Diagnosis of Hepatocellular Carcinoma in Cirrhosis by Dynamic Contrast Imaging: The Importance of Tumor Cell Differentiation

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Dynamic contrast imaging techniques are considered the standard of care for the radiological diagnosis of hepatocellular carcinoma (HCC) in cirrhosis. However, the accuracy of radiological diagnosis depends largely on the degree of arterial hypervascularization, which increases with tumor size. Owing to the interplay and prognostic relevance of tumor vascularization and cell differentation, we asked ourselves whether tumor grade also affects the outcome of radiological diagnosis. Sixty-two HCCs (47 of which measured 1-2 cm) were consecutively detected in 59 patients with compensated cirrhosis under surveillance with ultrasound and confirmed by way of echo-guided biopsy and concurrent investigations with contrast-enhanced ultrasound (CE-US), computed tomography (CT), and gadolinium magnetic resonance imaging (MRI). Tumor cell differentiation was evaluated using Edmondson-Steiner criteria in liver cores of 0.9-5.0 cm (median 1.6 cm). Eighteen (29%) HCCs were grade I (1.5 cm), 28 (45%) were grade II (1.5 cm), 16 (26%) were grade III (1.8 cm), and none were grade IV. Contrast wash-in and wash-out were concurrently demonstrated in 21 (34%) tumors by way of CE-US, including three (16%) grade I and 18 (41%) grade II-III ($P = 0.08$); in 32 (52%) tumors by way of CT, including three (16%) grade I and 29 (66%) grade II-III ($P = 0.0006$); and 28 (47%) tumors by way of MRI, including three grade I (16%) and 25 (57%) grade II-III ($P = 0.01$). Among 1- to 2-cm tumors, the radiological diagnosis was achieved in two of 16 grade I and 17of 31 grade II-III tumors ($P = 0.006$). *Conclusion:* Tumor grade, a relevant predictor of disease severity, influences the accuracy of dynamic contrast techniques in the diagnosis of HCC. (HEPATOLOGY 2010;52:1723-1730)

Abbreviations: AFP, alpha-fetoprotein; CE-US, contrast-enhanced ultrasound; CT, computed tomography; FNB, fine-needle biopsy; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; US, ultrasound.

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Surveillance with abdominal ultrasound (US) of patients with cirrhosis, who are at risk of hepatocellular carcinoma (HCC), is the standard of care to detect small, potentially curable tumors.[1] A standardized recall policy for liver nodules detected on US examination has been established that uses dynamic contrast imaging techniques to show the pathognomonic pattern of contrast wash-in in the arterial phase followed by wash-out in the venous phase. Nodules that escape radiological diagnosis can be investigated using echo-guided liver biopsy and/or as enhanced follow-up with imaging.[2] Whereas two contrast imaging techniques with concordant wash-in/wash-out patterns are required for the diagnosis of $\leq$2 cm tumors, contrast-enhanced US (CE-US), spiral computed tomography (CT), or dynamic magnetic resonance imaging (MRI) alone suffices to diagnose $>$2 cm nodules.[2,3] In a validation study performed by Forner and colleagues,[4] the concurrent application of

Table 1. Main Criteria to Distinguish Well-Differentiated HCC from High-Grade Dysplastic Nodules

Features	High-Grade Dysplastic Nodules	Well-Differentiated HCC
Thickness of plates	Up to 2	>2*
Cell crowding	1.5-2	>2*
Uniformly increased N/C ratio**	No	Yes
Irregular thin trabecular pattern	No	Yes
Frequent acinar arrangement	No	Yes
Diffuse steatosis	Rare	Frequent
Stromal invasion	Never detectable	May be detectable
Reticulin framework decrease/loss	Never detectable	May be detectable
Nodule in nodule growth pattern	Never detectable	May be detectable

*Compared with surroundings.
**Nucleus to cytoplasmic ratio.

