Improving the Prediction of Hepatocellular Carcinoma in Cirrhotic Patients With an Arterially-Enhancing Liver Mass

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In the United States, cirrhotic patients with known or suspected hepatocellular carcinoma (HCC) are prioritized for liver transplantation. Noninvasive criteria for the diagnosis of HCC rely on arterial enhancement of a mass. The aim of this study was to determine whether clinical, laboratory, and / or radiologic data can improve the prediction of HCC in cirrhotic patients with an arterially-enhancing mass. Between May 2002 and June 2003, dynamic gadolinium-enhanced magnetic resonance imaging (MRI) of consecutive patients with liver cirrhosis and a solid mass were reviewed by 2 radiologists blinded to the clinical diagnosis. Clinical, laboratory, and radiologic data were recorded for all patients. A total of 94 patients with cirrhosis and an arterially-enhancing liver mass were studied, 66 (70%) of whom had HCC. Alpha-fetoprotein (AFP) >20 ng/mL ($P = .029$), tumor size >2 cm ($P = .0018$), and delayed hypointensity ($P = .0001$) were independent predictors of HCC. Delayed hypointensity of an arterially-enhancing mass had a sensitivity of 89% and a specificity of 96% for HCC. The presence of delayed hypointensity was the only independent predictor of HCC among patients with arterially-enhancing lesions <2 cm (odds ratio, 6.3; 95% confidence interval [CI], 1.8-13), with a sensitivity of 80% and a specificity of 95%. In conclusion, delayed hypointensity of an arterially-enhancing mass was the strongest independent predictor of HCC, regardless of the size of the lesion. If additional studies confirm our results, the noninvasive criteria utilized to make a diagnosis of HCC should be revised. (*Liver Transpl 2005;11:281–289.*)

The incidence of hepatocellular carcinoma (HCC) in western countries is rising and is expected to further increase over the next 10–15 years. Furthermore, HCC has become a leading indication for liver transplantation in the United States due to granting of additional model for end-stage liver disease points to patients with known or suspected HCC.[1] To date, cytopathologic analysis remains the gold standard for a definitive diagnosis of HCC. However, liver biopsy carries a risk of bleeding and tumor seeding,[2,3] and is not always possible due to inaccessible location of the mass, ascites, and / or coagulopathy. In addition, the tissue sample may be insufficient for a definitive diagnosis. A study by Torzilli et al.[4] indicated that the preoperative diagnosis of HCC based on clinical, laboratory, and imaging data had an accuracy of 99%, suggesting that the use of needle biopsy for a diagnosis of HCC can be drastically reduced. The European Association for the Study of Liver Disease HCC Conference has provided nonhistologic criteria for a diagnosis of HCC,[5] and the United Network for Organ Sharing (UNOS) policy for the transplantation of patients with HCC, does not require histologic confirmation of the tumor (http://www.unos.org/PoliciesandBylaws from July 2004). The noninvasive criteria for the diagnosis of HCC proposed by UNOS rely heavily on imaging characteristics, in particular arterial enhancement. Using the UNOS criteria at a single center in the United States, 33% of patients transplanted for HCC did not have tumor after the explant was examined and 63% of the misdiagnosed tumors had arterially-enhancing lesions ≤2 cm in diameter.[6] These data suggest that arterial enhancement is a consistent but nonspecific feature of HCC and is less useful in cirrhotic patients with small (i.e., <2 cm) masses.

Magnetic resonance imaging (MRI) has been proposed as a sensitive and specific imaging modality for the evaluation of liver masses in patients with cirrhosis. A total of 3 studies of MRI with explant correlation showed a sensitivity of 55, 76, and 77%, and a specificity of 57, 75, and 86%, respectively, for the detection of

Abbreviations: HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; AFP, alpha-fetoprotein; UNOS, United Network for Organ Sharing; NSEN, nonspecific enhancing nodules.

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HCC in patients with cirrhosis.[7–9] These studies indicated that the sensitivity of MRI for a diagnosis of HCC decreases significantly with lesions <2 cm in diameter.

In the present study, 94 consecutive patients with known cirrhosis and an enhancing liver mass were prospectively evaluated with dynamic gadolinium-enhanced MRI. The aim of this study was to determine whether the combination of clinical, laboratory, and / or radiologic data can improve the prediction of HCC, especially among patients with enhancing masses <2 cm in diameter.

