resulting from the propagation of low-frequency (less than 1 kHz) shear waves that are propagated through deep tissue [4].

The low-frequency vibration is provided by an external source, such as an audio speaker or a piston shaker, which is brought into close contact with the patient or tissue sample. The shear source is then driven by signals in the audio frequency range. When a region of uniform tissue contains a hard lesion there is a local decrease in the peak vibration amplitude at the lesion [4].

Thus, the main principle of sonoelastography is the measurement of tissue distortion in response to external compression. Changes

in elasticity and tissue deformation elicited by compression are measured, processed and then shown in real time presentation with color coded elastograms [3].

One of the most important applications of sonoelastography is the evaluation of liver diseases, mainly liver fibrosis assessment and staging [5].

LITERATURE REVIEW

Anatomy of the liver

The normal liver is wedge shaped with its base towards the right abdominal wall, and its tip point to the spleen. It measures 12 cm to 15 cm cranio-caudally and 15 cm to 20 cm from corner to corner [6].

The liver is enclosed within a thin, fibrous hepatic capsule that is just beneath the visceral peritoneum. From the hepatic capsule, septa are seen projecting into hepatic parenchyma [7].

Understanding the segmental anatomy of the liver is vital for localization and appropriate management of liver tumors. The system projected by couinaud who provides the surgically significant imaging techniques and is applied easily to sectional imaging techniques [8].

The liver is divided according to Couinaud classification into 8 segments; each has its vascular flow, outflow and biliary drainage. The main portal vein is divided into two main branches, the right and the left branches. The plane of demarcation between the right and the left liver can be approximated as a plane going from the gall bladder fossa to the vena cava in which runs the middle hepatic vein [8].

Segment one is the caudate lobe. The rest of the liver segments are divided as follows: The right hepatic vein is the first landmark. All of the segments located anterior and to the left of the right hepatic vein will be included in the right anterior section (segments 5 and 8) and all the segments located posterior and to the right will be included in the right posterior section (segments 6 and 7). The third order bifurcation of the portal vein will be the second landmark (where the right sectorial branches separate into segmental branches). It is not necessary to follow the segmental branches as the plane where the segmental branches begin can be the plane passing by the main portal bifurcation approximately. In each sector the inferior segments 5 and 6 will lie inferior to the portal bifurcation, and the superior segments 7 and 8 will be superior to it [9].

Blood supply of the liver

The liver has dual blood supply receiving blood from both the portal vein (70%) and the hepatic artery (30%) [10].

Hepatic arteries: The Common Hepatic Artery (CHA) is the second branch of the celiac artery. It courses to the right all along the superior border of the pancreas in the right gastro-pancreatic fold. It ascends anterior to the portal vein and to the left of the bile duct and behind it [11].

The CHA bifurcates to the right and the left hepatic arteries to supply the right and left lobes respectively. The right and left hepatic arteries each bifurcates into two arteries that supply the right anterior and posterior sectors and the left medial and lateral sectors, respectively. The middle HA can arise from the right or the left hepatic artery and supplies the quadrate lobe. Anomalies of the HA are frequent and can be seen in about 50% of the people. It is important to known these variations because they are used in the advent of transplantation, aggressive resection, and in trans-arterial chemoembolization [11].

The portal vein: The second lumbar vertebra marks the beginning of the portal vein by the union of the superior mesenteric vein and the splenic vein. The neck of the pancreas lies anterior to it and the inferior vena cava lies posterior to it.

It ascends posterior to the first part of the duodenum and the common bile duct. It divides into two branches, the right and left branches at the level of portahepatis [12].

Anatomic variants of the portal vein are infrequent, however when they are found they are important to be recognized because they may have significant implications for hepatic resection. The portal vein divides into one left and two right branches in a small portion of population (11%). This is known as portal trifurcation. Another variant is the early branching of the right posterior portal from the left main portal vein (4%) or the left main portal vein may arise from the right anterior portal vein (5%) [12].

The arterial and portal venous branches supplying the liver are not separate systems. There are several connections between the vessels, including trans-sinusoidal and trans-plexal routes [12].

