Review

Medical Ultrasonography
2010, Vol. 12, no. 2, 145-149

The role of contrast enhanced ultrasound (CEUS) in the assessment of liver nodules in patients with cirrhosis

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Abstract

Liver cirrhosis is a major risk factor for the development of hepatocellular carcinoma, hence the need to screen those patients by means of liver ultrasound every 6 months. The differential diagnosis between a regenerative nodule, a dysplastic one and hepatocellular carcinoma is made based on a contrast imaging method (CEUS, MRI or CT) as they all have comparative sensitivities.

Key words: hepatocellular carcinoma, liver cirrhosis, contrast enhanced ultrasound (CEUS)

Rezumat

Ciroza hepatică este factor de risc major pentru dezvoltarea hepatocarcinomului de unde necesitatea supravegherii ecografice pentru structură hepatică, supraveghere care se face conform programului de screening prin ecografie pentru structură hepatică la 6 luni interval. Diagnosticul diferențial între un nodul de regenerare cirotică, un nodul displastic şi un hepatocarcinom se va face printr-o metodă imagistică cu substantă de contrast (CEUS, RMN sau CT) metodele având sensibilități comparabile.

Cuvinte cheie: hepatocarcinom, ciroză hepatică, ecografie cu substanță de contrast.

Liver cirrhosis of various etiologies has been known as a major risk factor for the development of hepatocellular carcinoma (HCC). Approximately 80% of HCCs occur in patients with cirrhosis of viral ethiology (hepatitis C virus-HCV and hepatitis B virus-HBV) [1].

In patients with liver cirrhosis, the risk of progression to HCC varies and it depends on the etiology. In hepatitis C related cirrhosis, the risk is reported to be about 2-8% per year [2]. In hepatitis B related cirrhosis, the risk is 2.5% or more [3] and in alcoholic cirrhosis it is almost equal to the one in hepatitis B related cirrhosis. The risk for HCC increases if more than one virus is present (HBV+HCV, HBV+HDV) or if there is an association of alcohol with hepatitis viruses.

Received 27.03.2010 Accepted 6.04.2010
Med Ultrason
2010, Vol. 12, No 2, 145-149
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Hepatocellular carcinoma is a highly malignant tumor, with a lethal prognosis due to the fact that it occurs and coexists with an advanced liver disease (cirrhosis). Currently, hepatocellular carcinoma is considered to be the third most common cause of death by cancer, being the fifth most prevalent cancer in the world [4]

The above mentioned facts warrant an early recognition of hepatocellular carcinoma, that requires an active screening program for patients at high risk. This is deemed necessary in order to detect the cancer at an early stage, when it may still be treatable. Thus, the screening for HCC is necessary in all patients at high risk and an *ultrasound examination (US) for the liver structure* is recommended every *6-12 months* [5]. An expert examiner with adequate skills can detect 80-95% of the lesions 3-5cm in diameter, by using standard B-mode ultrasound. This technique has 60-80% sensitivity in detecting lesions of up to 1 cm [6,7]. A systematic review estimated that US has 60% sensitivity (95% CI 44-76%) and 97% specificity (95% CI 95-98%) for the detection of HCC, as compared to the pathologic ex-

amination of the explanted liver considered to be the "gold-standard" [8].

Ultrasound surveillance of patients with liver cirrhosis can detect liver nodules of various sizes. In these patients, any new nodule is considered to be a HCC until proven otherwise.

One significant disadvantage of standard US is that it does not allow differentiation between a benign regenerative nodule and a malignant nodule. However, this disadvantage can be overcome using Contrast Enhanced Ultrasound (CEUS**)**. This technique has shown good sensitivity in differentiating between malignant and benign liver lesions. The method is able to show the vascular pattern of the nodules during the 3 vascular phases (arterial, venous and late phase). After detection of a hepatic nodule by standard US during the screening program, it must be evaluated using one of the advanced imaging methods (MRI, CT or CEUS) with a contrast agent. According to the "AASLD Guidelines on the management of hepatocellular carcinoma'' [5] CEUS can be used as an alternative to contrast CT or MRI for the diagnosis of HCC, since it has comparable sensitivity.

