Characterization of Dysplastic Nodules, Early Hepatocellular Carcinoma and Progressed Hepatocellular Carcinoma in Cirrhosis with Contrast-Enhanced Ultrasound

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Abstract. *Background: During the progression from low-grade dysplastic nodule (DN) to progressed hepatocellular carcinoma (HCC), intranodular portal tracts gradually disappear, while unpaired arteries develop increasingly. Contrast-enhanced ultrasound (CEUS) is highly accurate in depicting intranodular vascularity. This study evaluates the usefulness of CEUS in the characterization of DN, early HCC and progressed HCC in cirrhotic livers. Materials and Methods: Forty consecutive patients with cirrhosis and a single hepatic nodule ≤2 cm underwent CEUS and subsequent ultrasound-guided biopsy of the nodule. Imaging and pathological findings of DN and HCC were compared. Results: The homogeneous pattern of hypervascularization during the arterial phase identified progressed HCC with a sensitivity of 90.9% and a specificity of 100%, whereas the inhomogeneous and reticular pattern identified early HCC with a sensitivity of 85.7% and a specificity of 96.1%. Conclusion: DN, early HCC and progressed HCC can be accurately differentiated with CEUS on the basis of the vascularization pattern during the arterial phase.*

Hepatocellular carcinoma (HCC) is the seventh most common cancer worldwide. In 2008, an estimated 748,000 new cases were diagnosed and 696,000 deaths were registered (1). Incidence and mortality are similar because most cases of HCC are diagnosed at an advanced stage, especially in developing countries where over 80% of the global cases occur.

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Key Words: CEUS, HCC, dysplastic nodule, vascularity, characterization, cirrhosis.

HCC development in the setting of a cirrhotic liver can occur either as *de novo* hepatocarcinogenesis or through a multistep pathway that starts from a dysplastic focus arising within a regenerative nodule and eventually leads to an overt cancer. In 1995, the International Working Party (IWP) of the World Congress of Gastroenterology classified nodular lesions found in chronic liver disease into large regenerative nodule, low-grade dysplastic nodule (L-DN), high-grade dysplastic nodule (H-DN) and hepatocellular carcinoma (HCC), and defined small HCC as a tumor measuring less than 2 cm (2). More recently, the International Consensus Group for Hepatocellular Neoplasia (ICGHN) has divided small HCC into two clinical-pathological groups named early HCC and progressed HCC (3). Early HCC is well differentiated and vaguely nodular, the presence of neoplastic cells in the portal tracts (stromal invasion) differentiates it from H-DN. Progressed HCC has a well-defined nodular pattern and is usually moderately differentiated (3).

Patients with cirrhosis should be closely screened by conventional ultrasound (US) because the recurrence-free survival and the 5-year overall survival are considerably better for patients with early HCC compared to patients with progressed HCC (4). Unfortunately, the identification of an early HCC from the background nodularity of a cirrhotic liver by conventional US can be very challenging due to its small size and vague limits.

Contrast-enhanced ultrasound (CEUS) substantially improves the accuracy of US in the characterization of focal liver lesions by showing different vascular patterns between benign and malignant lesions during the arterial, portal and sinusoidal phases (5). As the nodule evolves from dysplastic to malignant, neoangiogenic unpaired arteries progressively supplant intratumoral portal tracts. Therefore, overt HCC is mainly fed by the hepatic artery, whereas normal liver parenchyma and premalignant nodules are mostly perfused by the portal branches (3). This arterialization of the blood supply accounts for the

hyperenhancement shown by malignant nodules during the arterial phase and for the wash-out during the portal and sinusoidal phases on CEUS. Previous studies have found a correlation between HCC enhancement on CEUS and tumor differentiation and diameter (6, 7). The vast majority of progressed HCC larger than 2 cm typically show an intense and homogeneous hyperenhancement during the arterial phase and a rapid wash-out during the portal and sinusoidal phases. By contrast, some small well-differentiated HCC appear hypo/isovascular throughout the phases and may actually resemble benign nodules (8-10). Furthermore, in our experience, many small HCC show a characteristic pattern of inhomogeneous and reticular enhancement during the arterial phase (11). This pattern results from a fine network of many hyperenhancing linear vessels filling the nodule on a hypoenhancing background. Wash-out is usually delayed in these cases and the same pattern of enhancement tends to persist throughout the phases. With reference to the ICGHN classification, we assumed that the reticular pattern of enhancement would be suggestive of early HCC that do not as yet appear as homogeneously hypervascular as progressed HCC.