Venous drainage: The blood conveys from the liver to the inferior vena cava *via* the hepatic veins. The veins start as intralobular veins, which draw the blood from the sinusoids and lead to sub lobular veins, which unite to form the hepatic veins. They come out from the posterior surface of the liver to open directly into the inferior vena cava groove on the posterior surface of the liver. Hepatic veins are organized in two groups, upper and lower groups. The upper group represents large veins and usually referred to as the right, middle and left hepatic veins. The right hepatic vein drains blood from segments V, VI, VII and VIII. The middle hepatic vein drains segments IV, V and VIII and lies between segments IV and VIII [13].

Segments II and III are drained *via* the left hepatic vein with some drainage from segment IV. The lower group varies in number and area of distribution. They are small veins that drain directly into the inferior vena cava from segment I and sometimes from segments VII and VIII. The hepatic veins are valveless. The caudate lobe frequently has small veins that drain directly into the inferior vena cava [13].

Ultrasound elastography of the liver

Ultrasound elastography is a new imaging technique that allows a noninvasive estimation and imaging of tissue elasticity distribution within biological tissues using conventional real-time ultrasound equipment with modified software [14].

Shear Wave Sono-Elastography (SWE) is a novel elastographic technique that has been suspected to be an alternative, easy, rapid, and noninvasive technique that is increasingly being used to assess liver elasticity. It gives a local assessment at point of interest of an organ in Kilopascals (kPa). The major advantages of SWE are the reproducibility, operator independency, higher spatial resolution, and the ability to establish a quantitative evaluation of stiffness values without manual compression artifacts. SWE technique generates shear waves at a focal point in the tissue, where the velocity of the wave provides an estimate of tissue stiffness [15].

SWE has been demonstrated to be helpful in assessment of liver fibrosis degree and may be used as an adjunct to conventional ultrasound in differentiation and characterization of hepatic focal lesions [16].

DISCUSSION

Focal Liver Lesions (FLL) are the leading cause of death, globally. Staging and early characterization of focal liver lesions are necessary to formulate optimal treatment methods to get better outcomes. Various contrast enhanced diagnostic modalities like CT and MRI need contrast agents, which require time, cost and leads to allergic reactions [17].

In the last decade, elastography has become a standard method for determining liver stiffness. Hepatic fibrosis, the outcome of long term liver injury, causes the liver to stiffen by producing an abnormally high amount of extracellular matrix *via* fibroblast like cells [18].

Noninvasively measuring liver stiffness with elastography is possible. Ultrasound (US) or Magnetic Resonance Imaging (MRI) can be used to monitor changes in tissue response to mechanical actuation from the outside or acoustic radiation from the inside MRI [18].

Ultrasound is a leading method in the examination of FLLs, due to easy to use, low cost and minimal radiation exposure. USG is a highly sensitive and specific technique in the evaluation and differentiation of these lesions. Elastography is ultrasonographic techniques [19].

Ultrasonographic devices built sono-elastography choice enable the more accurate imaging and evaluation of the nature of superficial focal lesions of many organs in the body. Ultrasound elastography in the evaluation and characterization of focal liver lesions by stiffness quantification has least literature coverage [16].

Considering that ultrasound elastography is a promising method undergoing rapid development and active research, this study was conducted and aimed to identify the role of sono-elastography in solid hepatic lesion to differentiate benign from malignant.

A prospective research study conducted by, recruited 100 cases with focal lesions referred for image guided biopsy or planned for surgical resection to evaluate and characterize the focal liver lesions by ultrasound Elastography and revealed that majority cases had malignant type (80%) of lesion than benign type (20%) [19]. Among 80 cases which were found to be malignant, 27.5% were Hepatocellular Carcinoma (HCC) type, 60% were metastasis type and 12.5% were cholangiocarcinoma type. The mean values of elastographic parameters between malignant and benign FLL show statistically significant difference in stiffness ratio, shear wave velocity, stiffness value and strain ratio ($p<0.05$). In this study, the mean stiffness value in cases with hemangioma was 12.63, Focal Nodular Hyperplasia (FNH) was 10.06, HCC was 36.42, Cholangiocarcinoma was 38.81 and metastasis was 28.64. The shear wave velocity in cases with hemangioma was 1.89, focal nodular hyperplasia was 2.01, HCC was 2.38, cholangiocarcinoma was 2.47 and metastasis was 2.53. The cut-off value of 15.98 for stiffness value with sensitivity 83.3% and specificity 84.5%. The cut-off value for stiffness ratio was 1.68 with sensitivity 70.23% and specificity 67.78%.