The biopsy of hepatic nodules in patients with liver cirrhosis is necessary only in cases in which the above mentioned contrast imaging methods fail to confirm a positive diagnosis.

Assessment of Hepatic Nodules found on Screening according to their size

When a new hepatic nodule is found during screening ultrasound in a patient with liver cirrhosis, it is mandatory to confirm or infirm the diagnosis of HCC. This can be done using one or more contrast enhanced imaging techniques. The duration and time intervals between follow up assessment of the nodule depend solely on its size.[5]

I. **Nodules smaller than 1 cm** detected during the screening program will be followed-up by ultrasound every 3-4 months, for 2 years. During this time period, if the nodule increases in size, a contrast enhanced imaging method would be considered as the next step in management. On the other hand, if this nodule does not grow or rather disappears, the patient would be advised to return and participate in the regular screening program, i.e., performing ultrasound every 6 months.
II. **Nodules ranging from 1-2 cm** have an increased risk to be hepatocellular carcinomas. These nodules might be regenerative or displastic type nodules, with malignant characteristics.

CEUS in the evaluation of liver nodules in cirrhotic patients

The CEUS evaluation of liver nodules must consider the 3 vascular phases (arterial phase: 20-35 sec, venous phase**:** 35-120 sec. and late phase**:** from 120 sec. to the elimination of contrast from the liver). CEUS plays a significant role in the differential diagnosis and classification of hepatic nodules.

1. Regenerative Nodules: upon administration of contrast, the regenerative nodules behave just like the surrounding liver parenchyma. These nodules would not appear as circumscribed lesions during the CEUS exam, and are not visible in any of the three vascular phases.

2. Displastic Nodules are generally hypovascular in the arterial phase, but sometimes they can be hypervascular, without "washout'' during the portal/late phases of CEUS.

Hepatic carcinogenesis is a "multi-step" process, from regenerative nodule (typical liver cirrhosis), to displastic nodule (a premalignant lesion) which, over time, becomes a hepatocellular carcinoma. Displastic nodules may have different degrees of differentiation. The differential diagnosis between "early'' hepatocellular carcinoma and a high grade dysplastic nodule is sometimes difficult using only imaging techniques. This differential diagnosis remains challenging even by means of pathological exam of the biopsy specimen.

In cases in which the differential diagnosis is not possible, the lesions should be considered HCCs and treated as such. In the study of Borzio et al. [9], 31% of the regenerative nodules and 63% of the high grade dysplastic nodules progressed to HCC.

In one study recently published in the *European Journal of Radiology* [10], 59 patients with liver cirrhosis and liver nodules 1-2 cm in diameter were examined and diagnosed by CEUS. The diagnosis of HCC was linked to the presence of early arterial enhancement. The confirmation of HCC diagnosis was made by the pathological examination of the explanted liver or of the resected liver specimen, or by clinical and imaging studies for a 12 month follow up period. All the nodules with early arterial enhancement were proven to be HCCs. The study concludes that the presence of early arterial enhancement in nodules with a diameter less than 2 cm is enough for the diagnosis of HCC.

3. Hepatocellular carcinoma shows a typical behavior in CEUS, characterized by early arterial enhancement upon administration of contrast agent, followed by „washout'' in portal and/or late phases (fig 1-3).

The typical behavior of HCC is a consequence of its blood supply, mainly arterial, in contrast to the normal

