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Diagnostic value of Virtual Touch Quantification (VTQ®) for differentiation of hemangiomas from malignant focal liver lesions

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Abstract

Aim: To evaluate the diagnostic value of Virtual Touch Quantification (VTQ®) for characterizing benign vs. malignant focal liver lesions (FLLs). **Material and methods:** From January 2015 to January 2016 all consecutive FLLs visualized during a conventional abdominal ultrasound (US), underwent VTQ® evaluation, taking five measurements of both the lesion and the surrounding parenchyma. **Results:** We studied 119 FLLs, consisting of 52 hemangiomas (HEs), 39 hepatocellular carcinomas (HCCs), and 28 liver metastases (METs). HEs showed a significantly lower shear wave velocity (SWV) values compared to malignant FLLs (HEs SWV median value 1.34 m/sec, IQR 0.9; malignant lesions SWV median value 2.69 m/sec, IQR 1.6; $p<0.001$). Moreover, a nodule-to-parenchyma SWV ratio showed a significant difference in HEs and METs ($p<0.001$) but not in HCCs ($p=0.03$). SWV values were able to correctly differentiate malignant lesions with c-statistics of 0.82 (95 % CI 0.74-0.90) and sensitivity of 74.6%/specificity of 80.7% at a cut-off of 2 m/sec. **Conclusions**: Our results suggest that VTQ® is able to distinguish HEs from malignant lesions (HCCs and METs) at a SWV cut-off of 2 m/sec.

Keywords: Virtual Touch Quantification; Acoustic Radiation Force Impulse; point shear wave elastography; hemangiomas; malignant focal liver lesions

Introduction

Focal liver lesions (FLLs) are frequent findings during conventional abdominal ultrasound (US). As a result, sonographers need to define them in order to indicate further in-depth diagnostic exams. This is true above all in the setting of an outpatient clinic or primary medical centers, where sophisticated radiological machines are not readily available and the patient could be lost at follow-up. Sometimes the diagnosis can be challenging as in the case of liver cirrhosis, since the detection of a FLL could be considered a malignancy until proven otherwise [1]. On the other hand, in some cases, the detection of liver metastases is the first finding in patients with unknown primary cancer. More accurate and expensive radiological exams are often required to define the FLLs, although contraindications for some patients are present: pacemakers or claustrophobia in the case of magnetic resonance imaging (MRI); moderate-severe renal failure or known hypersensitivity to iodate contrast medium in the case of computed tomography (CT); unstable cardiac

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disease or severe lung disease in the case of microbubbles US contrast enhanced (CEUS). For these reasons, recent studies have focused on identifying any non-invasive test to enhance the diagnostic accuracy in predicting the nature of FLLs. Evaluating the stiffness of FLLs and of surrounding liver parenchyma by ultrasound-based elastography method could respond to this need.

Point shear wave elastography (pSWE), also known as acoustic radiation force impulse (ARFI) quantification, was introduced as a new US modality, in which focused ultrasound produces shear waves in the tissue, providing information about the local mechanical properties of tissue quantitatively and non-invasively [2]. ARFI elastography produces localized displacements in tissue using acoustic pulse [3] and when tissue is mechanically excited, the displacement response can be ultrasonically tracked through time. Virtual Touch Quantification (VTQ®) provided by Siemens®, is a pSWE technique that uses the acoustic push to measure shear wave velocity (SWV) in a regional average only. VTQ® calculates SWV (m/sec) within the region of interest (ROI) by measuring the time to peak displacement at each lateral location, providing an objective numerical evaluation of the tissue elastic properties [3-6].

Among benign FLLs, hemangiomas (HEs) are the most frequent [7] and are present in 0.4–20% of the general population, typically being discovered incidentally during conventional abdominal US [8]. The prevalence of HEs is generally estimated to be around 5% in imaging series [9] but has been reported as high as 20% in autopsy series [10].

HEs can be diagnosed in all age groups but are more frequently diagnosed in women between 30-50 years of age [10]. HEs typically appear as hyperechoic lesions (brighter than normal liver) but can be also hypoechoic (darker than normal liver) in context of fatty liver, or heterogeneous in case of greater size [11-13]. Some malignant FLLs, both primitive and secondary, can mimic HEs, with the result that conventional, operator-dependent US can have a specificity as low as 48% for HEs [14].