Patients and Methods

Study Population

Between May 2002 and June 2003, consecutive patients with cirrhosis and a suspected liver mass who underwent MRI for further evaluation were included. The study was approved by the Institutional Review Board of the University of Michigan. The diagnosis of cirrhosis was made by histology (n = 67) or by the presence of clinical, laboratory, and / or ultrasound features of portal hypertension (n = 39).[10] These patients were enrolled from the Liver Clinics at the University of Michigan Medical Center. The indications for MRI included: an elevated (>20 ng/mL) alpha fetoprotein (AFP) level; suggestion of a mass on ultrasound or a computed tomography scan without arterial phase; or unexplained symptoms (such as abdominal pain, increased ascites, jaundice, or weight loss). The etiology of liver disease was determined as previously described.[11] Patient demographics, cause of cirrhosis, presence of ascites or hepatic encephalopathy, serum levels of aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, albumin, creatinine, AFP, international normalized ratio, model for end-stage liver disease score, Child-Turcotte-Pugh score, white blood cell count, and platelet count were obtained.

MRI Technique

All studies were performed on a 1.5-Tesla scanner (Signa; General Electric Medical Systems, Milwaukee, WI), and included the following sequences: axial longitudinal relaxation time–weighted, dual-echo gradient recalled-echo; axial transverse relaxation time–weighted fat-suppressed fast-recovery fast spin-echo; and dynamic gadolinium-enhanced imaging with a 3-dimensional spoiled gradient recalled-echo sequence.[12] This sequence was acquired precontrast, and following the injection of 20-cc gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ) via a power injector in the arterial-dominant, portal-venous, and equilibrium (2-minute delayed) phases of enhancement, followed by a delayed acquisition at 5 minutes postgadolinium.

MRI Data

The magnetic resonance images were reviewed by 2 radiologists (H.K.H. and H.V.N.) with expertise in hepatic imaging, prior to the actual knowledge of the etiology of the liver mass. The radiologists reviewed the images independently in the 1st 1 of 3 of the cases, and simultaneously with the final opinion rendered by consensus in the remaining 2 of 3 of the cases. The purpose of the independent review was to obtain a measure of agreement between readers. While aware of the diagnosis of cirrhosis but blinded to the remainder of the patient's clinical data, the 2 radiologists were asked to evaluate the imaging studies for the presence of an arterially-enhancing mass, including homogeneously-, heterogeneously-, and ring-enhancing lesions. The number, size, location, signal characteristics, lesion hypointensity relative to surrounding liver in the portal-venous, 2- or 5-minute postgadolinium delayed-phases, and the presence of vascular invasion was recorded for each case. Finally, the radiologists were asked to provide a global consensus on the probability that the lesion is HCC by assigning a high or low probability based on the above characteristics and their overall impression.

The radiologists used standard MRI features to characterize focal arterially-enhancing lesions in patients with cirrhosis.[7,13–16] Arterially-enhancing nodules were classified as 1 of 4 lesions: HCC included all arterially enhancing lesions >2 cm regardless of their other imaging features, and all arterially-enhancing lesions with transverse relaxation time–hyperintensity and / or delayed hypointensity regardless of their size; dysplastic nodule included ≤2-cm arterially-enhancing lesions with hyperintense longitudinal relaxation time signal, no transverse relaxation time hyperintensity, and no delayed hypointensity compared to the rest of the liver parenchyma; nonspecific enhancing nodules (NSEN) included ≤2-cm arterially-enhancing lesions with no corresponding signal changes on any of the other imaging sequences; and hemangiomas, based on a well-defined lesion with low longitudinal relaxation time and very high transverse relaxation time signal intensity compared to liver parenchyma, and one of 3 enhancement patterns: early uniform enhancement and delayed contrast retention; early peripheral nodular enhancement with centripetal progression to complete filling and delayed contrast retention; and early peripheral nodular enhancement with centripetal progression to incomplete filling and delayed contrast retention with nonenhancing central scar.

Verification

The final diagnosis of HCC and regenerative and dysplastic nodules was determined by histologic examination of the lesion of interest seen on MRI that led to the interpretation rendered by the radiologists. Hemangioma was verified by typical imaging features and NSEN by follow-up imaging. Patients with HCC were staged according to the UNOS-modified Tumor Node Metastasis staging system. Patients considered to have NSEN had a minimum of 3 (mean, 4 ± 2; median, 4; range, 3-9) MRI examinations over a mean follow-up of 26 ± 12 months (median, 25 months; range, 13-34) with no change in the number, size, and imaging features of the lesions, or the AFP value.

