Focal Lesions in Cirrhotic Explant Livers: Pathological Evaluation and Accuracy of Pretransplantation Imaging Examinations

Louis Libbrecht,[*] Didier Bielen,[†] Chris Verslype,[‡] Dirk Vanbeckevoort,[†] Jacques Pirenne,[§] Frederik Nevens,[‡] Valeer Desmet,[*] and Tania Roskams[*]

Imaging detection and diagnosis of hepatocellular carcinomas (HCCs) and dysplastic nodules (DNs) in cirrhotic patients is important because the number, size, and type of focal lesions strongly influence patient management. Focal lesions detected by imaging examinations during pretransplantation evaluation were correlated with focal lesions detected during detailed pathological examination of 49 cirrhotic explant livers. Within 6 months before transplantation, color Doppler ultrasonography (US), contrast-enhanced computed tomography (CT), and magnetic resonance (MR) imaging were performed in 94%, 33%, and 55% of patients, respectively. In 2% to 8% of patients, different types of benign focal lesions were present, and a considerable proportion was interpreted as (pre)malignant on imaging examination. US detected only the largest HCCs (patient sensitivity, 40%; specificity, 100%) and no DNs. On a per-patient basis, contrast-enhanced CT and MR imaging had poor sensitivity (20% and 27%, respectively) and good specificity (100% and 94%, respectively) for DNs. Patient sensitivity and specificity of both techniques for HCC were reasonable (50% for CT, 70% for MR imaging) and good (79% for CT, 82% for MR imaging), respectively. Neither technique was able to detect smaller (pre)malignant lesions. As a consequence, 10% of patients underwent transplantation, although they exceeded the tumor number limit. Currently used imaging techniques cannot correctly determine the exact tumor burden in some cirrhotic patients. Regular contrast-enhanced MR examination of cirrhotic patients waiting for liver transplantation is the best tool for the early detection of (pre)malignant lesions. (*Liver Transpl 2002;8:749-761.*)

Hepatocellular carcinoma (HCC) usually develops in a cirrhotic liver and is the result of a multistep process.[1-3] Based on morphological criteria, low-grade dysplastic nodules ([DNs] LGDNs) and high-grade DNs (HGDNs) have been proposed to represent distinct stages in the multistep process of hepatocarcinogenesis.[4] Recent immunohistochemical, molecular, and clinical follow-up studies support this morphological classification and have confirmed that LGDNs and HGDNs are precursor lesions of HCC, carrying a considerable risk for malignant transformation.[5-12]

Imaging detection and diagnosis of these premalignant and malignant focal lesions in a patient with liver cirrhosis is clinically very important because their number, size, and type strongly influence patient management.[13] For example, liver transplantation is the treatment of choice for HCC in a cirrhotic liver when the number and size of tumors present are limited, whereas it should not be performed when there is advanced HCC.[14,15]

Most previous studies have relied on needle biopsies or partial liver resections of focal lesions that were detected by imaging to evaluate the accuracy (sensitivity and specificity) of routine imaging techniques to diagnose HCCs and DNs in cirrhotic liver.[16-19] However, this type of study cannot correctly determine the accuracy of an imaging technique because patients with (false and true) negative imaging findings are not included, and it sometimes is impossible to distinguish premalignant from malignant lesions on a needle liver biopsy. The true accuracy of an imaging technique can be determined only when imaging data are correlated with the so-called gold standard, which is a detailed pathological examination of complete explant livers with classification of detected focal lesions according to internationally accepted and used criteria.[4,20] Routine slicing of the liver with 1- to 2-cm thick intervals does not suffice because a considerable proportion of focal lesions remain undetected when this rather broad sectioning is performed.[21] To date, only a few studies have used this gold standard.[22,23]

In the present study, we performed a thorough macroscopic and microscopic examination of 49 cirrhotic explant livers to determine the prevalence, size, and location of different types of focal lesions in cirrhotic

*From the *Departments of Pathology, †Radiology, ‡Hepatology, and §Abdominal Transplant Surgery, University Hospitals, University of Leuven, Leuven, Belgium.*

Address reprint requests to Louis Libbrecht, MD, PhD, Department of Pathology, University Hospitals, University of Leuven, Minderbroedersstraat 12, 3000 Leuven, Belgium. Telephone: 32-16-336588; FAX: 32-16-336548; E-mail: louis.libbrecht@uz.kuleuven.ac.be