CE-US and gadolinium MRI showed 33.3% sensitivity and 100% specificity for the diagnosis of 0.5- to 2-cm HCCs using histology with fine-needle biopsy (FNB) as a diagnostic gold standard. In that study, CE-US was combined with gadolinium MRI, because previous investigations by the same group in explanted livers showed better diagnostic performance of MRI than CT scan in the identification of small HCC nodules.[5] Recently, the accuracy of CE-US has been questioned owing to a discrete number of false positive diagnoses of HCC in patients with an intrahepatic cholangiocarcinoma, a tumor that is increasingly seen in patients with HCV-related cirrhosis and, at variance with HCC, is a contraindication for orthotopic liver transplantation.[6,7]

Because HCC growth depends not only on the rate of arterial vascularization, which accounts for the pathognomonic pattern of HCC on contrast imaging, but also on tumor grade,[8] we wondered whether the diagnostic accuracy of dynamic contrast imaging techniques could be influenced by the degree of tumor cell differentiation, as well. To address this question, we assessed tumor grade in the liver cores of de novo HCC nodules that were consecutively diagnosed in 59 patients with compensated cirrhosis who were under surveillance and were concurrently examined with CE-US, dynamic gadolinium MRI, and contrast CT.

Patients and Methods

This study was a subanalysis of a previous independent, investigator-driven, prospective study aimed to compare the accuracy of CE-US, CT, and MRI in the diagnosis of de novo HCC nodules in patients with compensated cirrhosis who were under surveillance with US.[9]

Between April 2006 and December 2009, all patients with Child-Pugh class A or B cirrhosis with a de novo liver nodule detected during surveillance were investigated consecutively. Excluded were patients with a pre-existing liver nodule, poor liver function (Child-Pugh C) indicating liver transplantation independently on HCC, or an echo-coarse US pattern of the liver without a well-defined liver nodule. After giving informed consent, patients underwent a detailed medical history, physical examination, and complete blood count and biochemical tests, including serum alpha-fetoprotein (AFP; normal, $\leq$ 20 ng/mL) (IRMA; Abbott, North Chicago, IL) and markers for viral hepatitis and autoimmunity. In all patients, abdominal CT, MRI, and CE-US examinations and a US-guided FNB were performed within 2 months of detection of a liver nodule.

Histology of Liver Nodules. The diagnostic reference standard was histology. In each patient, an FNB was concurrently performed within the nodule and the surrounding liver parenchyma. The procedure was repeated in all cases with unsolved histological diagnosis (i.e., patients showing similar histological features of cirrhosis within and outside the nodule). A 21-gauge trenchant needle for microhistology (Biomol, HS Hospital Service, Italy) was used, and the diagnosis was made according to International Working Party criteria.[10] Formalin-fixed,paraffin-embedded liver sections were examined by an experienced liver pathologist (G. R.) who was unaware of the results of the clinical and radiological examinations. All liver biopsy samples were re-evaluated by a second expert pathologist (M. R.) who was unware of the clinical, radiological, and pathological diagnoses. The criteria for diagnosing small and well-differentiated HCCs, which include the so-called very early HCC, are well standardized.[11,12] Table 1 shows the criteria used to distinguish well-differentiated HCCs from high-grade dysplastic nodules. Tumor cell differentiation was evaluated according to the Edmondson-Steiner grading system.[13] Figure 1 shows the representative histological features of HCC grading of the series under study.

Vascular Pattern of HCC. Arterial hypervascularization (contrast wash-in) was a contrast hyperenhancement of the nodule (hyperechogenicity on US, hyperdensity on CT, hyperintensity on MRI) taking place during the arterial phase of the radiological examination, as compared with the surrounding liver parenchyma. Portal/venous contrast wash-out was a hypoenhanced pattern of the nodule (hypoechogenicity on US, hypodensity on CT, hypointensity on MRI) with respect to the surrounding liver parenchyma taking place during the portal/venous phase of the radiological examination. The typical radiological pattern of