Statistical Analysis

Log transformation was used for AFP to account for skewness. Kappa statistics was used to determine the level of agreement between the 2 radiologists for the cases read independently (with regard to tumor size, number of lesions, presence of arterial enhancement, signal characteristics, and delayed hypointensity). We performed a per-patient analysis in which the final diagnosis of the main lesion seen on MRI, and later verified by pathology or imaging follow-up, was the main diagnosis. Pearson correlation was used to correlate the consensus diagnosis of the radiologists to the actual diagnosis of the liver mass. A 1-way analysis of variance was used to determine differences in continuous variables among the various diagnoses of liver masses. The Wilcoxon test was used for model for end-stage liver disease score and tumor size. Fisher's exact test was used to determine differences among categoric variables.

Univariate analysis was performed to identify demographic, laboratory, clinical, and radiologic correlates of HCC. The laboratory and clinical criteria included etiology of liver disease, albumin, creatinine, total bilirubin, AFP, international normalized ratio, model for end-stage liver disease score, Child-Turcotte-Pugh score, white blood cell count, and platelet count. The radiologic criteria examined were the presence of arterial enhancement, delayed hypointensity, number of lesions, largest diameter of the main lesion, and portal vein thrombosis. Variables with P values $<.10$ in the univariate analysis were then subjected to multivariate analysis by forward logistic regression to identify independent factors associated with HCC. The adjusted odds ratio and its confidence interval were obtained from the final model. A 2-tailed P value of $<.05$ was used to determine statistical significance. All analyses were performed using SAS 8.1 (SAS Institute, Cary, NC).

Results

Patients

During the study period, 106 patients with cirrhosis and a suspected liver mass underwent MRI. A total of 12 patients were excluded from the analysis; 8 had no visible mass on MRI and 4 had simple hepatic cysts. The 8 patients in whom no mass was identified have been followed for a mean of 18.3 months (range, 14-29 months) and have undergone a mean of 2.1 $\pm$ .7 MRI examinations with no evidence of an enhancing mass. The remaining 94 patients form the basis of this study. Demographics, etiology of underlying liver disease, and laboratory values at presentation for the patients who had solid arterially-enhancing liver mass(es) on MRI are listed in Table 1.

Liver Masses

A total of 65 (69%) patients had a diagnosis of HCC, 1 (1%) had a regenerative nodule, and 3 (3%) had dysplastic nodules based on histologic analysis. A total of 20 (21%) patients were diagnosed with nonspecific enhancing nodules for which histology was not possible due to the small size of the nodules; all had follow-up imaging showing no change in number or size of the lesions over a period of 13–34 months. A total of 4 of the 65 patients with HCC were initially considered to have nonspecific enhancing nodules, but interval growth of the nodules on repeat MRI after 6 months led to biopsies that revealed HCC. Delayed-phase hypointensity was not present on the initial MRI, but became apparent during follow-up imaging when HCC was diagnosed. A total of 5 patients (4%) had hemangiomas based on typical MRI features. Figure 1 shows the algorithm of how the main liver mass diagnosis was achieved.

Radiologic Characteristics of the Liver Masses

An average of 2.6 liver masses per patient (range, 1-6) and a mean maximal diameter of 3.6 cm (range, .5-15) were found. There were 26 (28%) patients with lesions <2 cm. A total of 71 (76%) patients had unilobar masses. A total of 60 (64%) had delayed hypointensity of the arterially-enhancing mass, and 5 (5%) had portal vein thrombosis. The imaging characteristics of the masses according to the diagnoses are shown in Table 2. The 2 radiologists had excellent agreement with regards to the probability of HCC and radiologic characteristics, with a kappa value of .837 (95% confidence interval [CI], .77-.90). Furthermore, there was excellent correlation between the radiologists' consensus diagnosis and the final pathologic diagnosis of HCC (correlation coefficient, .64; 95% CI, .78-.89; $P < .001$). Examples of a patient with a HCC and a nonspecific enhancing nodule are shown in Figures 2 and 3, respectively.