FLLs other than HEs are rare: focal nodular hyperplasia (FNH) accounts for the second most frequent benign tumor of the liver with an estimated prevalence of 0.4–3% in unselected autopsy series, although this is reduced to 0.03% considering clinically relevant prevalence [15,16]; hepatocellular adenoma (HCA) incidence and prevalence are not well established, although the reported prevalence is between 0.001 and 0.004% [17,18], approximately 10 times less common than FNH [18].

Several studies have already investigated the potential usefulness of ARFI quantification to evaluate FLLs [19-28]. Results vary among studies and are discordant.

The aim of this study was to evaluate the diagnostic value of VTQ® pSWE for characterizing benign vs. malignant FLLs in a wide population of patients brought to a tertiary hospital center for a conventional US.

Material and methods

From January 2015 to January 2016 all consecutive patients with FLLs were asked to participate in the study. Inclusion criteria were the good visualization of the FLLs using a conventional US and localization at a maximum depth of 8 cm from the skin surface; definite diagnosis by histological evaluation or ≥1 radiological exam with contrast medium (CT, MRI, CEUS) if clinically indicated.

VTQ® pSWE was performed with Acuson S3000 ultrasound system (Siemens®, Munich, Germany) using a 1-4 MHz curved array probe. All VTQ® pSWE measures of FLLs were conducted by a single liver sonographer, with more than 2 years of experience in ARFI elastography, blinded to the patients' clinical data and the final diagnosis of FLLs. The patients who fasted assumed a supine or left/right lateral decubitus posture depending on the lesion's position. After the target lesion was identified by conventional B-mode US imaging, the patients were asked to hold their breath and VTQ® measurements identified by the ROI were started. The ROI was characterized by a box with a fixed size of 10x5 mm and was entirely located in the solid portion of the lesion excluding any vascular, biliary structures or fibrotic and necrotic tissue. The VTQ® results were expressed in m/sec as median and mean value. Five measurements of the lesion and five measurements of the surrounding liver parenchyma at the same depth about 2-3 cm away from the target lesion were performed, both in right (by intercostal or subcostal window) and left lobe (by subcostal or sub-xiphoid window) according to the position of FLLs. In the case of multiple lesions, the largest FLL or the FLL best visualized by US was considered; in case of larger FLLs, the ROI was positioned in the same point in order to obtain reproducible measures. According to the data provided by Siemens Corporation, the SWV range from 0.5 (softer or cystic portions of FLLs) to 5.00 m/sec (harder or calcific portions of FLLs); any value outside of this range is displayed as ''x.xx m/sec'', which means not applicable (NA). After excluding unreliable measures, in accordance with previous studies [23], we decided to attribute to the "x.xx" result the meaning of a stiffness 5.00 m/sec. To this purpose, only solid portions of FLLs were considered and tested. Moreover, a "x.xx" result was considered reliable only when a VTQ® pSWE measure was obtained from the liver parenchyma immediately surrounding the nodule, testifying optimal technical conditions.

The SWV ratio of each FLL to surrounding liver parenchyma was also calculated. The final diagnoses of the FLLs were determined by clinical diagnoses or histological diagnoses (by percutaneous liver biopsy or surgery). For patients that underwent liver biopsy, VTQ® was performed just before the biopsy, on the same day. For patients with a solitary liver mass that was clinically diagnosed, VTQ® was performed at the time of enrollment in this study. In cases lacking the pathological results, the recent guidelines were referenced, and all the data of the patients were reviewed by a senior radiologist with more than 10 years of experience in liver imaging. A clinical diagnosis of HCC was made according to the recommendation by the European and American Association for the Study of Liver Diseases when typical findings of arterial hypervascularity and subsequent washout were documented on dynamic CT or MRI in patients with liver cirrhosis [29,30].

According to the recent literature [31] the HEs were confirmed by typical imaging findings on contrast-enhanced CT or MR. Specifically, HEs appear as masses with hypoattenuation on unenhanced CT, very high signal intensity on T2-weighted images in MRI, peripheral nodular enhancement in the arterial phase, and progressive filling-in of enhancement with no washout in later phases [7].

The clinical investigation was conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the Ethical Committee of the University Hospital, and informed consent was obtained from all the patients due to the prospective nature of the study.

Statistical analysis

The main baseline characteristics of the FLLs were shown according to their origin using descriptive statistics. Continuous variables were expressed as median and interquartile range (IQR), while categorical ones as number and percentage (%). Comparison of SWV between groups of FLLs were carried out by the Kruskal-Wallis test and were graphically shown through box-and-whisker plots.