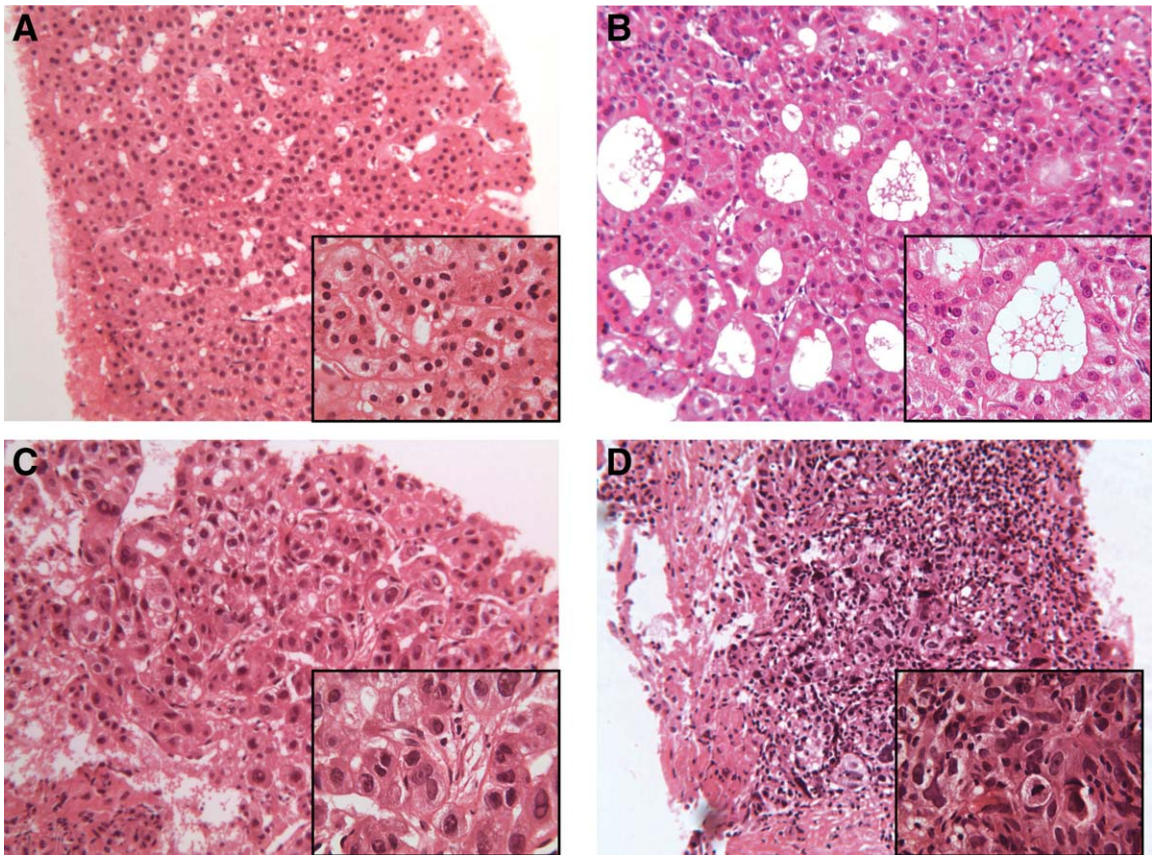

Fig. 1. Representative histological features of HCC grading. (A) Grade I microtrabecular tumor with uniformly small, regular neoplastic hepatocytes (×10, inset magnification ×40). (B) Grade II pseudoglandular tumor with malignant hepatocytes displaying irregular nuclear contours and nucleoli (×25, inset magnification ×40). (C) Grade III solid tumor with more pleomorphic cells (×25, inset magnification ×40). (D) High magnification of a grade IV tumor showing more anaplastic changes (archived specimen; ×10, inset magnification ×40).

HCC was the presence of wash-in followed by washout of the contrast medium. According to the American Association for the Study of the Liver Disease guidelines, the radiological diagnosis of HCC in 1- to 2-cm HCC was the presence of the typical radiological pattern on two dynamic imaging techniques. For >2-cm nodules, a single dynamic study showing the typical vascular pattern for HCC is required.[2] CT and MRI images were blindly and independently read by two experienced radiologists (L. V. F. and P. B.) who were unaware of the liver biopsy results.