Ultimately, Reddy K.P, et al., concluded that the mean values of elastographic parameters were significantly higher in malignant lesions than benign lesions. Strain ration found to be recommended parameter to differentiate focal liver lesions [19].

Abdel-Latif M et al., conducted a prospective study that included 75 patients with variable focal liver lesions (52 malignant and 23 benign) to evaluate the role of Shear Wave Sonoelastography (SWE) in characterization of benign and malignant hepatic focal lesions and revealed that Cholangiocarcinoma (CCC) was the stiffest malignant lesion with median stiffness value (35.9 kPa) [4]. Focal Nodular Hyperplasia (FNH) was the stiffest benign lesion (26.7 kPa) [4]. The median stiffness value of malignant focal lesions (20.22 kPa) was significantly higher than that of benign focal lesions (10.68 kPa) (p-value<0.001). ROC curve of SWE median stiffness values for differentiation of benign from malignant hepatic focal lesions had AUC=0.834, and using cut of value 14.165 kPa, yielding 98.1% sensitivity, 78.3% specificity, and 92% accuracy. Consequently, SWE has high accuracy in differentiating benign form malignant liver focal lesions with promising results in individual characterization of some malignant (HCC and CCC) and benign hepatic focal lesion (FNH from other benign lesions).

A study by Qiang Lu, et al., found that the mean stiffness values in cases with heamangioma was 9.3, focal nodular hyperplasia was 10, cirrhotic nodules was 11, HCC was 34, Cholangiocarcinoma was 25 and metastasis was 30 [20]. The malignant tumour ($p<0.001$) had significantly higher stiffness values and stiffness ratio than benign lesions ($p<0.001$). The cut-off value >13 for stiffness value with sensitivity 78% and specificity 83%, positive predictive value 94% and negative predictive value 52% and the cut-off value >1.3 for stiffness ratio with sensitivity 79% and specificity 45%, positive predictive value 83% and negative predictive value 38% [20].

In agreement with Guibal et al., who reported that SWE mean stiffness value was for FNH 33 ± 14 kPa, and for the hemangiomas 13.8 ± 5.5, also with Park et al., study results that included that the mean stiffness value for hemangiomas 12.91 ± 9.42 and for FNH 27.02 ± 4.14 [21].

These studies of Guibal, et al., Qiang et al., Gerber, et al., and Park et al., described that hemangioma had elevated stiffness value in comparison with the surrounding hepatic parenchyma as in Park, et al., study hemangioma mean stiffness value was 12.91 ± 9.42, while parenchymal mean stiffness value was 5.5 ± 2.8, as well as in Gerber et al., study heamangioma median stiffness value was 16.35 kPa, while parenchymal median stiffness value was 8.5 kPa, and the results of Abdel-Latif M et al., study had similar observations as the median stiffness value of heamangioma was 10.5 kPa, the surrounding hepatic parenchymal median stiffness value was 5.84 kPa with statistically significant p-value ≤ 0.004 [20-23].

Kim, et al., explained these results by those heamangiomas histologically composed of large blood-filled endothelial-lined spaces separated by fibrous septa, vascular thrombi likely responsible for the high stiffness values [24].

A study by Nagarajan KB et al., found that the mean difference between stiffness value, stiffness ratio, shear wave velocity and strain ration was highly significant between malignant and benign lesions. The cut-off value 16.5 for stiffness value with sensitivity 79.50% and specificity 81.80% and cut-off value 1.75 for stiffness ratio with sensitivity 66.70% and specificity 63.60%. The shear wave velocity had cut-off value 1.95 m/s with sensitivity 82.10% and specificity 81.80%. The strain ratio had cut-off value 2.3 with sensitivity 100% and specificity 100% [14].

A study by Nagolu et al., found significant difference in the stiffness value between malignant and benign lesions with sensitivity 68% and specificity 69%. With ARFI 2D images, stated that malignant lesions were predominantly stiffer and larger, whereas benign lesions are softer and regular in size. The mean SWVs in benign, malignant, and metastatic lesions were 1.30 ± 0.35 m/s, 2.93 ± 0.75 m/s, and 2.77 ± 0.90 m/s, respectively [25].

