Real Time Elastography – a Non-invasive Diagnostic Method of Small Hepatocellular Carcinoma in Cirrhosis

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Abstract

**Background:** Small nodules (<3 cm) detected on ultrasound (US) in cirrhotics represent the most challenging category for noninvasive diagnosis of hepatocellular carcinoma (HCC). **Aim:** To evaluate real-time sonoelastography as a noninvasive tool for the diagnosis of small HCC nodules in cirrhotic patients. **Methods:** 42 cirrhotic patients with 58 nodules (1-3 cm) were evaluated with real-time elastography (Hitachi EUB-6500); the mean intensity of colors red, blue, green were measured using a semi-quantitative method. Analysis of histograms for each color of the sonoelastography images was performed for quantifying the elasticity of nodule tissue in comparison with the cirrhotic liver tissue. AUROC curves were constructed to define the best cut-off points to distinguish malignant features of the nodules. Univariate and multivariate logistic regression analysis was performed. **Results:** 595 sonoelastography images from 42 patients (25 men; 17 women) were analyzed. The mean age was 56.4±10.7 years and 69% patients were in Child-Pugh class A, 19% class B, 11% class C. For the mean intensity of green color AUROC=0.81, a cut-off value of <108.7 being diagnostic for HCC with a Sp=91.1%, Se=50%, PPV=92.1%, NPV=47.1%. Mean intensity of blue color proved to be an excellent diagnostic tool for HCC (AUROC=0.94); for a cut-off value>128.9, Sp=92.2%, Se=78.9%, PPV=95.4%, NPV=68%. Independent predictive factors of HCC for a small nodule in cirrhotic patients were: blue color>128.9 at sonoelastography and hypervascular appearance at Doppler US. **Conclusions:** US elastography is a promising method for the non-invasive diagnosis of early HCC. Blue color at elastography and hypervascular aspects are independent predictors of HCC.

Key words


Introduction

Hepatocellular carcinoma (HCC) is a leading solid organ malignancy in the world as a result of the high prevalence of chronic liver damage caused by viral hepatitis or cirrhosis [1]. Much attention has been given to a recently increased incidence of HCC in Western regions, linked, at least in part, to a rise in incidence of chronic hepatitis C. In Romania it was recently proved [2] that the prevalence of HCV infection is not different from the Southern Europe (2.5-3.5%). According to this, based upon a Markov decision model, it was estimated that the prevalence of cirrhosis and HCC due to HCV infection will continue to increase in Romania from 88,124 and 1,708 in 2009 to 146,209 and respectively 2,686, in 2030 (Gheorghe L, unpublished data). European cohort studies have reported that, among subjects who have died of a liver-related cause, HCC was the cause of death in 54%-70% of patients with compensated cirrhosis of different etiologies and in 50% of patients with HCV-related cirrhosis [3, 4].

Early diagnosis and treatment of HCC in cirrhotic patients is the only approach to improve overall outcome. Ultrasound (US) every 6 months is the method of choice for screening, since it has adequate sensitivity, specificity, positive and negative predictive values [5]. An abnormal screening US needs to be confirmed by either an US-guided liver biopsy (histologic criteria) or imaging studies (noninvasive criteria, restricted to cirrhotic patients). The gold standard for certain diagnosis of a malignancy traditionally requires cytologic or histologic confirmation. Given the potential complications of liver biopsy in a patient with decompensated liver cirrhosis, noninvasive criteria have been proposed for the diagnosis of HCC in patients with cirrhosis by the European Association for the Study of Liver Diseases (EASL) and the American Association for the Study of the Liver (AASLD) [6, 7]. The diagnostic algorithm largely depends upon the size of nodules, and small nodules (<3cm) detected on
US in cirrhotics represent the most challenging category for noninvasive diagnosis of HCC. Currently the proposed criteria to differentiate between benign and malignant focal liver lesions are based on the pattern of contrast enhancement during arterial, portal and late phases.