MRI. MRI was performed with a 1.5-T system (Avanto; Siemens Medical Systems, Erlangen, Germany) using a phased-array torso coil for signal detection. All patients underwent transverse T1-weighted and T2-weighted MRI and multiphasic contrast-enhanced dynamic three-dimensional MRI of the whole liver with fat suppression. T1-weighted imaging included breath-hold in-phase gradient echo (175/5 TR/TE, 256 × 112 matrix, 70° flip angle) and out-of-phase gradient echo (175/2.38 TR/TE, 256 ×112 matrix, 70° flip angle). T2-weighted imaging included fat suppression sequences (1310/70 TR/TE, 320 × 192 matrix). Dynamic MRI was performed with a three-dimensional volumetric interpolated breath-hold examination sequence in an axial plane using the following parameters: 4.7/2.3 TR/TE, 320 × 157 matrix, 10° flip angle, 3-mm slice thickness. Gadolinium (Gadobenate Dimeglutamine [0.5 mmol/L]; Multihance, Bracco, Milan, Italy) was injected at a dose of 0.2 mL/kg at a rate of 2 mL/second. Arterial phase, portal venous, and delayed venous phase images were acquired approximately 30, 80, and 180 seconds from the start of contrast injection, respectively. A breath-hold T1-weighted two-dimensional gradient echo with fat suppression MRI (4.7/2.3 TR/TE, 256 × 157 matrix) and three-dimensional volumetric interpolated breath-hold examination sequences were performed 2 hours after contrast injection (hepatocyte phase).

CT. CT was performed with a 64-detector CT scanner (Definition Siemens, Erlangen, Germany) at 2.5-mm slice thickness and a rotation time of 0.5 seconds. A total of 1.5 mg/kg iodinated contrast medium (Iomeron 400; Bracco, Milan, Italy) was injected with

Table 2. Demography of the 59 Patients with Compensated Cirrhosis and a De Novo HCC Nodule

Male sex	41 (69)
Age, years	66 (44-85)
HCV-RNA	42 (71)
HBsAg	7 (12)
Alcohol	4 (7)
Other risk factors	6 (10)
HCC size	
0.5-1 cm	3 (5)
1-2 cm	47 (76)
2-3 cm	12 (19)

Data are presented as n (%) or median (range).
Abbreviations: HBsAg hepatitis B surface antigen; HCV, hepatitis C virus.

a 4.0 mL/second flow. In all patients, the acquisition time from the start of contrast injection and the start of acquisition sequences was 40 seconds for the arterial phase, 80 seconds for the portal venous phase, and 180 seconds for the delayed phase. Patients with an unsatisfactory acquisition of arterial phase were to repeat the examination using a bolus tracking technique.

CE-US. US studies were performed with a Philips iU22 system (Philips Ultrasound, Bothell, WA), using a multifrequency (5-2 MHz) convex transducer (C5-2). A preliminary gray-scale US examination of the upper abdomen was performed. On identifying the nodule, CE-US was performed with up to two bolus injections of 2.4 mL of a second-generation contrast agent (SonoVue; Bracco, Milan, Italy), having 8-μm microbubbles and stability for 6-8 minutes. The bolus was followed by a 10-mL saline flush. Low mechanical index (<0.1) was set for CE-US examination. Enhancement patterns were studied during the vascular phase for up to 3 minutes, including the arterial phase (0-35 seconds), portal phase (35-120 seconds), and late phase (120-180 seconds). All examinations were obtained and evaluated in real time by two expert echographists (M. F. and S. M.) and digitally stored and documented by a commercially available system or videotapes. Patients with a discrepant result were re-evaluated in a dedicated reading session by the two echographists, who were unaware of the liver biopsy results.

Statistical Analysis. The baseline characteristics of the patients are expressed as the median and range or count and proportion. Comparisons between the vascular pattern and tumor cell differentiation of the nodules were performed using a Student *t* test or Mann-Whitney test for continuous variables and Fisher's exact test for categorical variables. A conventional P value < 0.05 was considered statistically significant. Calculations were performed with the Stata version 10.0 statistical package (Stata 1944-2007, College Station, TX).

Results

Sixty-two HCC nodules were detected consecutively in 59 patients with cirrhosis who were under surveillance with US (Table 2). The diagnosis of HCC was histologically confirmed in liver biopsy cores ranging from 0.9 to 5.0 cm (median 1.6 cm). To assess intra-assay variation, 18 tumors (29%) were sampled twice during the same session, and the cores were blindly assessed for tumor cell differentiation by the same pathologist. Thirteen (72%) tumors yielded concordant readings (mean size 1.8 cm, weighted K 0.615), whereas in the five nodules with discordant results (mean size 1.8 cm), the worst grading was considered. Only one of the five discordant HCCs was a grade I versus grade II tumor, whereas the remaining four nodules were discordant for grade II versus grade III.