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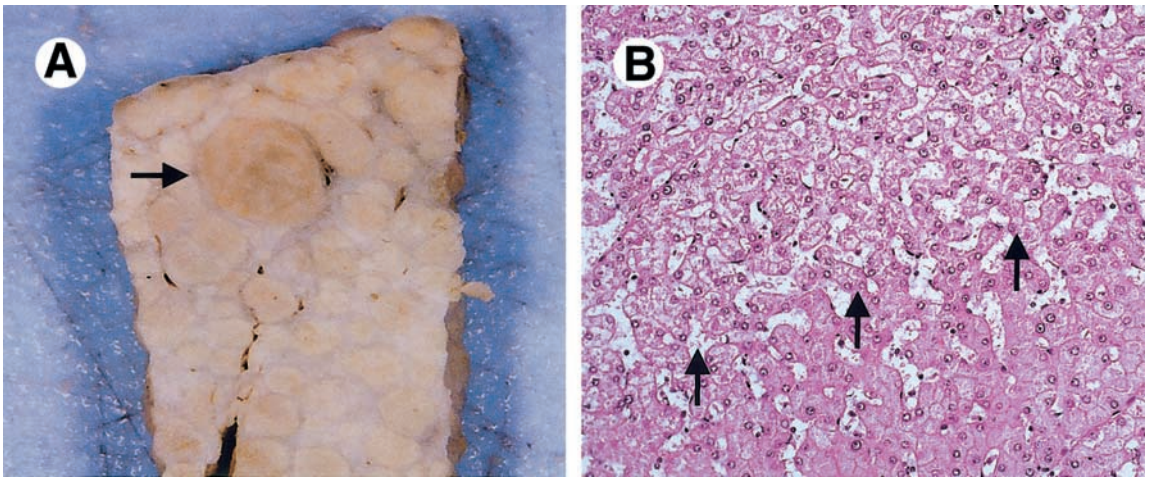

Figure 1. (A) LGDN with a diameter of 5 mm (arrow). (B) Clone-like population of hepatocytes within the LGDN showing clear cytoplasm and nuclear deviation toward sinusoids (arrows). (Original magnification: [B] ×200.)

liver. By correlating these pathological results with pretransplantation clinical and imaging data, we were able to evaluate the accuracy of different imaging techniques performed during pretransplantation evaluation.

Patients and Methods

Pathological Examination of Explant Livers

Between January 2000 and July 2001, a total of 52 patients with liver cirrhosis underwent liver transplantation at our institution. All cirrhotic explant livers were examined without knowledge of clinical or imaging data by using the following protocol.

After explantation, the cirrhotic liver was fixed in formalin for 24 to 48 hours. Subsequently, the liver was sectioned at 5-mm intervals, and each section was carefully inspected. Every lesion that was macroscopically different from the surrounding liver tissue in terms of size, color, texture, or degree of bulging beyond the cut surface was removed and embedded in paraffin. Maximal diameter and segmental localization of each focal lesion was noted. Liver segments were defined according to Couinaud.[24,25] Four-micron thick sections were made from the paraffin-embedded material and routinely stained with hematoxylin and eosin and Gordon and Sweet reticulin.[26] Microscopic examination of sections was performed by two hepatopathologists (L.L. and T.R.) in consensus using a multiheaded microscope.

Each focal lesion was classified according to internationally accepted criteria as LGDN, HGDN, HCC, or other type