Among the patients with small nodules, contrast-enhanced US, dynamic computed tomography and magnetic resonance imaging (MRI) may lead to major problems due to the false-positive (in the presence of arteriovenous shunts and in patients with macrogeneic nodules with dysplastic liver cells) [8] and false-negative results (smaller than 2 cm nodules are hypovascular) [9].

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 [10]. Elasticity imaging has been reported to be useful for the diagnosis and characterization of various tumors, which are usually stiffer than normal tissues [11]. Up to now, elastography has been implemented as a real time strain imaging modality for breast [12-17], prostate [18-21] and thyroid cancer [22, 23]. In the gastroenterology field, real-time elastography (RTE) proved its utility in differentiating between benign and malignant pancreatic lesions and lymph nodes [24-26] as well as for different solid tumors located in the wall or nearby gastrointestinal tract which can be also visualized and characterized by endoscopic ultrasound elastography [27].

The aim of our study was to evaluate real-time elastography as a noninvasive tool for the diagnosis of small (1-3 cm) HCC nodules in cirrhotic patients. Furthermore we aimed to identify predictors of HCC diagnosis in nodules less than 3 cm in diameter detected at US examination in cirrhosis.

**Material and Methods**

Real-time sonoelastography was carried out with a conventional Hitachi 6500 ultrasound system with an embedded Sono-Elastography module (Hitachi Medical Systems Europe Holding AG, Zug, Switzerland), a dedicated software with a complex algorithm that is able to process in a very short time all the data coming from the lesion as radiofrequency impulses and minimizes the artifacts due to lateral dislocation, allowing accurate measurement of the degree of tissue distortion. Sonoelastography was realized during the ultrasound examination after the usual mode B evaluation with a convex probe, visualization of the hypo or hyperechoic nodule, Color and Power Doppler evaluation, visualization of the nodule with the linear L54M probe and recording of the elastography movies while the patient held his/her breath. Elastography was performed by using a two panel image with the usual conventional gray-scale B-mode image on the right side and with the elastography image on the left side. The linear probe was set to a frequency of 6.5 MHz for the transabdominal examination of liver. The transabdominal examination was performed with this kind of transducer in order to obtain the maximum penetrability and to be able to include as much as possible of the tissues surrounding the lesion. One or several elastography movies were registered in order to have at least 10 elastography images for each nodule per patient for minimization of variability and for increasing the repeatability of the acquisitions. The compression threshold was set between 3 and 4 and for the standardization of the examination only the images with this compression were included in the analysis. The same conditions of luminosity, contrast, intensity and gain of the ultrasound system were used for all examinations. All the echographic measurements were made by a single experienced physician who also was aware of the clinical condition of the examined patient. The sonoelastography examination was performed before abdominal MRI and guided liver biopsy. All the elastography images should include the target lesion as well as the surrounding tissue because all the elasticity values are displayed relatively to the average strain inside the region of interest. For the elastography calculations a rectangular manually selected region of interest, with constant dimensions for all examinations of a patient and without including any large vessel was used. Calculation of the tissue elasticity distribution was carried out in real time and displayed in color superimposed over the conventional B-mode imaging. The color scale included a 256-entry red-green-blue (RGB) rainbow color coded map. In order to eliminate the interobserver variability, the obtained sonoelastography images were analyzed by a single person using the program Adobe Photoshop 7. Each pixel of the image was automatically separated by the Adobe program into the red, green and blue green components (0-255). The program then computed the mean intensity of each component (i.e. red, green and blue). The histogram provided a mean value and a standard deviation for the respective color, corresponding to the global elasticity which indicated the homogeneity of the lesion.

For each nodule at least 10 static elastography images from the registered movie were selected, which fulfilled the following criteria: images obtained with the same transparietal approach with the probe oriented perpendicular on the examined lesion, compression grade 3-4, the whole lesion to be included together with surrounding cirrhotic tissue, without intercepting large vessels.

The color histograms obtained for the static images were calculated in an interest region, which had the same dimensions for all patients. The mean values provided by the histograms were used for AUROC calculation.