A total of 23 patients were placed on the liver transplant waiting list. A total of 7 patients had suspected HCC (1 had an AFP value >200 with an arterially-enhancing lesion >2 cm; 3 had an arterially-enhancing lesion >2 cm; 3 had a suspicious lesion that was treated with radiofrequency ablation prior to transplant), and 16 had a histology-confirmed HCC. MRI detected 39 nodules (maximal diameter, 2.6 $\pm$ .5) in these patients, while 34 (maximal diameter, 2.9 $\pm$ 1.4) nodules were detected at the time of explant examination ($P = .405$ for difference in number of nodules; $P = .32$ for difference in diameter). Of the 34 nodules identified by explant examination, 1 was a high-grade dysplastic nod-

Table 1. Comparison of Cirrhotic Patients With HCC Vs. Benign Liver Masses*

	HCC (n = 65)	NSEN (n = 20)	DN (n = 3)	RN (n = 1)	Hemangioma (n = 5)	All (n = 94)
Age (years)	58 ± 10†	53 ± 8	45 ± 7	53	52 ± 9	56 ± 11
Gender (M:F)	45 : 20	13 : 7	2 : 1	1 : 0	4 : 1	65 : 29
Ethnicity (NHW:AA:As:H)	46 : 9 : 5 : 5	16 : 3 : 0 : 1	2 : 0 : 0 : 1	1 : 0 : 0 : 0	3 : 1 : 0 : 1	68 : 13 : 5 : 8
Etiology n (%)						
HCV	46 (71)	10 (50)	2 (67)	1 (100)	2 (40)	61 (65)
HBV	3 (5)	4 (19)	1 (33)	0	2 (40)	10 (11)
Cryptogenic	12 (18)	3 (15)	0	0	0	15 (16)
Alcohol	4 (6)	2 (12)	0	0	1 (20)	7 (7)
PBC	0	1 (4)	0	0	0	1 (1)
Indication n (%)						
AFP > 20 ng/mL	21 (31)	7 (33)	1 (33)	0	0	29 (31)
Abnormal US/CT	41 (64)	13 (67)	2 (67)	1 (100)	5 (100)	62 (66)
Symptoms	3 (5)	0	0	0	0	3 (3)
AFP (median) ng/mL n (%)	34†	13.3	98.8	56	2.3	21.2
<20	26 (39)	13 (67)	1 (33)	0	5 (100)	45 (48)
20–200	21 (33)	7 (33)	2 (67)	1 (100)	0	31 (33)
>200	18 (28)	0	0	0	0	18 (19)
MELD score	11 ± 4‡	9 ± 2	8 ± 2	9	7 ± 0.2	9.4 ± 3.7
CTP score	7.1 ± 1	6.9 ± 1	7.2 ± 1.4	8	6.3 ± 0.7	7 ± 2
Total bilirubin (mg/dL)	2.4 ± 2	1.1 ± .6	1.2 ± .6	1.8	.8 ± .3	1.95 ± 1.3
Platelet (k/mm^3)	112 ± 52	114 ± 61	106 ± 48	113	118 ± 46	115 ± 41
Listed for OLT n (%)	21 (31)	0	1 (33)	1 (100)	0	23 (24)
Staging	5 / 16 / 27 / 18	NA	NA	NA	NA	NA

Abbreviations: HCC, hepatocellular carcinoma; NSEN, non-specific enhancing nodule; DN, dysplastic nodule; RN, regenerative nodule; NHW, non-Hispanic white; AA, African American; As, Asian; H, Hispanic; HCV, hepatitis C; HBV, hepatitis B; PBC, primary biliary cirrhosis; US, ultrasound; CT, computed tomography; MELD, model for endstage liver disease; CTP, Child-Turcotte-Pugh score; OLT, orthotopic liver transplant.
*Staging is the UNOS TNM system.
†P = .005 HCC vs. DN, NSEN, Hemangioma.
‡P = .006 HCC vs. DN, NSEN, Hemangioma.

ule (1 patient), 1 was a regenerative nodule (1 patient), and 32 (21 patients) were HCC on explant examination. The patient with a regenerative nodule had an enlarging mass from 8 mm (initially classified as a non-specific enhancing nodule) to 2.0 cm by MRI over a 12-month period, and the lesion had homogeneous arterial enhancement without delayed hypointensity.