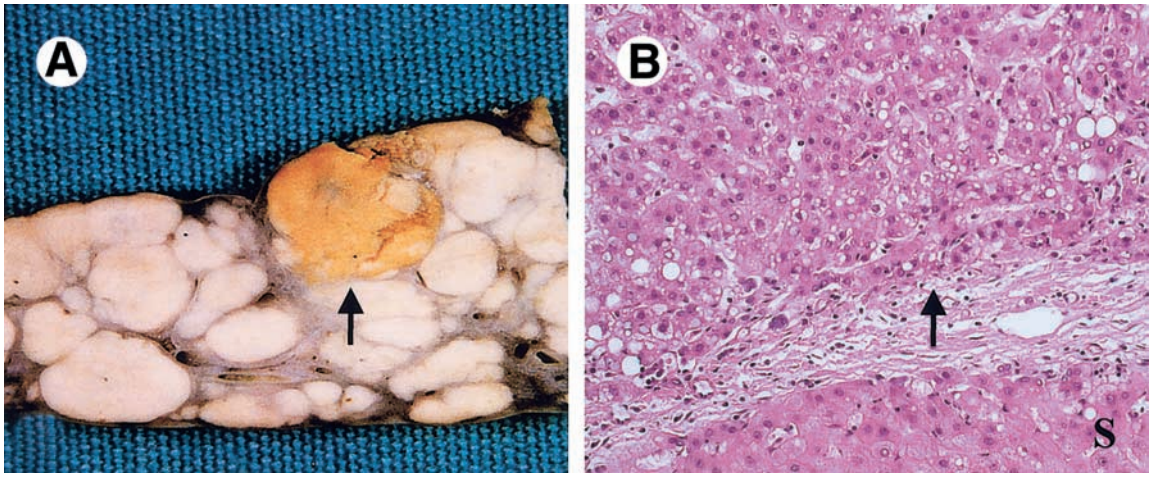

Figure 2. (A) HGDN with a diameter of 7 mm (arrow). (B) The HGDN (arrow) contains hepatocytes with an increased nucleocytoplasmic ratio and nuclear hyperchromasia compared with surrounding cirrhotic nodules (S). (Original magnification: [B] ×200.)

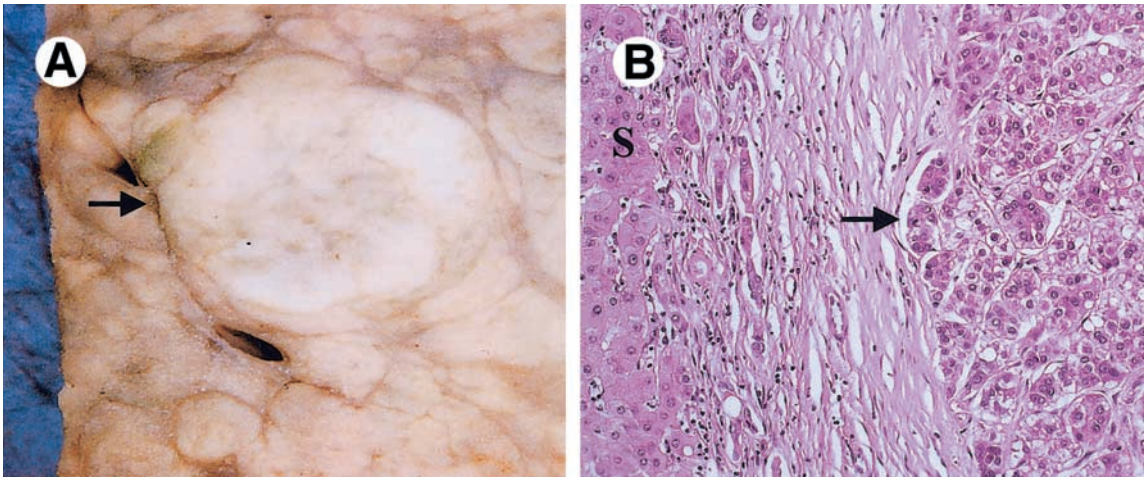

Figure 3. (A) HCC with a diameter of 15 mm (arrow). (B) The HCC (arrow) consists of hepatocytes forming thick plates. Hepatocytes show an increased nucleocytoplasmic ratio, nuclear hyperchromasia, and cytoplasmic basophilia. (S, surrounding cirrhotic nodule; original magnification: [B] ×200.)