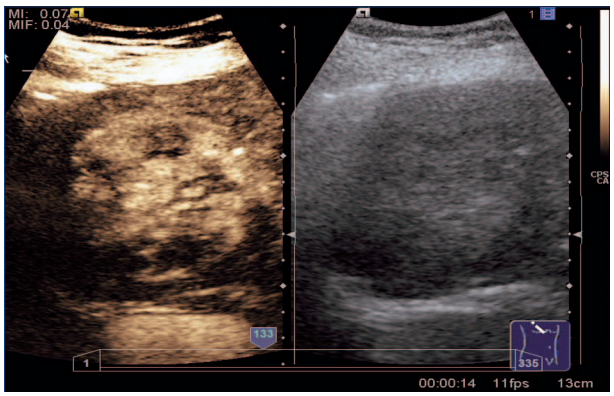


Fig 1. Rapid enhancement in the arterial phase

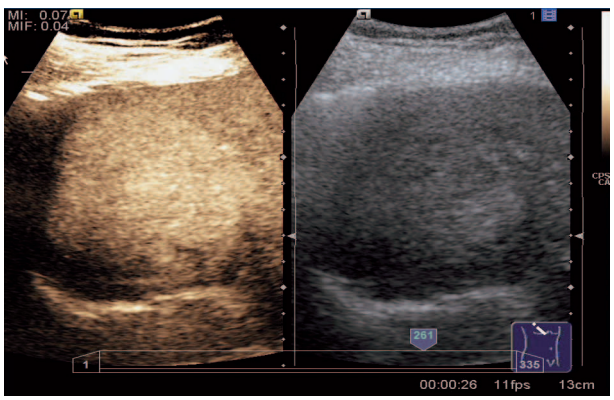


Fig 2. Rapid enhancement in the arterial phase

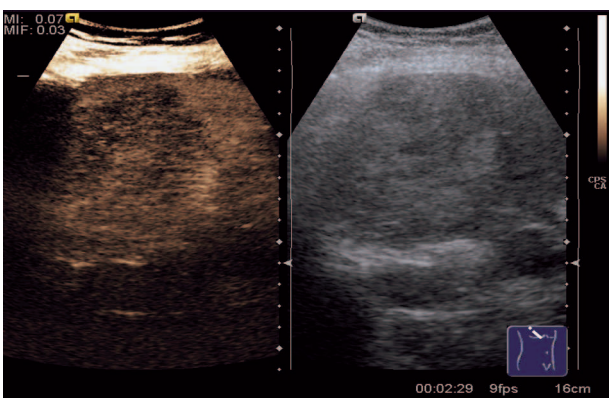


Fig 3. „Washout'' in the late phase

liver parenchyma, that thrives on dual blood supply (i.e., the portal vein and the hepatic artery). This unique pattern of blood supply in HCC is the outcome of malignant changes in the regenerative nodules, of tumoral neoangiogenesis.

The arterial enhancement in HCC is usually homogeneous, but it can also be heterogeneous, due to fatty degeneration or intratumoral necrosis. During the early arterial enhancement phase, the nutrition artery of HCC can often be visualized.

CEUS sensitivity as compared with contrast CT and MRI in finding early arterial enhancement of hepatocellular carcinoma is related in Tabel I.

„Real-time'' ultrasound evaluation often allows us to visualize the HCC's nutrition artery and the peripheral vessels that penetrate the tumor and create the typical „basket pattern'' appearance. The early arterial enhancement of HCC is a feature that leaves few lesions undiagnosed. The CEUS sensitivity for the diagnosis of early arterial enhancement is equal to the one of contrast CT and MRI and is correlated with the degree of tumor differentiation (12). Using CEUS, the early arterial enhancement is observed in 91-96% of HCCs, so, maybe, it could be the method of choice for the assessment of tumoral neoangiogenesis [10, 14].

In the study performed by Forner et al. (13), the pathologic exam was considered to be the „gold-standard'' for the diagnosis of the liver nodules smaller than 2 cm in diameter. The sensitivity of CEUS for suspected HCCs was found to be only 78.3%. In only 51.7% of the cases the result was conclusive for the diagnosis, with a specificity of 93.1%.

In well differentiated HCCs, the tumor blood supply may be mainly portal, that is evident by the presence of portal tracts within the tumor [15]. Thus, *well differentiated HCCs and small HCCs can be hypovascular, so that they will not display early arterial enhancement.* In these cases, the diagnosis is established by a pathologic examination.