A study by Wang Y et al., found that the ultrasound Elastography has sensitivity (76.36%), specificity (80.95%) and accuracy

(78.35%) for the malignant focal liver lesions [26].

A prior research study performed prospectively to evaluate the solid focal liver lesions by Shear Wave Sonoelastography (SWE) and correlate Shear Wave Sonoelastography findings with that of FNAC, that enrolled 50 patients who were diagnosed to have solid focal liver lesions on sonography. Nagolu et al., revealed that benign vs. malignant hepatic lesions could be differentiated using a cut off value of 25 kPa. The overall sensitivity and specificity of SWE was found to be 66% and 30% respectively as a standalone technique, however the predicative accuracy of SWE in conjunction with gray scale sonographic findings was 91.4% and concluded that shear wave elastography can be used as an adjunct in routine sonological practice to evaluate solid focal lesions of the liver. It can help to categorize benign versus malignant lesions [25].

Park HS et al., evaluated 136 FLLs in 118 patients with SWE for quantitative and qualitative assessment of stiffness. Stiffness values of malignant lesions (n=85, 60.41 (47.81) kPa) were significantly higher than those of benign lesions (n=51, 22.05 (17.24) kPa, p<0.0001) [23]. Mean stiffness of hepatocellular carcinoma (45.72 (35.65) kPa) was significantly lower than that of metastasis (67.43 (43.39) kPa) and was significantly higher than benign FLLs (22.05 (17.24) kPa). Another study done by Cesario V, et al., also concluded that percutaneous sonoelastography can differentiate benign versus malignant focal lesions of the liver, metastases, with good diagnostic performance [27].

Sonoelastographic performance

In order to evaluate the accuracy of diagnostic tests used in the staging of liver fibrosis, the area under the receiver operating curve (Az) is often calculated. If the Az is 1.00, the diagnostic tool is considered ideal; if it's greater than 0.90, it's excellent; and if it's greater than 0.80, it's good [28].

Sonoelastographic limitations

Since the velocity of a shear wave depends on both the stiffness of the tissue and the frequency at which the wave is delivered, it is difficult to directly compare the stiffness values measured by different manufacturers and methods. Findings may differ even when assessing the same subject at the same time since operator expertise contributes to the procedure's accuracy. Still, despite these disadvantages, US elastography is a reliable noninvasive method for assessing liver fibrosis. In addition to measuring liver stiffness, the controlled attenuation parameter approach may assess hepatic steatosis by measuring the amount of ultrasonic attenuation by hepatic fat. Using the controlled attenuation parameter as a surrogate for steatosis, this research revealed that it accurately predicted steatosis severity. Ultrasound elastography (US elastography) can provide not just anatomic imaging but also biopsy guidance, meaning it may one day replace many diagnostics [29,30]. More precise evaluations of livers of variable homogeneity are possible because of the operator's ability to select Region of Interests (ROIs). Predictive of patient outcomes in chronic liver illness, portal hypertension must be determined in tandem with spleen stiffness measurement [18].

CONCLUSION

Although Shear Wave Elastography (SWE) is a recent technique, which needs more evaluation and several researches are needed to assess its use as an alternative to liver biopsy and other radiological imaging techniques, its initial results are promising as described.

Ultrasound elastography is a novel imaging technique which is quick imaging and non-contrast enhanced method. Elastography can be incorporated onto a conventional ultrasound machine, which allows the combination, in one exam, of quantitative elastography assessment of the liver tumor after the morphological ultrasound examination of the liver and thus paving way to a better and more targeted approach and management. Shear wave elastography is a useful technique with high sensitivity and accuracy in differentiating benign form malignant liver focal lesions as the results demonstrated that malignant lesion stiffness values were higher comparable to the benign lesions values.

Significant differences in elastographic parameters among various benign and malignant liver lesions were apparent. The mean values of elastographic parameters were significantly higher in malignant liver lesions compared to benign liver lesions. Among the elastographic parameters, strain ratio was found to be a better parameter to differentiate between focal liver lesions. These data may justify the more routine use of this technique in the characterization and assessment of focal liver lesions.

The technique shows promising results in individual characterization of some malignant (HCC and CCC) and benign hepatic focal lesion (FNH from other benign lesions).

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