In view of this, the aim of the present study was to prospectively investigate the usefulness of CEUS with a second-generation contrast agent in differentiating L-DN, H-DN, early HCC and progressed HCC.

Patients and Methods

Patients. Our Institutional Review Board approved this prospective study and written informed consent was obtained from all patients. From February to October 2009, we enrolled 40 consecutive patients with cirrhosis and a single hepatic nodule ≤2 cm in diameter, among 625 patients with cirrhosis referred to our institution for investigation of one or more focal liver lesions suggestive of HCC that had been newly detected during conventional US surveillance. All 40 patients underwent CEUS and US-guided biopsy of the nodule. Cirrhosis had been previously diagnosed on the basis of liver biopsy findings in 13 patients and of clinical and sonographic data in the remaining 27 patients. In all patients, cirrhosis was due to chronic viral hepatitis; 28 patients had chronic hepatitis C and 12 patients had chronic hepatitis B. Thirty-two patients had Child-Pugh A cirrhosis and 8 had Child-Pugh B cirrhosis. Serum levels of α-fetoprotein were below 20 ng/ml in 31 patients and between 20 and 40 ng/ml in 9 patients.

According to EMEA recommendations on the use of SonoVue, none of the patients included in the study were pregnant, breast-feeding or had acute coronary syndrome, right-to-left cardiac shunts, severe pulmonary hypertension, uncontrolled arterial hypertension or adult respiratory distress syndrome. We then selected the 36 patients (26 men and 10 women; mean age 60 years, age range 49-64 years) whose hepatic lesions (mean diameter 14 mm, range 9-20 mm) were diagnosed as DN or HCC on pathological examination and compared CEUS findings with pathological diagnosis.

CEUS procedure. All patients underwent CEUS of the liver performed by the same physician with over 25 years of experience in sonography. Examinations were performed using Prosound α10 Premier equipment (Aloka, Tokyo, Japan) or Aplio XG equipment (Toshiba, Tokyo, Japan) with 3.0-6.0 MHz convex array broadband probes and software for contrast media. The scanning plane of the liver that included the nodule was accurately determined before SonoVue (Bracco, Milan, Italy) injection.

SonoVue is a second generation US contrast agent composed of microbubbles of sulfur hexafluoride (SF6) gas stabilized with phospholipids and suspended in saline (0.9% sodium chloride). SonoVue was supplied as a sterile lyophilized powder (25 mg) in a gaseous atmosphere (SF6) in 10 ml vials and it was reconstituted by adding 5 ml sterile saline to the vial just before administration. After the baseline liver US evaluation and the determination of the best scanning plane for the nodule, a volume of 2.4 ml of SonoVue was injected intravenously in bolus through a 20-gauge needle, followed by a 5 ml saline flush.

A low mechanical index (0.1), automatically defined by the contrast media software, was used in order to avoid disruption of microbubbles. Scans were performed with simultaneous dual imaging (gray-scale and contrast-specific imaging), so that localization of the lesion was continuously possible throughout the procedure. The nodule examined was continuously observed for 4-6 min following contrast agent injection, until the overall enhancement had disappeared. The whole vascular phase, consisting of the arterial phase (15 to 30 s following contrast injection), the portal phase (30 to 60 s) and the sinusoidal phase (60 to 240 s), was accurately studied and recorded. A second injection of further 2.4 ml of SonoVue was needed in two patients because of inadequate visualization of the overall vascular enhancement after the first injection.