The diagnostic performance of VTQ® pSWE in discriminating HEs from malignant FLLs was estimated by using receiver operating characteristic (ROC) curve analysis and expressed as areas under the ROC curve (AUROC). The coordinates of ROC curves were used to identify the best cut-off values able to distinguish between the compared groups. For each cut-off, related sensitivity and specificity was provided. All analyses were performed using R 3.3.3 software for Mac (R Foundation).

Results

Over a total consecutive period of twelve months, 137 focal lesions from 137 patients were tested. From these, 11 patients were excluded because the lesions were smaller than the ROI or deeper than 8 cm (n=7) or because of a poor compliance or inability to hold their breath as required (n=4). A "x.xx" result was obtained from 7 FLLs, 2 HCCs and 5 METs, and in all these cases the result was considered reliable since a VTQ® measure was obtained from the liver parenchyma immediately surrounding the nodule. Therefore, 126 lesions were selected, among 52 HEs, 39 HCCs, 28 METs and 7 other benign lesions: 1 HCA, 3 FNHs and 3 regenerative liver nodules (RNs). After careful consideration, due to the strong prevalence of HEs in the group of non-malignant FLLs, and to the very limited and heterogeneous contribution of the other types of benign FLLs, we decided to exclude the 7 latter, in order to test malignant FLLs only with respect to HEs and avoid the misleading classification of non-malignant FLLs to a group prevalently composed by HEs.

Finally, 119 FLLs with valid VTQ® values were considered for the study, and benign lesions being only HEs. FLLs included in the study were diagnosed by US on the left lobe in 49 cases (41.2%) and on the right lobe in 70

Table I. General features of focal liver lesions, shear wave velocity values of nodules and surrounding parenchyma.

	Total masses	Hemangiomas	Hepatocellular carcinomas	Metastases
n	119	52	39	28
Histologic confirmation	28.6%	3.8%	30.8%	71.4%
Site, left lobe	41.2%	50%	41%	25%
Size (mm)	22 (15.5)	17.5 (8.5)	30 (18.5)	30 (30)
Depth (cm)	5.1 (2)	5.15 (2.125)	5.3 (2.35)	5 (1.225)
SWV value nodule (m/sec)	2 (1.88)	1.34 (0.9125)	2.47 (1.425)	3.29 (1.2325)
SWV value parenchyma (m/sec)	1.4 (1.535)	1.11 (0.31)	2.79 (0.965)	1.47 (0.33)

Results are expressed as percentage (%) or median (Interquartile Ranges). SWV: shear wave velocity.

cases (58.8%), with a median depth of 5 cm (IQR 2). We analyzed 52 HEs (median diameter 17.5 mm, IQR 8.5 mm), 39 HCCs (median diameter 30 mm, IQR 18.5 mm) and 28 METs (median diameter 30 mm, IQR 30 mm) (Table I).

Among the 119 FLLs included, 34 (28.6%) received targeted biopsy for histological confirmation: 20/28 METs (71.4%), 12/39 HCCs (30.8%) and 2/52 HEs (3.8%). The remaining diagnoses of HCCs were made by surgery in one patient and by typical radiological findings in 26 patients. METs were either diagnosed by biopsy, or, in the case of known primitive cancer, by newly detected lesions in the liver and typical findings on contrast-enhanced CT or MRI. The primitive cancers for METs were breast (n=3), gastrointestinal tract (n=17), bronchopulmonary system (n=4), kidney (n=1), prostate (n=2), or unknown (n=1). All the patients with HCCs had Child Pugh A liver cirrhosis and there was no clinical or biochemical evidence of chronic liver diseases in patients with METs. The median diameter of the lesions was 22 mm (IQR 15.5 mm), higher in malignant lesions than in HEs (p<0.0001).

HEs had a significantly lower SWV values compared to malignant FLLs (HEs median value 1.34 m/sec [IQR 0.9]; HCCs median value 2.47 m/sec [IQR 1.4]; METs median value 3.29 m/sec [IQR 1.2]) (p<0.001). The difference was preserved after considering HCCs together with METs as a single malignant FLLs group (SWV median value of 2.69 m/sec [IQR 1.6]; p<0.001) (fig 1). METs had the higher SWV values among all FLLs (p<0.001).