Table 3. Patient Characteristics Stratified According to Tumor Cell Grading (No Grade IV Tumors)

Characteristics	Grade I	Grade II-III	P Value
HCC nodule	18 (29%)	44 (71%)	–
Male sex	12 (66%)	32 (73%)	0.75
Age, years	70 (52-83)	64 (44-85)	0.04
HCV etiology	15 (83%)	30 (68%)	0.35
Child-Pugh class A	17 (94%)	42 (95%)	1.0
Serum AFP, ng/mL	8 (1-353)	14 (2-2156)	0.6
Nodule size, cm	1.5 (1.1-2.5)	1.6 (0.8-3.0)	0.6
0.5-1 cm	0	3	0.26
1-2 cm	16	31	–
>2 cm	2	10	–
Typical vascular pattern on CE-US	3 (17%)	18 (41%)	0.08
Typical vascular pattern on CT	3 (17%)	29 (66%)	0.0006
Typical vascular pattern on MRI	4 (22%)	25 (57%)	0.01

Data are presented as n (%) or median (range).
Abbreviations: HCV, hepatitis C virus.

Table 4. Correlation Between Tumor Size and Rates of Typical Vascular Pattern (Wash-in Followed by Wash-Out) for HCC in Contrast Imaging Techniques

Tumor Size	No. Of Nodules	Wash-In + Wash-Out Positives			Radiological Diagnosis of HCC
		CE-US	CT	MRI	
0.5-1 cm	3	0	1	1	–
1-2 cm	47	15	21	19*	19
>2 cm	12	6	10	9	10

*Two patients with HCC not investigated with MRI owing to claustrophobia and a bone metallic plaque, respectively.

Table 5. Rates of Radiological Diagnosis of 1- to 2-cm Tumors with Single or Dual Imaging Techniques According to Tumor Cell Grading

Imaging Techniques	Grade I	Grade II-III
CE-US	3 (19)	12 (39)
CT	3 (19)	18 (58)
MRI	4 (25)	15 (52)*
CE-US + MRI	1 (6)	6 (21)*
CE-US + CT	1 (6)	8 (26)
MRI + CT	2 (13)	11 (38)*
Any dual combination	2 (13)	17 (55)

Data are presented as n (%).

*Two patients with HCC not investigated with MRI owing to claustrophobia and a bone metallic plaque, respectively.

There were 18 (29%) grade I tumors with a median size of 1.5 cm (range 1.1-2.5 cm), 28 (45%) grade II tumors with a median size of 1.5 (range 1.0-3.0 cm), 16 (26%) grade III tumors with a median size of 1.8 (range 1.0-2.6 cm), and no grade IV tumors. Of the 47 tumors measuring 1-2 cm in size, 16 (34%) were grade I, 20 (43%) were grade II, and 11 (23%) were grade III. Table 3 shows the correlation between the results of contrast imaging techniques and tumor cell grading. CE-US yielded a combined pattern of contrast wash-in and wash-out in three (17%) grade I and 18 (41%) grade II-III tumors ($P = 0.08$). CT yielded the typical vascular pattern in three (17%) grade I and 29 (66%) grade II-III nodules ($P = 0.0006$). Finally, MRI gave the typical vascular pattern in four (25%) grade I and 25 (57%) grade II-III nodules ($P = 0.01$). The distribution of tumor cell grading was similar according to patient age, disease etiology, serum levels of liver enzymes, tumor size, and serum AFP values (Table 3). Table 4 shows the correlation between the results of contrast imaging techniques and tumor size. Of the 1- to 2-cm nodules showing two coincidental results by contrast imaging techniques, a radiological diagnosis was obtained in two of 12 (17%) grade I tumors and 17 of 31 (55%) grade II-III tumors ($P = 0.006$) (Table 5). Multivariate analysis revealed that tumor cell dedifferentiation (odds ratio 12.38; 95% confidence interval 2.39-64.13; $P = 0.003$) and tumor size (odds ratio 3.73; 95% confidence interval 1.15-12.13; $P = 0.029$) were found to directly correlate with an increased likelihood of a radiological diagnosis of HCC (Table 6).