CEUS imaging interpretation. The intravenous injection of sonographic contrast agents that remain within the blood pool results in echo enhancement of up to 30 dB (12). With blood pool contrast media, enhancement represents vascularity.

After contrast agent injection, both the intensity and pattern of lesion enhancement on contrast-specific imaging were carefully analyzed in real time. Enhancement features of the lesion were compared to those of the surrounding liver parenchyma and related to the vascular phase. Lesions that showed the same echogenicity of the surrounding liver parenchyma, being for this reason indistinguishable on contrast-specific imaging, were defined as isovascular. Lesions that appeared hypoechoic compared to the background liver parenchyma were defined as hypovascular. Lesions that appeared hyperechoic compared to the background liver parenchyma were defined as hypervascular. Hypervascular lesions were further differentiated into inhomogeneously hypervascular lesions and homogeneously hypervascular lesions, on the basis of hyperenhancement distribution within the lesion. In the former case, the pattern of hypervascularization was defined as 'reticular' when a fine network of many hyperenhancing lines filling the nodule on a hypoenhancing background was observed. The patterns considered in the study are shown in Figure 1.

Washout was defined as a change from a hyperechoic lesion, relative to the background liver parenchyma, to an isoechoic or hypoechoic lesion at any vascular phase.

The same experienced examiner who performed all CEUS was asked to define the type of enhancement observed in each vascular phase. At the time of CEUS imaging interpretation, the examiner was unaware of the pathological diagnosis.

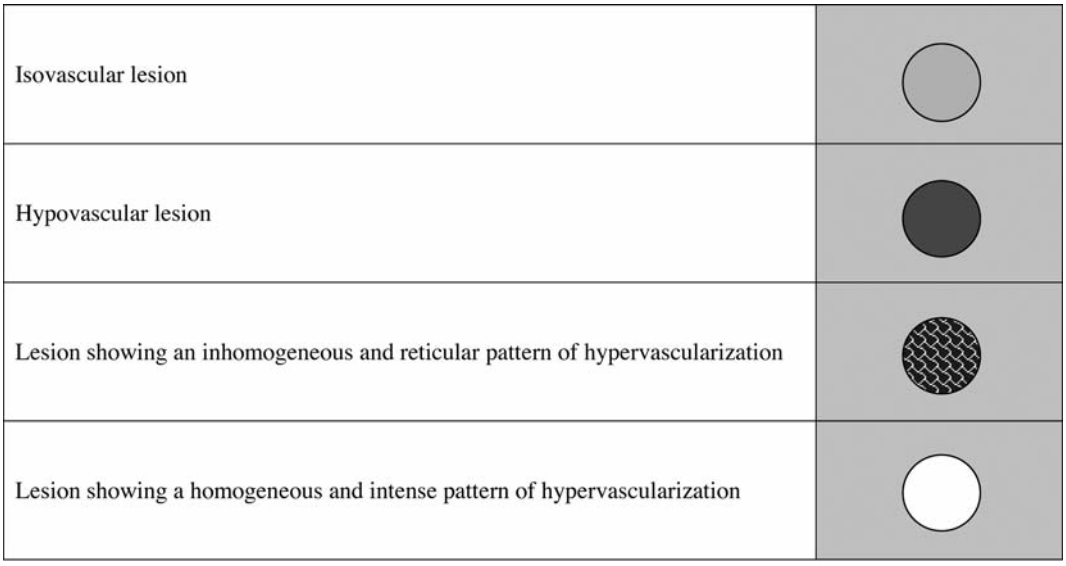

Figure 1. *Patterns of vascularization observed on contrast-specific imaging.*

Pathological examination. Specimens of all liver nodules were obtained by US-guided biopsy with modified Menghini 16-gauge cutting needles. All biopsies were performed on the same day of CEUS and always after the CEUS, in order to avoid alteration of the imaging appearance. Specimens were all examined by the same pathologist with over 25 years of experience in liver pathology. On the basis of histological findings, dysplastic nodules and hepatocellular carcinoma were classified according to the criteria proposed by the ICGHN into: L-DN, H-DN, early HCC and progressed HCC (3).