The gold standard diagnosis for HCC was considered the morphopathologic diagnosis obtained by guided liver biopsy from nodule or by surgical resection. For patients in which liver biopsy or surgical therapy was not possible due to the advanced stage of cirrhosis or contraindications, the time criteria was used for establishing the malignancy of the nodules – follow-up of the nodules for 6 months.

Inclusion criteria consisted of cirrhotic patients with liver nodules (one or multiple) between 1 and 3 cm, without or
Real time elastography of small hepatocellular carcinoma in cirrhosis

with mild ascites, but not perihepatic; localization of all the nodules within a liver region that could be visualized by transparietal elastography. Exclusion criteria were obese patients or with a thick thoracic wall (>3cm), patients with negative histopathology results despite the presence of 2 imaging methods indicating presence of HCC, patients who refused liver biopsy, patients with nodules localized close to large vessels or with dysplastic nodules according to histology.

All cirrhotic patients admitted to our Clinic underwent abdominal ultrasound for screening; after detection of a nodule with 1 to 3 cm, Echo Doppler and sonoelastography were performed, followed by abdominal MRI with Resovist® (Ferucarbotran, Schering AG, Berlin, Germany) and then guided liver biopsy from the tumor. Ferucarbotran is a SPIO (superparamagnetic particles of iron oxide) agent that can be injected as a bolus, which enables dynamic T1 MR imaging to be performed during different vascular phases than we are accustomed to in liver imaging with extracellular contrast agents. In the accumulation phase, 10 min after the injection, when the SPIO particles are taken up by the Kupffer cells of normal liver parenchyma or by Kupffer cells located in liver lesions, T2 and T2* are used in lesion detection and characterization [28].

All patients underwent also imaging investigations in order to exclude extrahepatic liver disease. For each patient, we recorded age, gender, etiology of cirrhosis, serum alpha-fetoprotein (AFP) level, Child-Pugh and BCLC (Barcelona Clinic Liver Cancer) [29] classification, tumor variables: size, number, location, ultrasound characteristics, Edmondson and Steiner grading [30], outcome at the end of follow-up period (February 2009). All patients signed an informed consent before inclusion into the study. The study protocol was approved by the Institutional Ethics Review Board of the Fundeni Clinical Institute and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical analysis
Continuous data were expressed as means ± standard deviation or medians. Categorical data were expressed as the number or the proportion of patients with a specific feature. The chi-square test was used for comparing categorical data and Student’s t-test or Mann-Whitney-U-test, when appropriate, were used for comparing continuous variables. To identify potential predictors of HCC nodules in cirrhotic patients, univariate and multivariate analysis was performed. The diagnostic performance of the colors obtained at real time elastography was determined in terms of sensitivity, specificity, positive and negative predictive values and area under receiver operating characteristics (AUROC) curves. AUROC curves were constructed to define the best cut-off points to distinguish malignant features of the nodules. The optimal cut-off value was determined at the highest sensitivity with a specificity forced no less than 90%. An AUROC of 1 indicates a perfect diagnostic test; an AUROC between 0.8 and 0.9 indicates an excellent diagnostic accuracy and a parameter with an AUROC over 0.7 should be considered clinically useful. A kappa reliability test was used for establishing the concordance between the sonoelastography results and the MRI with the histopathology result of HCC. A kappa value of 0.61 to 0.8 indicated a good concordance between tests, while a kappa value of 0.81 to 1 indicated a very good concordance. Two-tailed p values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results
Forty two patients met all criteria in order to be evaluated by sonoelastography, by abdominal MRI ± biopsy between February 2007 – August 2008. Five hundred and ninety five sonoelastography images were prospectively obtained from these 42 patients by transparietal ultrasound, evaluating 58 nodules with sizes between 1 and 3 cm.

The characteristics of the entire cohort are outlined in Table 1.

### Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>No of patients</th>
<th>Means ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male (%)</td>
<td>25 (59.5%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.4 ± 10.7</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>26.1 ± 3.7</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>6 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>Etiology of cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>23 (54.8%)</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>8 (19%)</td>
<td></td>
</tr>
<tr>
<td>HBV+HDV</td>
<td>7 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>4 (9.5%)</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class A</td>
<td>29 (69%)</td>
<td></td>
</tr>
<tr>
<td>Class B</td>
<td>8 (19%)</td>
<td></td>
</tr>
<tr>
<td>Class C</td>
<td>5 (11%)</td>
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</tbody>
</table>

Viral hepatitis was the most important etiology of liver cirrhosis, and HCV prevailed. The majority of patients were in Child class A in order to be able to undergo liver biopsy.

HCC diagnosis was confirmed in 30 patients and 12 patients proved to have regenerative nodules. Guided nodule liver biopsy (LB) was performed in 36 patients, 3 patients were transplanted and the liver explant was analyzed; 3 patients had contraindications due to coagulopathy and thrombocytopenia and did not perform biopsy. Twenty six patients had HCC and 10 patients had only regenerative nodules according to histology. From transplanted patients, 2 had histological confirmation of the HCC and one had only a regenerative macronodule. During follow-up, 2 of the patients without a biopsy proved to have HCC due to the increase of the size and number of nodules and one patient had a stable size of the nodule during a 21 month period of follow-up.

Patients with HCC were classified according to the BCLC system in class A (26/30, 86.7% of patients) and D
According to Edmondson-Steiner grading, patients had well differentiated (18/28, 64.3%) and moderately differentiated (10/28, 35.7%) HCC. It is worth noting that none of the patients had poor differentiated HCC.

The k-concordance test between abdominal MRI with Resovist and histology of the examined nodules was very good (k=0.88).

Most of the patients had only one nodule (27/42, 64.3%), 14 patients (33.4%) had 2 nodules and one patient (2.3%) had 3 nodules. Mean nodule size was 2.29 ± 0.71 cm. The localization of the nodules evaluated by transparietal elastography was the following: 9 patients (21.4%) had nodules in the left hepatic lobe, 21 patients (50%) in the right hepatic lobe and 12 patients (28.6%) in both lobes. The distribution of the focal liver lesions according to the anatomic segments of the liver was as follows: segment I – none, II – 4 nodules, III – 6 nodules, IV – 11 nodules, V – 7 nodules, VI – 10 nodules, VII – 12 nodules and VIII – 8 nodules. The median alpha-fetoprotein (AFP) level was 12.7 ng/ml (range 2.2 – 2137 ng/ml).

The median value for the intensity of blue, green and red colors from the elastography images of the nodules were 133.5, 115.6 and 84.6 in the whole group, 142.7, 108.6, 80.9 in the HCC group and 105.9, 135.7, 87.6 in the non-HCC group, respectively. There were significant correlations between the presence of HCC and elastography values obtained for the intensity of blue, green and red colors (p<0.0001 for blue and green colors; p=0.0002 for red color) (Fig. 1).

The area under the ROC curve for diagnosis of HCC for blue, green and red colors obtained at the sonoelastography were 0.94 (Fig. 2a), 0.81 (Fig. 2b) and 0.63. Based on the elastography measurement colors distribution according to the presence or absence of HCC and AUROC curves, the best discriminant cut-off values were determined, as well as their corresponding positive predictive value (PPV), negative predictive value (NPV), sensitivity (Se) and specificity (Sp) (specificity of at least 90%) (Table II). A positive result tends to rule in the diagnosis when the index has a high specificity (more than 90%). Both blue and green colors had also PPV >90%, indicating a correct diagnosis of the patients with a positive test. Because the mean intensity of red color has an AUROC <0.7, this color has no clinical utility for HCC diagnosis.