Unlike the early arterial enhancement, present in most of HCCs, the „washout'' in the late portal phase is rather rare, present only in approximately 43% of cases 90 seconds after contrast injection. In later stages of the

Tabel I. CEUS sensitivity as compared with contrast CT and MRI in finding early arterial enhancement of hepatocellular carcinoma

Authors	Number of lesions	Size of the lesions	Found by CEUS	Found by CT / MRI
Gaiani et al [11]	103	2.8 ±1, 3 cm	91%	CT 100%
Bolondi et al [12]	41	1-2 cm	61%	CT 49%
	31	2-3 cm	97%	CT 87%
Forner et al [13]	60	0.5-2 cm	78%	MRI 85%

Tabel II. CEUS sensitivity and specificity as compared to contrast MRI or multi-detector CT

Authors	Number of patients	Number of lesions	Size of the lesions	Sensitivity	Specificity
Forner et al [13]	60	60	0.5-2 cm		
CEUS				52%	93%
MRI				62%	97%
Dai et al [17]	72	103	1-2 cm		
CEUS				91%	87%
CT				80%	98%

examination (90-180 seconds after contrast), 26% of the HCCs displayed „washout''. In the study of Jang HJ et al, only 22% of the carcinomas presented a delayed „washout'' (181-300 seconds after contrast) [16].

For the positive diagnosis of HCC *in nodules less than 2 cm* in diameter, any two of the three contrast imaging methods are required (CEUS, MRI, CT). The diagnosis is confirmed based on the typical behavior of HCC that displays early arterial enhancement and „washout'' in the late portal phase. If the results are inconclusive, a pathologic examination should be performed. CEUS sensitivity and specificity as compared to contrast MRI or multi-detector CT is related in Tabel II.

III. **Liver nodules larger than 2 cm in diameter in cirrhotic patients** found during screening programs are often HCCs. In order to confirm this diagnosis, *only one contrast imaging method is enough,* esp. a method that shows typical HCC behavior: early arterial enhancement and „washout'' in the late portal phase.

The sensitivity of CEUS in the diagnosis of HCC is directly related to the size of the tumor. For nodules ≤ 2 cm, Giorgio et al. [18] and Gaiani et al [11] observed 53.6% and 83.3% sensitivities respectively, while for nodules > 2 cm the sensitivities were found to be 91.3% and 94.5%, respectively. Another recently published study in the *Journal of European Ultrasound* [18], shows that HCCs behavior is influenced by their size, so that early arterial enhancement is more frequent in tumors >3 cm in diameter as compared to tumors ≤ 3 cm. This feature is only valid in well differentiated (G1) HCC but not in moderate or less differentiated tumors. Thus, early arterial enhancement was found in 95% of the HCCs > 3 cm in diameter and only in 43% of the well differentiated HCCs ≤ 3 cm in diameter ($p<0.001$). In the late phase, in the G1 subgroup, hypo-echoic demarcation was found in 95% of the lesions > 3 cm, but in only 64% of the lesions < 3 cm ($p<0.001$). In contrast, among less differentiated HCC (excluding G1), hypo-echoic demarcation was found in 91% of HCC > 3 cm and in 82% of HCC < 3 cm) (p=ns).

During the malignant transformation of a liver nodule, major hemodynamic changes occur due to tumoral neoangiogenesis with changes in the blood supply: increased arterial flow and decreased portal venous flow. These hemodynamic changes provide the underlying basis for diagnostic imaging with contrast agents and they can be demonstrated in early stages by means of CEUS.

Conclusion

Contrast Enhanced UltraSonography (CEUS) is a sensitive diagnostic method for the diagnostic of HCC. It is a method with no side effects (the US contrast agent does not induce allergic reactions and is not excreted through the kidneys) and it does not expose the patient to harmful radiations. On the other hand, CEUS allows a „real-time'' evaluation of liver nodules, followed by an immediate result. CEUS may be the only imaging technique required for the diagnosis of a hepatic lesion larger than 2 cm in diameter in the presence of liver cirrhosis. Following contrast, the suspected nodule displays typical behavior, characteristic for hepatocellular carcinoma.

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