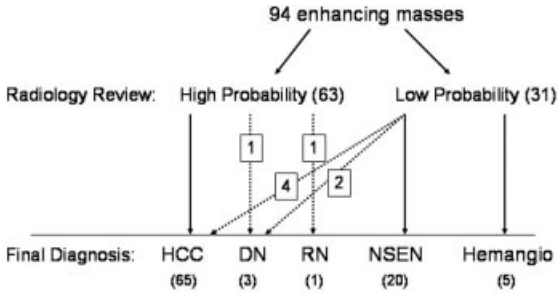

Figure 1. Algorithm indicating how patients with cirrhosis and a liver mass were evaluated.

Of the 37 nodules seen on MRI in the HCC patients, 33 had delayed hypointensity (21 patients transplanted for HCC had arterial enhancement in the main nodule and 20 had delayed hypointensity).

Predictors of HCC

In the univariate analysis, age >50 years, AFP >20 ng/mL, model for end-stage liver disease (MELD) score >10, size >2 cm, and the presence of delayed hypointensity of an arterially-enhancing mass were predictors of HCC. In the logistic regression model, AFP >20 ng/mL (P = .029), tumor size >2 cm (P = .0018), and delayed hypointensity of an arterially-enhancing mass (P = .0001) were independent predictors of HCC (Table 3). The presence of delayed hypointensity of an arterially-enhancing mass had a sensitivity of 89% (59 / 65 patients with HCC) and a specificity of 96% (1 – [1 / 29] without HCC) in predicting a diagnosis of HCC.

Table 2. Radiological Characteristics of the Liver Masses*

	HCC (n = 65)	NSEN (n = 20)	RN (n = 1)	DN (n = 3)	Hemangioma (n = 5)	All (n = 94)
No. of mass	2.5 ± 1.4	2.6 ± 1.8	1	1.8 ± 1.3	2 ± 2.6	2.6 ± 1.6
n (%) 1	21 (33)	11 (55)		3 (100)	2 (40)	36 (38)
n (%) 2	15 (23)	4 (20)		0	1 (20)	20 (18)
n (%) ≥3	29 (44)	5 (25)		0	2 (40)	36 (38)
Size (cm)	4.3 ± 3†	1.1 ± 0.2	2.0	2.2 ± 1.3	4.8 ± 7	3.6 ± 3
n (%) <2	5 (8)	20 (100)	0	1 (33)	0	26 (28)
n (%) ≥2	60 (92)	0	1 (100)	2 (6)	5 (60)	68 (72)
Location (R:L:B)	39 : 10 : 16	11 : 4 : 5	1 : 0 : 0	3 : 0 : 0	2 : 1 : 2	56 : 15 : 23
Arterial enhancement n (%)	65 (100)	20 (100)	1 (100)	3 (100)	5 (100)	94 (100)
Delayed hypointensity n (%)	59 (89)‡	1 (5)	0	0	0	60 (64)
Portal vein thrombosis n (%)	5 (8)‡	0	0	0	0	5 (5)

Abbreviations: HCC, hepatocellular carcinoma; NSEN, non-specific enhancing nodule; RN, regenerative nodule; DN, dysplastic nodule; R, right; L, left; B, bilobar.
*Data presented as mean ± SD unless indicated otherwise.
†$P < .001$ HCC vs. DN, NSEN.
‡$P < .001$ HCC vs. DN, NSEN, and Hemangioma.

Table 4 compares the clinical and radiologic characteristics of the patients with liver masses <2 or ≥2 cm. A total of 5 patients with HCC had lesions <2 cm in diameter. All 5 HCC patients with arterially-enhancing lesions <2 cm had delayed hypointensity, but only 1 of 21 (5%) patients with benign arterially-enhancing liver mass had delayed hypointensity ($P = .001$). The univariate analysis showed that age >50 years, AFP > 20 ng/mL, and delayed hypointensity were associated with HCC lesions <2 cm. However, the presence of delayed hypointensity was the only independent predictor of HCC among patients with HCC and lesions <2 cm (odds ratio, 6.3; 95% CI, 1.8-13). For arterially-enhancing lesions <2 cm, the presence of delayed hypointensity had a sensitivity of 80% (4 / 5 in patients with HCC) and a specificity of 95% (1 – [1 / 21] in patients without HCC) for the diagnosis of HCC.