<table>
<thead>
<tr>
<th>Color</th>
<th>Cut-off</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Diagnostic accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue</td>
<td>&gt;128.9</td>
<td>78.9</td>
<td>92.2</td>
<td>95.4</td>
<td>68</td>
<td>83.2</td>
</tr>
<tr>
<td>Green</td>
<td>&lt;108.7</td>
<td>50</td>
<td>91.1</td>
<td>92.1</td>
<td>47.1</td>
<td>63.6</td>
</tr>
<tr>
<td>Red</td>
<td>&lt;71.2</td>
<td>15.1</td>
<td>91.1</td>
<td>77.7</td>
<td>34.3</td>
<td>40</td>
</tr>
</tbody>
</table>

There was a good concordance between real-time elastography and HCC diagnosis according to the cut-off set for the mean intensity of blue color and the MRI (k=0.72). The same kappa value was for the concordance between the mean intensity of blue color and the histology results.

Analyzing predictive factors for HCC diagnosis in cirrhotic small nodules, we found a positive correlation between HCC presence and age at diagnosis (p=0.01), INR (p=0.01), AFP value (p=0.0001), nodule size (p=0.0004), hypervascular aspect at Doppler US (p=0.0003), sonoelastography aspect according to the mean intensity of blue (p<0.0001) and green color (p=0.01). HCV etiology reached only a marginal level of significance (p=0.07). Results of univariate analysis
Multivariate logistic regression analysis revealed the following independent variables associated with HCC diagnosis of small nodules in cirrhotic patients: intensity of blue color over the established cut-off at sonoelastography image and hypervascular nodule at Doppler US (Table IV).

During the follow-up period 3 patients died: one due to aggressive HCC recurrence after liver resection, one due to an acute coronary accident 3 days after liver resection and one due to massive upper digestive bleeding despite endoscopic therapy.

**Table III. HCC diagnosis in small nodules: results of univariate analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HCC</th>
<th>No HCC</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.6 ± 9.9</td>
<td>48.5 ± 8.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>56.7%</td>
<td>66.7%</td>
<td>0.55</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>25.8 ± 3.9</td>
<td>27 ± 3</td>
<td>0.35</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13.3%</td>
<td>16.7%</td>
<td>0.78</td>
</tr>
<tr>
<td>HCV etiology</td>
<td>63.3%</td>
<td>33.3%</td>
<td>0.07</td>
</tr>
<tr>
<td>Child-Pugh class B/C</td>
<td>33.3%</td>
<td>25%</td>
<td>0.59</td>
</tr>
<tr>
<td>Thrombocytes (/mm3)</td>
<td>123,833.3 ± 58,056.1</td>
<td>117,183.3 ± 70,576.8</td>
<td>0.75</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>1.53 ± 0.95</td>
<td>1.78 ± 1</td>
<td>0.46</td>
</tr>
<tr>
<td>INR</td>
<td>1.1 ± 0.1</td>
<td>1.3 ± 0.2</td>
<td>0.01</td>
</tr>
<tr>
<td>AFP value (ng/mL)</td>
<td>235.2 ± 490.2</td>
<td>12.2 ± 27.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Spleen diameter (cm)</td>
<td>15.1 ± 2.3</td>
<td>15.2 ± 5.1</td>
<td>0.37</td>
</tr>
<tr>
<td>Multiple nodules</td>
<td>63.3%</td>
<td>66.7%</td>
<td>0.83</td>
</tr>
<tr>
<td>Nodule size (cm)</td>
<td>2.55 ± 0.5</td>
<td>1.64 ± 0.6</td>
<td>0.0004</td>
</tr>
<tr>
<td>Hypervascular nodules</td>
<td>70%</td>
<td>8.3%</td>
<td>0.0003</td>
</tr>
<tr>
<td>Hyperechoic nodules</td>
<td>46.7%</td>
<td>66.7%</td>
<td>0.24</td>
</tr>
<tr>
<td>HCC according to blue color</td>
<td>86.7%</td>
<td>8.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HCC according to green color</td>
<td>56.7%</td>
<td>16.7%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Table IV. Results of multivariate analysis for HCC diagnosis of small nodules in cirrhosis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>Chi-square (β=0)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC according to blue color at elastography</td>
<td>4.75</td>
<td>1.77</td>
<td>7.17</td>
<td>0.007</td>
</tr>
<tr>
<td>Hypervascularization at Doppler US</td>
<td>4.41</td>
<td>2.03</td>
<td>4.71</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Discussion**