Results

Baseline pre-contrast US features. On conventional US, 11 nodules were isoechoic relative to the surrounding liver parenchyma, 24 were hypoechoic and 5 were hyperechoic.

CEUS findings. On CEUS arterial phase, 10 nodules were hypovascular (25%), 7 were isovascular (17.5%), 13 showed the reticular pattern of vascularization (32.5%) and 10 were homogeneously hypervascular (25%). On CEUS portal and sinusoidal phase, 9 nodules were hypovascular (22.5%), 18 were isovascular (45%) and 13 showed the reticular pattern of vascularization (32.5%), while none was homogeneously hypervascular.

Pathology findings. On pathological examination, 2 lesions were focal steatosis (5%) and 2 were regenerative nodules (5%). Of the remaining 36 nodules, 6 were L-DN (15%), 5 were H-DN (12.5%), 14 were HCC (35%) and 11 were progressed HCC (27.5%).

Correlation between pathological findings and CEUS. The two nodules of focal steatosis were isovascular throughout the three CEUS phases. One regenerative nodule remained isovascular during all phases; the other one appeared hypovascular in the arterial phase and became isovascular in the portal and sinusoidal phases.

On CEUS arterial phase, 3 L-DN were isovascular and 3 were hypovascular, whereas all 5 H-DN appeared hypovascular. All DN maintained the same enhancement behavior shown during the arterial phase in the subsequent vascular phases. Among the 14 early HCC, during the arterial phase, 1 lesion was isovascular, 1 was hypovascular and the remaining 12 showed the inhomogeneous and reticular pattern of hypervascularization. The enhancement pattern during the portal and sinusoidal phases did not change in any of the early HCC, nor was wash-out observed in the 12 cases showing the inhomogeneous and reticular pattern of hypervascularization.

Ten progressed HCC were intensely and homogeneously hypervascular during the arterial phase. All of them washed out during the portal phase, becoming isovascular. None of the lesions appeared hypovascular following wash-out. One progressed HCC showed the inhomogeneous and reticular pattern of hypervascularization throughout the vascular phases.

The presence of hypervascularization of any type, homogeneous or reticular, during the arterial phase of CEUS differentiated HCC from other lesions with a sensitivity of 92%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 88.2%. Considering specifically the different types of hypervascularization, the

homogeneous and intense pattern identified progressed HCC with a sensitivity of 90.9%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 96.6%, whereas the inhomogeneous and reticular pattern identified early HCC with a sensitivity of 85.7%, a specificity of 96.1%, a positive predictive value of 92.3% and a negative predictive value of 92.5%.

Discussion

All patients with cirrhosis should be regularly screened by means of periodic AFP level testing and conventional US of the liver because they are at higher risk of developing HCC (13). The objective of surveillance for HCC is to detect the tumor as early as possible because all therapeutic options (*i.e.* liver transplantation, hepatic resection or percutaneous ablation techniques) have the best chance of cure when the tumor is still small and well-differentiated; recurrence rates after treatment are lower and the long-term survival rates are better (14-16).

The importance of US as a screening test for HCC in high-risk populations is well established, however its specificity is limited, especially in the context of liver cirrhosis where the hepatic texture may appear markedly altered and regenerative macronodules can be as large as 2 cm, while some early HCC can be smaller than 1 cm. Contrast agents greatly improve US accuracy (5). CEUS with blood pool agents provides useful information about the blood supply pattern and, thus, the grade of malignancy of the nodules. During hepatocellular carcinogenesis, in fact, changes in intranodular hemodynamics occur in a sequential fashion that correlates with histopathological and radiological findings. As the regenerative nodule evolves to HCC, intranodular portal tracts, including the portal vein and the hepatic artery, gradually disappear, while abnormal neoangiogenic unpaired arteries increasingly develop (17). Hence, from a blood supply mainly provided by the portal circulation, the tumor becomes mostly perfused from the neoangiogenic unpaired arteries and thus becomes hypervascular in the arterial phase of CEUS. Before pathological arterialization of the nodule occurs, a transient phase in which both arterial and portal blood supplies decrease may be observed (18). Due to its supreme spatial and temporal resolution, CEUS can represent the vascular changes occurring during the progression of L-DN into progressed HCC with high accuracy.