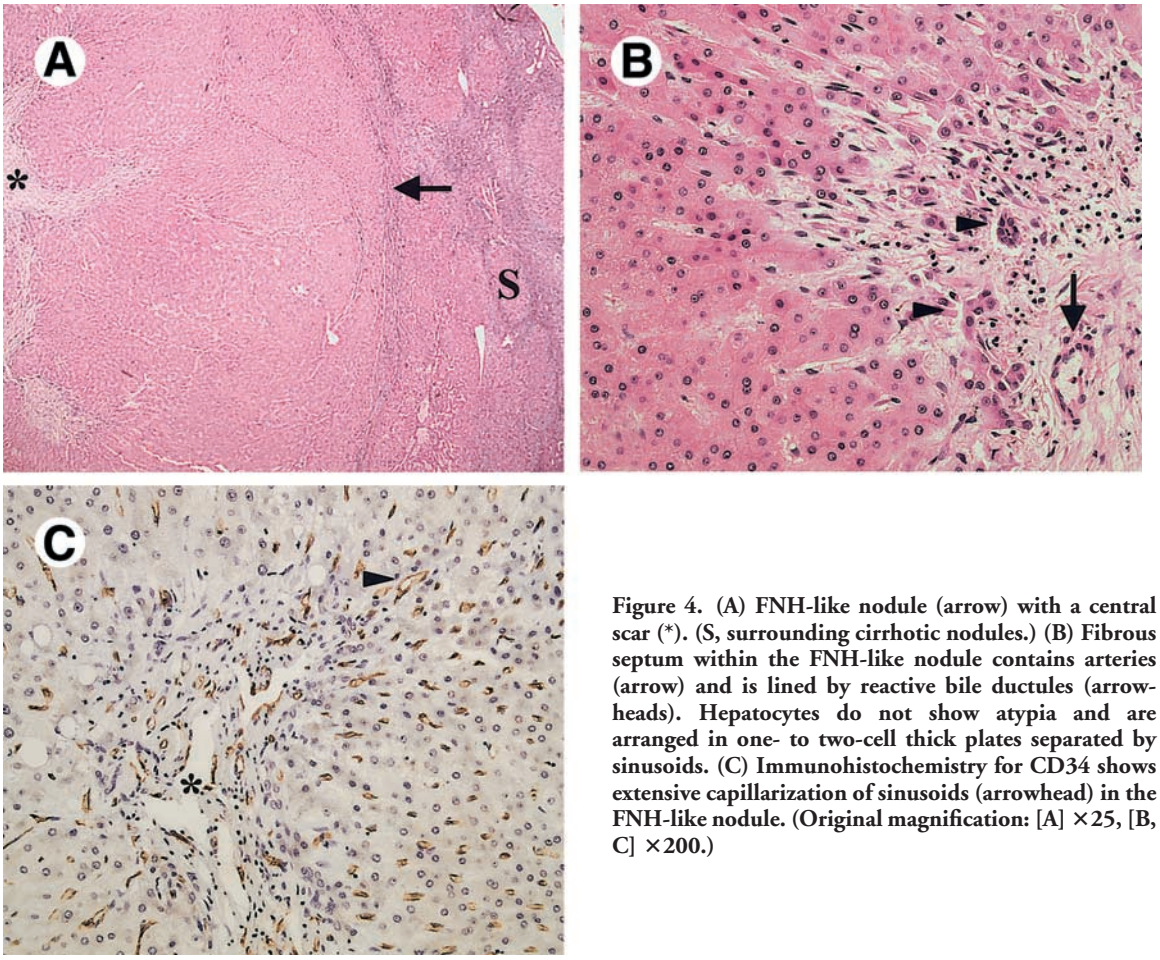

Figure 4. (A) FNH-like nodule (arrow) with a central scar (*). (S, surrounding cirrhotic nodules.) (B) Fibrous septum within the FNH-like nodule contains arteries (arrow) and is lined by reactive bile ductules (arrowheads). Hepatocytes do not show atypia and are arranged in one- to two-cell thick plates separated by sinusoids. (C) Immunohistochemistry for CD34 shows extensive capillarization of sinusoids (arrowhead) in the FNH-like nodule. (Original magnification: [A] ×25, [B, C] ×200.)

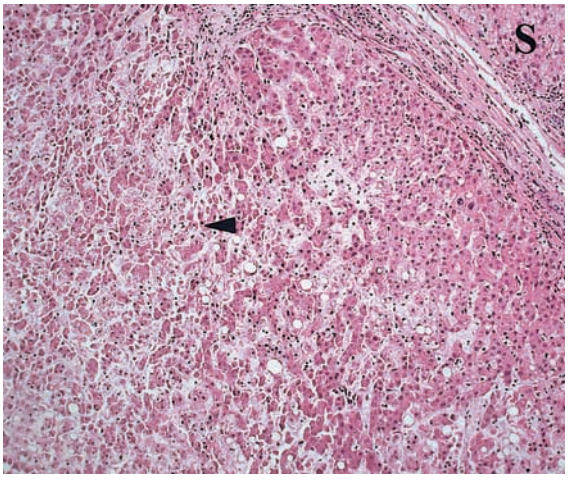

Figure 5. IRN showing ischemic coagulative necrosis of hepatocytes (arrowhead). (S, surrounding cirrhotic nodule; original magnification ×100.)