Hepatocellular carcinoma is a slow growing tumor and hepatocarcinogenetic process may evolve in a stepwise fashion for years from premalignant to overt HCC, making possible the detection of early, potentially curative tumors by surveillance of patients at risk, especially cirrhotics [31]. Prognosis largely depends on the evolutionary stage at which HCC is detected, vascular invasiveness and degree of liver impairment. For tumors larger than 2 cm, demonstration of arterial hypervascularization of the nodule by contrast US,
Elastography is a method in which the “stiffness” of the tissue is used to detect and classify disease, usually tumors. Malignant tumors are stiffer than benign tumors and up to 100 times stiffer than the normal soft tissue; when mechanical compression or vibration is applied, cancer deforms less than benign tumors and benign tumors deform less than the normal surrounding tissue [34]. This technology is commonly used in practice in the differential diagnosis of breast, prostate, thyroid, pancreatic tumors, as well as for distinguishing between inflammatory or malignant lymph nodes. Itoh et al [12] reported that RTE had a sensitivity of 86.5%, a specificity of 89.8% and a diagnostic accuracy of 88.3% when a cut-off point between scores 3 and 4 was used (according to a qualitative scoring system – Tsukuba Elasticity Score). A rather accurate diagnosis (sensitivity 97%, specificity 100%, PPV 100% and NPV 98%) can be established in case of thyroid nodules [22]. Detection of cancer prostate was improved by using elastography (sensitivity 76%, specificity 84%) [20], and it was also proven that RTE is a feasible method to guide high intensity focused US therapy [35]. Giovanni et al [24] explored for the first time the potential add-on endoscopic ultrasound (EUS) elastography for differentiating between benign and malignant pancreatic lesions and lymph nodes. Saftoiu et al recently confirmed that real-time EUS elastography represents a reliable method for differentiating between benign and malignant lymph nodes, adding complementary information to conventional EUS imaging by qualitative and quantitative pattern analysis [25, 26]. Computer-enhanced dynamic analysis based on hue histograms of the EUS elastography movies was the first quantitative measure of elastography and showed a sensitivity of 85.4%, a specificity of 91.9% and a diagnostic accuracy of 88.5% on the basis of a cut-off level of 166 (middle of green-blue rainbow scale) [26]. In contrast to this study, we used still images for analysis, which in the opinion of other authors could induce a possible selection bias. We agreed to this for EUS elastography, but for transcutaneous elastography of the liver where the elastography movies include gray scale frames due to the low penetrability, this type of analysis can induce bias. In order to eliminate the selection bias we included in the analysis all the obtained color coded images and measured the mean intensity of the blue, green and red colors. A recent paper [36] showed that RTE with transcutaneous US is a feasible method in the diagnosis of pancreatic diseases, identifying 77.4% of the lesions and observed 60% of the cancers, 100% of the endocrine tumors, 92% of the cases of chronic pancreatitis based on a qualitative assessment of the elastography color. Transient, as well as real-time elastography (RTE) has been used to measure the stiffness of the liver in vivo and is a noninvasive alternative to liver biopsy for determining a fibrosis score [37-41].

This is, to our knowledge, the first study to assess and validate the diagnostic accuracy of transabdominal RTE for diagnosis of HCC nodules in cirrhotic patients based upon a computerised semi-quantitative analysis of the images. Another recent study [42] showed that the application of RTE in intra-operative exploration provided significant information about the elasticity of liver tumors. According to the same study, a qualitative classification system (elasticity type of liver tumor – type A even strain to type D no strain), based on the distribution and degree of strain within the lesion, permitted to distinguish rather accurately between the two common liver malignancies (HCC and metastatic adenocarcinoma). HCC was classified as type B with a sensitivity of 95.5%, a specificity of 90.9% and an accuracy of 92.7%, while the metastasis were classified as type C or D with a sensitivity of 100%, a specificity of 80.6% and an accuracy of 89.1%. This study can not be accurately compared to our study due to the following: it had a different objective in comparing HCC to the metastasis aspect, only 11 out of 44 patients had cirrhosis as a surrounding tissue of the lesion, the qualitative assessment and thus highly subjective categorizing of the lesions, different sizes of the tumors, and close contact of the probe to the tumors.