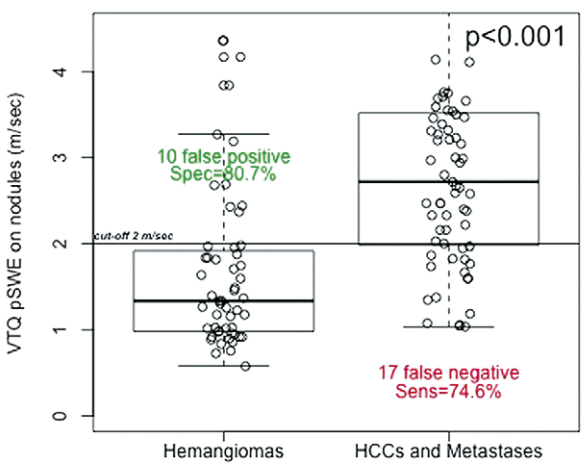

Fig 1. Boxplot representation of point shear wave elastography (pSWE) measurements by Virtual Touch Quantification (VTQ®), in the two groups of lesions: hemangiomas vs. hepatocellular carcinomas (HCCs) plus metastases. The lines through the boxes represent the medians. We inserted a thin black line to identify the cut-off of 2 m/sec for discrimination of hemangiomas from malignant liver lesions

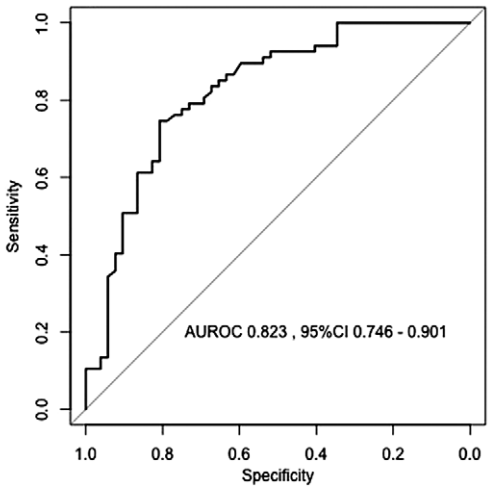

Fig 2. Receiver operating characteristic curve (ROC) of Virtual touch Quantification (VTQ®) values for differentiation of hemangiomas from malignant liver lesions
AUROC: Area under the receiver operating characteristic curve, CI: 95 % confidence interval

The liver parenchyma surrounding HCCs had higher SWV values than in HEs and METs FLLs, related to a background of cirrhosis in all cases (HCC liver SWV median value 2.79 m/sec [IQR 0.9] vs. 1.11 m/sec [IQR 0.3] and 1.47 m/sec [IQR 0.3] in HEs and METs liver respectively, p<0.001).

The nodule-to-parenchyma SWV ratio showed significant difference in HEs and METs groups (due to a "normal" surrounding liver, p<0.001) but not in HCCs group (p=0.03). HCCs were softer than surrounding liver, although the difference was not significant. Only one patient with HE had a diagnosis of chronic liver diseases related to hepatitis C virus (well compensated liver cirrhosis).

The AUROC for discriminating HEs from malignant FLLs was 0.82 (95% CI 0.74-0.90). To maximize the sum of sensitivity and specificity, a SWV value of 2 m/s was selected as the cut-off value to differentiate HEs from malignant FLLs by VTQ® pSWE, with a sensitivity of 74.6%, specificity of 80.7%, positive predictive value (PPV) 83% and negative predictive value (NPV) 71% (fig 2).

Discussions

Firstly, our results showed that HEs were significantly softer than malignant FLLs. This result is not surprising from a pathological point of view, because HEs present as well marked cavities filled by blood and a thin wall of endothelial cells. As shown in Table II, our data agree with the majority of other authors [20, 22-28], although they

differ from the results of Gallotti et al study [3], in which the 7 HEs examined were stiffer than HCCs but not than METs. Heide R et al [21] showed also a higher stiffness of HEs (>2 m/sec) in a study on 62 FLLs and 13 HEs, although HEs were softer than HCCs, METs and cholangiocarcinomas (CCCs). The authors concluded that high SWV values occur in benign as well as in malignant FLLs and do not permit differentiation between them [21]. This variability could be explained by the pathological heterogeneity of HEs, which can show some degrees of fibrous septa, vascular thrombus, or calcifications.