In our study, the vascular changes occurring during this progression (from L-DN, to H-DN, to early HCC and finally to progressed HCC) were related to characteristic CEUS findings. According to our results, dysplastic nodules, whose blood supply is mainly portal, are usually iso/hypovascular during the arterial phase (Figure 2). We observed the inhomogeneous and reticular pattern of hypervascularization almost exclusively in early HCC. We believe that this pattern may result from the disappearance of the majority of portal tracts, along with the emergence of unpaired arteries that are still inadequately developed to show a homogenous hypervascularization (Figure 3). Finally, progressed HCC, from which portal tracts are virtually absent and the blood supply is completely arterial, show the typical homogeneous and intense pattern of hypervascularization in the arterial phase of CEUS (Figure 4) and rapid portal wash-out due to intratumoral arteriovenous shunts.

Our study has some limitations. Firstly, the relatively small sample size of our study might have hampered sensitivity and specificity analysis, therefore further studies on larger patient series are required so that these values can be estimated more precisely. Secondly, we did not determine time-intensity curves of the enhancement patterns that we describe. In order to define these patterns more precisely, further studies should use quantitative methods. Thirdly, we did not consider other radiological tests such as enhanced magnetic resonance imaging (MRI) and computed tomography (CT), but the aim of our study was to investigate the value of CEUS in assessing in vascularity between benign, premalignant and malignant liver lesions, and for this purpose, pathology was considered the gold standard. However, with regard to the usefulness of other imaging techniques in differentiating nodules encountered in a cirrhotic liver on the basis of the histological grading, the hepatobiliary phase of enhanced MRI has proven useful in a recent retrospective study: decreased Gd-EOB-DTPA uptake by HCC seems to be an earlier finding than decline in portal blood flow (19). Similarly, CT during arterial portography and during hepatic arteriography can provide useful information in determining the grade of malignancy of nodules occurring in cirrhotic livers (20, 21).

Recently Kudo *et al.*, investigating the value of pure arterial phase US imaging in the depiction of portal supply in early HCC and DN with Sonazoid (a contrast agent that is uptaken by Kupffer cells that is not available in Italy), reported results very similar to those of our study (22).

In conclusion, our results indicate that CEUS is a reliable technique for differentiating DN, early HCC and progressed HCC in cirrhotic livers. The occurrence of an inhomogeneous and reticular pattern of hypervascularization is strongly suggestive of early HCC and requires further workup in order to confirm the diagnosis, since all therapeutic options at such stage have high rates of cure.

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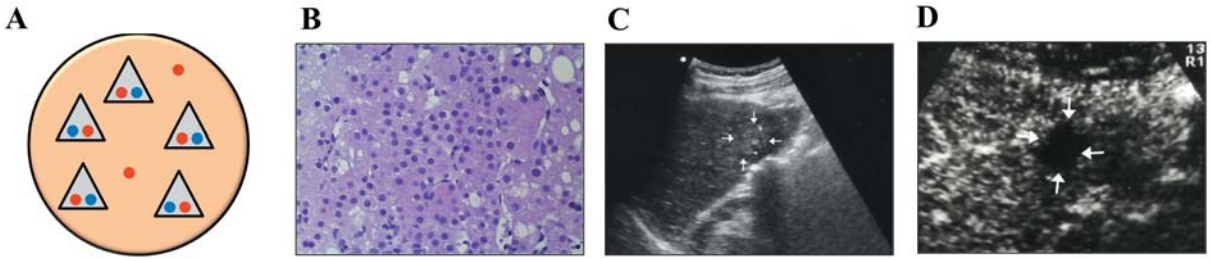