Discussion

In this prospective study of 94 cirrhotic patients, we found that delayed hypointensity of an arterially enhancing lesion was the most important independent predictor for a diagnosis of HCC regardless of the tumor size. Arterial enhancement (vascularity) is considered an essential characteristic of HCC,[17,18] and is used as the only radiologic feature for noninvasive diagnosis of HCC by UNOS. However, arterial enhancement is a nonspecific feature, and may be seen in other benign lesions such as hemangiomas (type 1), focal nodular hyperplasia, hepatic adenoma, dysplastic nodules, and, rarely, regenerative nodules.[16] Furthermore,

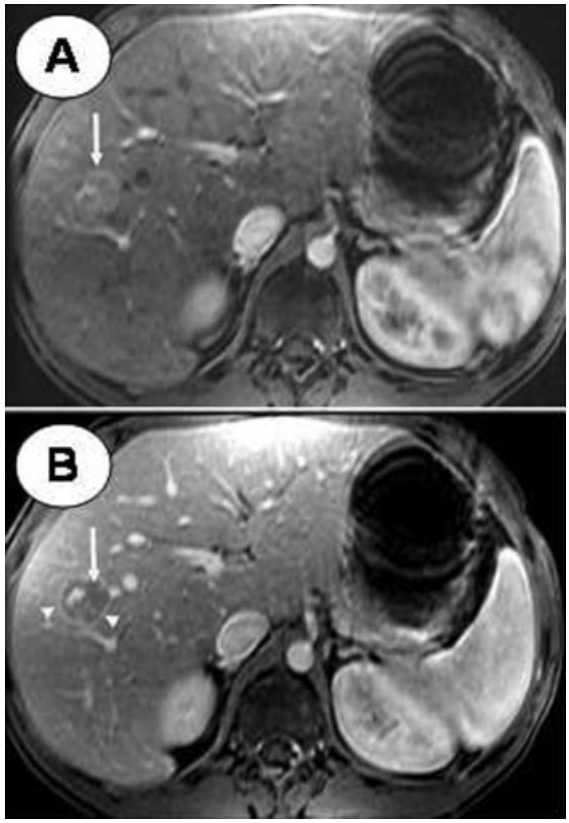

Figure 2. MR imaging of HCC in a cirrhotic patient. Axial dynamic magnetic resonance images through the liver in the arterial-phase (A), and at 2 minutes following gadolinium injection (B). There is a 2-cm arterial-enhancing lesion (arrow) in the right lobe, which becomes hypointense (arrow) to the liver in the delayed phase. Biopsy showed the lesion to be HCC. Note the pseudocapsule (arrowheads) around the lesion on the 2-minute delayed postgadolinium image.

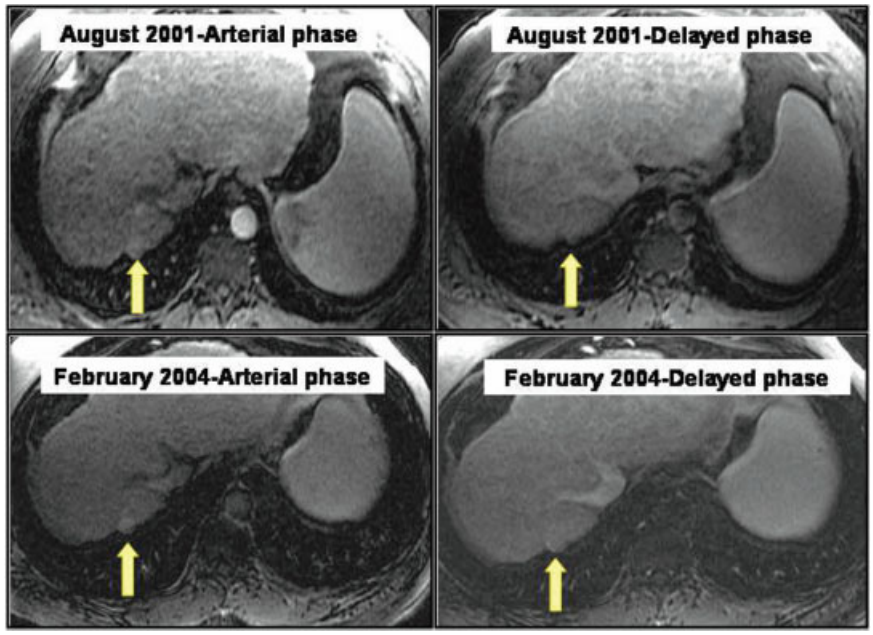

Figure 3. A 1.5 × 1.6 cm arterially-enhancing nodule (arrows) remains stable between August 2001 and February 2004. The lesion does not show hypointensity (arrows) on delayed postgadolinium imaging. Note that the lesion is better seen on the delayed image of 2004. The patient underwent 6 scans between the dates mentioned above. Due to its stability, this lesion was labeled as a NSEN.