Discussion

Tumor grade has clinical implications in HCC, because it correlates with well-established predictors of disease severity and recurrence after surgery, such as number and size of tumor nodules and portal invasion by tumor cells.[14-18] The present study is the first to evaluate cell grading in small HCC nodules detected during surveillance of patients with cirrhosis, thus adding to the data regarding cell grading in both small and large HCC nodules in surgically resected livers. In our series of early detected tumors, the vast majority (71%) of the nodules were grade II and III, whereas none of the tumors was grade IV. The stratification of cell grading in early HCC nodules investigated before any treatment differs substantially from that reported in surgical specimens, where the HCC nodules were greater in size and more dedifferentiated (42%-60% grade II and III versus 28%-46% grade IV).[14,18-22] Although a correlation has been demonstrated between cell grading and volume of the tumor in surgical studies,[11] such a correlation was not apparent in our study, which only included HCCs <3 cm. Indeed, the median volume of tumors we investigated was the same across all the grading categories (no patient with grade IV tumors), each volumetric set of HCC (<1 cm, 1-2 cm, >2 cm) containing more grade II and III than grade I tumors. Although we acknowledge that medium to poorly differentiated HCC nodules can be more confidently diagnosed by FNB than well-differentiated tumors, our approach of comparing intranodular and extranodular tissue and the yield of liver cores

Table 6. Variables Associated with Radiological Diagnosis of HCC According to AASLD Criteria

Features	HCC Diagnosed (n = 29)	HCC Undiagnosed (n = 33)	P Value
Male sex	23 (79)	20 (61)	0.11
Age >66 years	11 (41)	18 (55)	0.19
HCV-positive	21 (72)	24 (72)	0.97
Child-Pugh class A	28 (97)	31 (94)	0.63
AFP >100 ng/mL	4 (14)	3 (9)	0.56
Tumor size 1-2 cm	18 (62)	29 (88)	0.035
Tumor grade 1	2 (7)	16 (48)	0.0003

Data are presented as n (%).

Abbreviations: AASLD, American Association for the Study of Liver Diseases; HCV, hepatitis C virus.

of adequate length as those obtained with a trenchant needle, should have reasonably attenuated the risk of underestimation of tumor grade in our study. The lack of concordance we demonstrated in 28% of paired FNB examinations should not have subverted our correlation analysis in small tumors, because only one of the five discordant nodules was grade I versus grade II, whereas the remaining four nodules were discordant for grade II and III, to give a clinically meaningful discordance between paired FNB examinations of 5% only.

A previous study from our group comparing the accuracy of dynamic contrast imaging techniques and FNB to diagnose HCC in cirrhosis allowed us to assess whether tumor cell grading had any influence on the accuracy of dynamic contrast imaging techniques that are endorsed for the noninvasive diagnosis of HCC.[9] To maximize the diagnostic accuracy of FNB, we used a 21-gauge trenchant needle for microhistology, resulting in tissue cores of 1.6 cm, on average. Moreover, by sampling all patients for both nodular and extranodular liver parenchyma, the differential diagnosis between low-grade tumors and dysplastic macroregenerative nodules was eased.[23] Finally, to evaluate the sensitivity of the study, a set of patients underwent two intranodule biopsies, and the biopsy specimens were blindly examined by two pathologists who were unaware of the clinical findings.

In our study, the diagnostic accuracy of dynamic contrast imaging techniques appeared to be attenuated in well-differentiated tumors compared with less differentiated tumors. This may have clinical implications, because the current standard of care for the radiological diagnosis of HCC, represented by the combination of CE-US and MRI, has been shown to have a sensitivity of 33.3% and a specificity of 100% in the setting of 0.5- to 2-cm tumors occurring in patients with cirrhosis.[4] Similar figures were reported by other studies investigating the combinations of CE-US + CT and CT + MRI in the setting of 1- to 2-cm HCC nodules.[9,24] In the present study, regardless of the dual combination of dynamic contrast imaging technique applied, no more than 13% of grade I tumors $\leq$2 cm were correctly identified on radiological examination, compared with >50% for grade II and grade III tumors of similar size. As a consequence, of the 29 radiologically identified tumors, only 7% were grade I HCC, which in turn accounted for the 48% of tumors that were not identified on radiological examination ($P = 0.0003$). Altogether, these findings reinforce the relationship that exists between arterial vascularization of the tumor, cell grade, and detectability by dynamic contrast imaging that was only partially reported by previous studies.[25-29]