In our study METs were the stiffest FLLs, even more than HCCs. These results might be due in some degree to the presence of a desmoplastic reaction, calcification, and expansive growth. The results coincide with all studies reviewed in the literature [3,22-28] except for that of Cho SH et al [20], although also in this latter study METs were stiffer than HEs, and Heide R et al [21], that showed as CCCs and FNHs were the stiffer FLLs. However, these latter results might be related to a limited CCCs sample (only 2 cases) and to the well-known pathological features of FNH, with characteristic central scar and radiating fibrous septa.

Moreover, we found a SWV difference with surrounding parenchyma in HEs by calculating a ratio between nodule-to-liver parenchyma. As for the SWV ratio of HEs-liver parenchyma, the SWV ratio of nodule-to-liver parenchyma in the METs group showed a significant difference from surrounding liver, which can be explained by the presence of a normal liver in the background. However, the liver stiffness of the METs group was slightly higher than that of HEs group, probably due to the presence of multifocal lesions or drug-induced liver diseases in some cases. On the other hand, the HCCs group did not show a significant SWV difference from the surrounding liver parenchyma and the liver stiffness in these cases was higher than that of FLLs. This could be due to the liver cirrhosis in the background, in all our cases.

Finally, using the area under the ROC curve, we identified a SWV cut-off of 2 m/sec to differentiate HEs from malignant FLLs. Currently only three other studies have investigated the diagnostic value of pSWE in differentiating HEs from malignant FLLs, with some different results but all confirming that HEs were softer than malignant lesions [20,22,26].

Our study had some limitations. Firstly, we did not include other benign liver tumors such as FNHs, HCAs, or RNs, nor we did include many heterogeneous types of primitive or metastatic tumors. This could be explained by an inclusion bias due to the expertise of our tertiary reference center for liver diseases. Secondly, we did not correlate the VTQ® pSWE measurements with pathologic specimens because this correlation was beyond the scope of this study. Finally, intra-and interobserver agreement for VTQ® pSWE measurements were not estimated.

In **conclusion**, our results suggest that VTQ® pSWE would be a helpful technique in differentiating HEs from malignant FLLs during a conventional abdominal US.

Conflict of interest: none

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Table II. SWV values for different focal liver lesions (FLLs), and SWV cut-off for differentiation of benign vs. malignant FLLs and hemangiomas vs. malignant FLLs, according to different authors.

	N of lesions	HCCs*	METs*	CCCs*	FNHs*	HEs*	HCAs*	Cut-off (m/sec)
Gallotti A et al [3]	40	2.17±0.85	2.87±1.13	NA	2.75±0.95	2.3±0.95	1.25±0.37	NS
Cho SH et al [20]	60	2.18±0.96	2.45±0.81	NA	NA	1.51±0.71	NA	2#
Heide R et al [21]	62	2.63±1.09	2.88±1.16	3.78±1.73	3.11±0.93	2.36±0.77	2.23±0.97	NS
Davies G et a l[22]	45	NA	4.23±0.59	NA	NA	1.35±0.48	NA	2.5#
Guo LH et al [23]	134	3.07±0.89	2.74±1.06	3.44±1.18	2.3±1.18	1.48±0.7	NA	2.13
Yu H et al [24]	105	2.49 ±1.07	2.73±0.89	NA	2.18 ±0.84	1.75±0.8	1.79±0.14	1.9
Park H et al [25]	47	2.48±0.84	2.35±1.18	NA	0.97±0.48	1.83±0.62	NA	1.82
Kim JE et al [26]	74	2.66±0.94	2.82±0.96	3.27±0.64	NA	1.8±0.57	NA	2.73#
Zhang P et al [27]	170	2.59±0.91	3.2±0.62	3.74±0.54	1.9±0.45	1.33±0.38	NA	2.16
Frulio N et al [28]	79	2.4±1.01	2.53±0.83	NA	3.14±0.63	2.14±0.49	1.9±0.86	NS

N: number; *: results as mean SWV±standard deviation (m/sec); #: SWV cut-off differentiating HEs from malignant liver lesions; CCCs: Cholangiocarcinomas; FNHs: Focal Nodular Hyperplasias; HCAs: Hepatocellular Adenomas; HCCs: Hepatocellular Carcinomas; HEs: Hemangiomas; METs: Metastases; NA: Not available; NS: Not significant; SWV: shear wave velocity

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