vascular abnormalities commonly seen in cirrhotic livers, such as nontumorous arterioportal shunts, also enhance in the arterial phase and may mimic HCC.[15] Longitudinal relaxation time and transverse relaxation time signal characteristics may help distinguish some of these lesions, but are not always helpful.[19] A review by UNOS of 666 patients with HCC in whom the explant pathology report was available showed that 146 (22%) patients had no tumor on explant examination, and 68 (10%) had no nodule or evidence of HCC.[20] The reliance on arterial enhancement alone led to a significant number of patients receiving higher priority for transplant than was necessary. In our study, arterial enhancement was present in all patients with HCC and cirrhotic patients with other liver masses. By contrast, delayed hypointensity of the arterially enhancing mass was present in 89% of the patients with HCC and only 5% of patients with other arterially-enhancing liver masses.

Table 3. Independent Predictors of HCC

Variable	OR (95% CI)	*P* Value
AFP > 20 ng/mL	11.7 (2.3–30.7)	.02
Size > 2 cm	27.9 (3.5–36)	.001
Delayed-hypointensity*	61 (3.8–73)	.0001

*Of an arterially enhancing mass.

The exact reason why HCC lesions become hypointense compared to surrounding liver parenchyma on delayed postgadolinium imaging is unknown. The total number of intranodular arteries (preexisting hepatic arteries and neovascularized arteries) is often greater in HCC nodules than it is in the surrounding nonneoplastic hepatic parenchyma.[21,22] It is possible, therefore, that early venous drainage (washout) via neovascularity is the cause for delayed hypointensity. It is also possible that there is no early venous drainage but lesions appear relatively hypointense compared to surrounding fibrotic parenchyma, which retains contrast and appears hyperintense on delayed imaging, or that the lesion does not have portal venous supply and appears hypointense relative to the surrounding liver.[23] We avoided the term "washout" and used delayed hypointensity instead, since gadolinium washout may not be the only cause for lesion hypointensity. Moreover, we did not quantitatively evaluate for gadolinium washout; we only qualitatively compared the lesion signal intensity relative to that of surrounding parenchyma.

The diagnosis of a solid liver mass in patients with cirrhosis is a clinical challenge for radiologists and cli-

Table 4. Comparison of Patients With Lesions < and > 2 cm

Variable	>2 cm (n = 67)	<2 cm (n = 27)	*P* Value
Age	58 ± 10	52 ± 8	.005
Gender (M:F)	47 : 20	18 : 9	.496
Race (NHW:AA:As:H)	48 : 9 : 4 : 6	20 : 4 : 1 : 2	.629
Etiology (HCV:HBV:Crypto:Alc)	44 : 7 : 10 : 5	17 : 3 : 5 : 2	.643
AST	94 ± 22	88 ± 27	.452
ALT	73 ± 18	67 ± 25	.395
Bilirubin (ng/mL)	1.9 ± 2	1.3 ± 0.7	.104
MELD	10.2 ± 4	9.4 ± 2	.108
CTP	7.2 ± 1.4	6.8 ± 1.3	.243
Platelet	113 ± 21	111 ± 34	.121
AFP (ng/mL) n (%)	2941 ± 12859	51.6 ± 139	.006
<20 ng/mL	26 (38)	17 (65)	
>20 ng/mL	39 (57)	9 (35)	
Lesion number	2.5 ± 1.4	2.3 ± 1.8	.916
Arterial enhancement n (%)	66 (97)	25 (96)	.229
Delayed hypointensity n (%)	54 (81)	6 (23)	<.0001
Portal vein thrombosis n (%)	5 (8)	0	0.02
Liver mass diagnosis			<0.001
HCC	60	5	
DN	2	1	
RN	1	0	
NSEN	0	20	
Hemangioma	5	0	