In our study, the intensity of blue and green colors at RTE had high specificity (92.2% and respectively 91.1%) and positive predictive value (95.4% and respectively 92.1%) in identifying patients with small HCC. However, their sensitivities were limited and not sufficient to recruit patients with HCC who required treatment. The area under the ROC curve of the mean intensity value of blue color used for the discrimination of regenerative and malignant small nodules was 0.94 (CI 95% 0.91-0.97). More than half of the small nodules included in our study were malignant and the fact that the prevalence of the underlying condition of interest was >50% is certainly one of the strengths of this study, as well as the good diagnostic concordance of the elastography criteria and the histological result and MR imaging.

Because surveillance with conventional US is considered cost-effective, generally leading to the identification of a single <3cm tumor in 50-70% of the patients at risk and because RTE requires an expensive US device, this new technique should be reserved only for non-invasive confirmation of the suspected nodular lesions together with contrast enhanced and Doppler US. This can lead to the sparing of guided needle liver biopsy in patients with cirrhosis and small nodules included on the waiting list for liver transplantation, in which the risk of seeding is still of concern for surgeons.
The detection rates of intratumoral vasculature in HCCs ≤ 2 cm were reported at 21.7-38.2% on color Doppler US and 30.4-64.7% on power Doppler US [43]. In our study, by combining color and power Doppler US we were able to detect intranodular vessels within 70% of small HCCs (≤ 3 cm). By adding power filter to the color Doppler US, the sensitivity of the method can be considerably increased especially for small nodules [43, 44].

The independent predictors of malignant nodules (hypervascular aspect at Doppler US and mean intensity of blue color > 128.9 at elastography) can cover the non-invasive diagnosis of both hypervascular and non-hypervascular HCCs. The characterization of such non-hypervascular nodules is important in clinical practice, mainly in the setting of cirrhosis, because it can signify high-grade dysplastic nodules (potentially premalignant lesions) or even well-differentiated HCC [45].

During the past two decades, MRI has increasingly been applied for evaluation of liver lesions with good results, although several investigators reported [46, 47] decreased SPIO accumulation with a heterogeneous enhancement pattern in severe cirrhosis, influencing thus the accurate detection of liver lesions. Also, as these non-hypervascular nodules have Kupffer cell distribution [48], observation of the SPIO MR images could not easily characterize them. However, in our study, there was a good diagnostic concordance between MRI and histological diagnosis of HCC.

The main limitation of this study is the absence of the SonoElastography module available for convex transducer in order to allow adequate visualization of the whole liver and good penetrability. Another drawback is the absence of a standardized quantitative measurement to perfectly characterize the mixture of tissue hardness depicted by elastography images. The quantitative histogram analysis of the fundamental colours (red-green-blue) in images recorded during real time transabdominal or EUS Elastography (Adobe Photoshop 7.0; Image J) may be used instead of the qualitative, highly subjective, observer dependent assessment of the tumoral pattern. However, other prospective, randomized and larger studies are required in order to test the selected cut-offs for the mean intensity of blue color in the diagnosis of hepatocellular carcinoma. It is worth noting that the surrounding cirrhotic liver tissue may also influence our findings.

In conclusion, elastography imaging of the small liver nodules in cirrhosis might be used as a non-invasive tool for accurate diagnosis as well as selection of patients for curative therapy, but not for screening. Its utility in patients with non-vascularised nodules can help to eliminate the false negative diagnosis of contrast enhanced imaging of the liver and to improve their outcome.

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Conflicts of interest

None to declare.

References