Figure 2. *A 61-year-old man with HCV-related cirrhosis and dysplastic nodule. A: Diagram showing the vascularity of a dysplastic nodule: numerous portal tracts (grey triangles) with normal hepatic artery (red dots) and portal vein (blue dots) are still present and there are some isolated unpaired arteries (red dots outside the triangles). B: On histology, mild alteration of the nuclear-cytoplasmatic ratio and a mild increase in cell density are apparent. C: Conventional US shows a small (18 mm) hyperechoic lesion at the edge of the VI segment. D: On CEUS arterial phase, the nodule is hypovascular.*

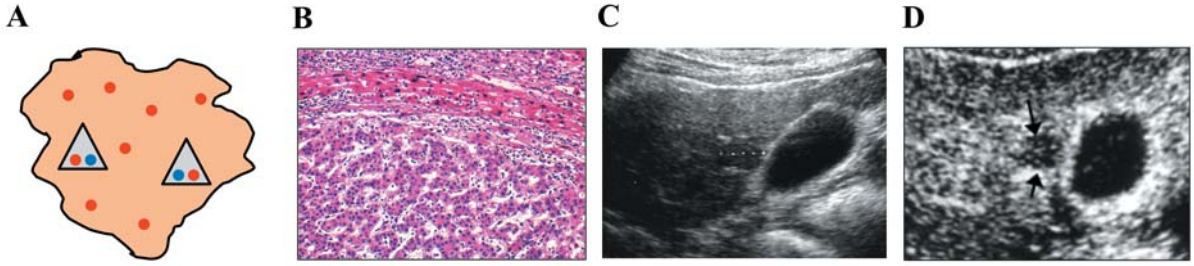

Figure 3. *A 50-year-old man with HBV-related cirrhosis and early hepatocellular carcinoma. A: Diagram showing the vascularity of a vaguely nodular early hepatocellular carcinoma: portal tracts (grey triangles) are partially substituted by neoangiogenic unpaired arteries (red dots outside the triangles) that increase in number. B: On histology, well-differentiated HCC with irregular trabecular pattern and focal cytologic atypia of hepatocytes are apparent. C: Conventional US shows a small (14 mm) hypoechoic lesion in the V segment. D: On CEUS arterial phase, the nodule shows an inhomogeneous and reticular pattern of hypervascularization.*

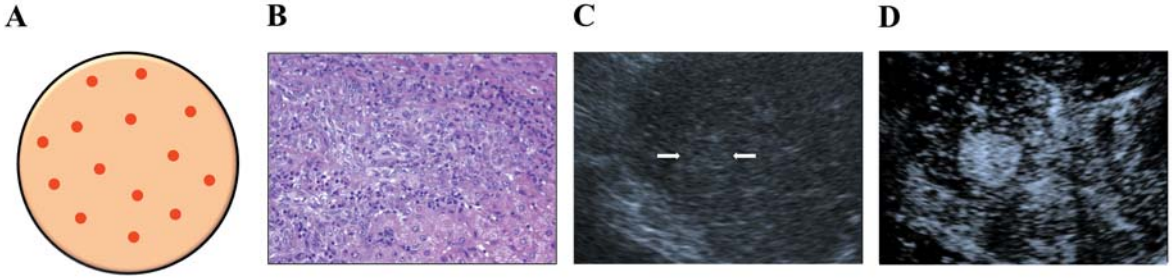

Figure 4. *A 70-year-old man with HCV-related cirrhosis and progressed hepatocellular carcinoma. A: Diagram showing the vascularity of a progressed hepatocellular carcinoma: unpaired arteries (red dots outside the triangles) have completely substituted portal tracts. B: On histology, moderately differentiated HCC with irregular trabecular pattern and moderate cytological atypia of hepatocytes are apparent. C: Conventional US shows a small (19 cm) isoechoic lesion in the VII segment. D: On CEUS arterial phase the nodule is homogeneously and intensely hypervascular.*

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Received August 13, 2011
Revised October 12, 2011
Accepted October 13, 2011