The fact that in our study multivariate analysis showed tumor cell grading and nodule size to be the only two independent predictors of a radiological diagnosis of HCC further reinforces the association between HCC grade and vascularization. The lack of any correlation between tumor size and cell grading in our series of small HCC nodules does not contrast with the well-known correlation between tumor size and cell grading that has been reported in surgical HCC nodules. Medium to large tumors are known to be heterogeneous in cell grading and to be generally less differentiated than small HCC nodules. We were not surprised to find no correlation between tumor grade and serum AFP values, because this could reflect the selection of patients with small tumors that rarely circulate high serum levels of AFP. A correlation between serum AFP levels and tumor cell grade has been reported in other clinical settings,[30] even though AFP synthesis in malignant hepatocytes does not merely reflect cell dedifferentiation, but it is a more complex phenomenon related to HCC heterogeneity.[31] Gene expression studies have shown that HCC subgroups with consistent AFP overexpression are likely related to a progenitor cell phenotype with up-regulation of developmental and imprinting genes mainly occurring in a hepatitis B virus–related background.[32] Most of our patients were hepatitis C–related, and it has also been shown that AFP-negative subgroups are enriched in HCC with different prognosis (i.e., showing both excellent and poor survival).[33]

The grade I tumors that we could not classify as HCC by contrast imaging likely correspond to Barcelona Clinic Liver Cancer stage 0 tumors (very early HCC) originally described in Japan as <2 cm HCCs having a vaguely nodular appearance and an intact portal tract–based structure.[34,35] In the original report, all those tumors were grade I and had a favorable outcome following hepatic resection compared with tumors of similar size with a distinctly nodular pattern that were made out by contrast imaging techniques. The latter tumors were more often dedifferentiated and tended to recur after hepatic resection.[35] The paradigm of radiological diagnosis of HCC in cirrhosis rests on the excess unpaired arteries with respect to portal vein branches, which accounts for the typical vascular pattern of wash-in followed by wash-out, a feature that is expected to be increasingly detected in parallel with tumor growth. Our finding of low rates of contrast wash-in followed by wash-out in grade I tumors in general, and in particular in those <2 cm,

speaks in favor of a correlation between tumor cell grading and arterial vascularization of the tumor, even though it is unclear which of these variables drives the prognosis of HCC.[11] Furthermore, the fact that small tumors not identified by contrast imaging have a benign prognosis ultimately calls for repeat liver biopsy examinations during the time the nodules remain unchanged at imaging, because this approach might help to improve early diagnosis of HCC.

The recent reclassification of small HCC, which resulted from a consensus meeting between eastern and western pathologists, emphasized the role of tumor grading and vascular remodeling in the classification and prognostication of HCC.[11] Indeed, the most differentiated form of very early HCC, which is usually <2 cm, displays grade I histology and grossly shows the vaguely nodular architecture mentioned before, is unlikely to infiltrate the portal vein system and to disseminate into the liver. Interestingly enough, this tumor is characterized by an incomplete neovascularization, whereby it often escapes detection by contrast imaging.[2] Conversely, the small but more aggressive early HCC is characterized by a gross nodular architecture, a less differentiated histology, and a complete and extensive arterial neovascularization. The latter, unlike very early HCC, has a less favorable prognosis, because it is able to infiltrate the portal vein system and to disseminate into the liver in 27% and 10% of cases, respectively.[8]

In conclusion, our study indicates that the accuracy of dynamic contrast imaging techniques to diagnose early HCC in cirrhosis is largely affected not only by the degree of arterial vascularization but also by cell grading of the nodule. Although this observation speaks in favor of a better prognosis for these nodules compared with those readily identified by radiological analysis, it further endorses the need for the histological examination of all small nodules arising in cirrhotic livers that are left undiagnosed by radiology.

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