Abbreviations: NHW, non-Hispanic white; AA, African American; As, Asian; H, Hispanic; HCV, hepatitis C; HBV, hepatitis B; Crypto, cryptogenic; Alc, alcohol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MELD, model of endstage liver disease; CTP, Child-Turcotte-Pugh score; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; DN, dysplastic nodule; RN, regenerative nodule; NSEN, non-specific enhancing nodule.

nicians. Only 1 other study has evaluated radiologic and clinical characteristics as predictors of HCC.[24] The authors found that the number of lesions (odds ratio, 1.5; 95% CI, 1.03-2.31), AFP level (odds ratio, 3.2; 95% CI, .92-9.86), and delayed hypointensity (described as venous washout) (odds ratio, 9.2; 95% CI, 1.89-45) were found to be the most important predictors of HCC. However, that study did not include cirrhotic patients with benign liver masses as controls, the data was not stratified according to tumor size, and the imaging characteristics were based on retrospective review of radiology reports. In our study, cirrhotic patients with benign liver masses were also included, the images were prospectively read by 2 radiologists who were blinded to clinical data and final diagnosis, and a broader range of clinical and laboratory values were analyzed.

Correct interpretation of liver masses in patients with cirrhosis can be difficult due to the underlying nodularity, the dual blood supply, and the hemodynamic disturbances associated with cirrhosis.[25] Hepatic lesions <2 cm in size that enhance in the arterial phase are even more problematic; some studies found that less than 20% of these lesions turn out to be HCCs.[26,27] We showed that only 19% (5 / 26) of arterially-enhancing lesions <2 cm in diameter were HCC. We also showed that the presence of delayed hypointensity in arterially-enhancing nodules <2 cm was predictive of HCC, with a sensitivity of 80% and specificity of 95%. In addition, 4 patients were initially classified as having an NSEN that on subsequent MRI showed interval growth and delayed hypointensity, leading to the diagnosis of HCC. Although we used specific criteria to classify arterially-enhancing lesions into NSEN, dysplastic nodule, and HCC, there is overlap in the signal characteristics of these lesions, and the purpose of the NSEN classification was to ensure imaging follow-up of these small arterially-enhancing lesions <2 cm, which are difficult to visualize and biopsy with ultrasound. Thus, for patients with arterially-enhancing nodules <2 cm, MRI should be repeated in 6 months to determine interval growth and imaging characteristics in the delayed phase of the suspected nodule.

We acknowledge that there are several limitations with this study. First, our study involved 2 academic radiologists with an interest in hepatic MRI, who have

worked together for several years so our results may not be generalizable to other centers. Second, histologic diagnosis was not available for all patients classified as nonspecific enhancing nodules because of the technical difficulties of performing guided biopsies on such small lesions. Nonetheless, all patients had at least 3 repeat MRI examinations and were followed for a median of 25 months with no change in the number, size, or imaging characteristics of the lesions, making it very unlikely that these nodules were HCC. Recent reports indicate that nodules <2 cm in patients with cirrhosis undergoing liver transplantation were common, and pathologic examination revealed that the majority were nondysplastic nodules[28] or showed no growth over time.[29] It is possible that most of the nonspecific enhancing nodules are regenerative nodules. Finally, we do not have explant examination in all our patients in order to do a lesion-by-lesion analysis. However, in the 23 patients who underwent liver transplantation there was excellent correlation between MRI and explant examination with regard to the number of nodules and the maximal diameter of the largest lesion, and the majority of the nodules were HCC.

In summary, our prospective study of patients with cirrhosis and a liver mass showed for the 1st time that delayed hypointensity of an arterially-enhancing mass was the strongest independent predictor of HCC, regardless of the size of the lesion. The only clinical or laboratory parameter that was an important independent predictor of HCC was an AFP >20 ng/mL in nodules >2 cm. However, none of the other laboratory, clinical, or demographic data were important predictors of HCC. Our data showed that not all arterially-enhancing masses in patients with cirrhosis are due to HCC. Further studies in a larger population of patients and in other centers should be performed to validate our results. Our findings may have important implications in defining noninvasive criteria for diagnosis of HCC and in reducing unnecessary liver transplants in patients with compensated cirrhosis and benign liver masses.

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