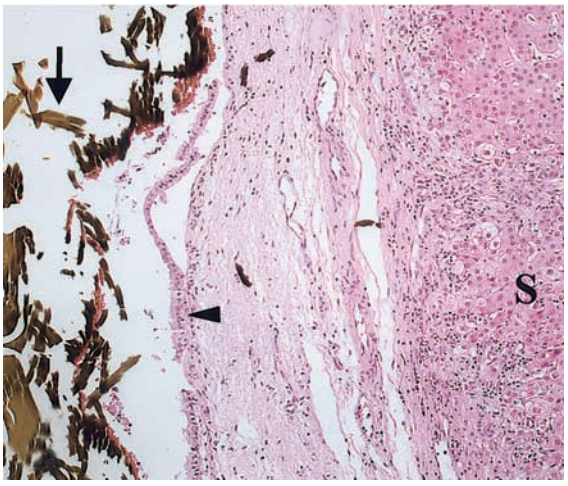

Figure 6. Intrahepatic bile duct (arrowhead) containing biliary sludge (arrow). Stones were removed before processing of tissue. (S, surrounding cirrhotic nodules; original magnification ×100.)

of lesion (Figs. 1 through 7).[4,20] The most serious diagnosis and its diameter was given when several histopathologic diagnoses coexisted, e.g., an HCC in an HGDN was diagnosed as HCC. Routine pathological investigation of the explanted livers also was performed and correlated with clinical and laboratory data to confirm or determine the presence of cirrhosis and cause of the chronic liver disease.

Imaging Reports and Radiological-Pathological Correlation

Original reports of color Doppler ultrasonography (US), contrast-enhanced helical computed tomography (CT) and contrast-enhanced magnetic resonance (MR) examinations performed in the setting of pretransplantation evaluation were collected after pathological examination of the explant liver. These reports were made by a fellow and one of three different abdominal radiologists who interpreted results of imaging examinations in consensus according to internationally accepted criteria.[27-29] On US, hyperechoic, hypoechoic, and mixed echogenic nodular lesions were interpreted as HCC. On contrast-enhanced CT, nodular lesions that were hypodense during the arterial phase were interpreted as DNs, and enhanced nodules during the arterial phase were interpreted as HCCs. On contrast-enhanced MR imaging, nodular

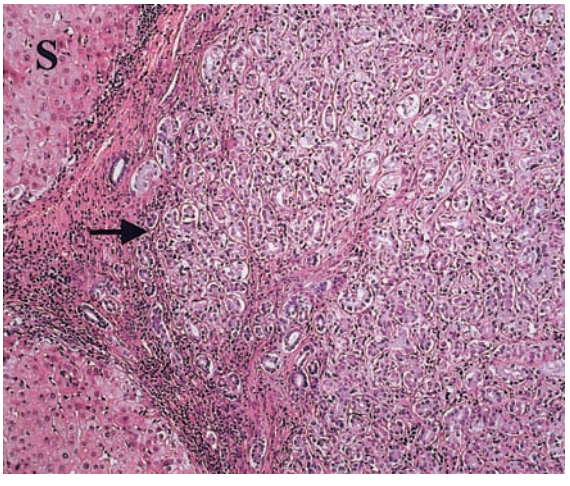

Figure 7. A BDA (arrow) composed of bile ductules organized in a tortuous configuration and lined by small cuboidal cells. (S, surrounding cirrhotic nodules; original magnification ×100.)

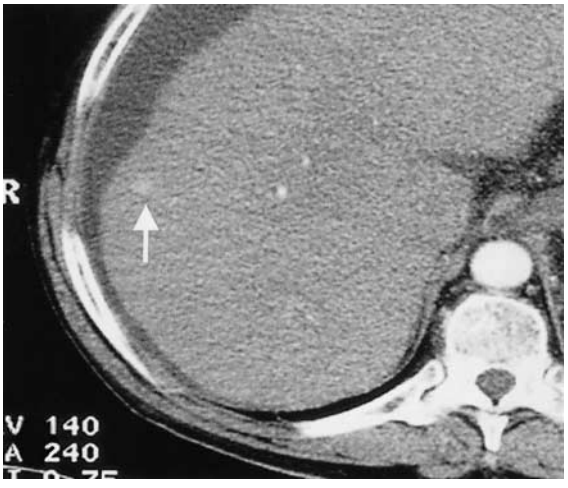

Figure 8. A small focal lesion showing enhancement on the arterial phase of contrast-enhanced CT (arrow). The lesion was diagnosed as HCC, but examination of the cirrhotic explant liver showed the lesion was an FNH-like nodule with a diameter of 1 cm (see lesion in Fig. 4).

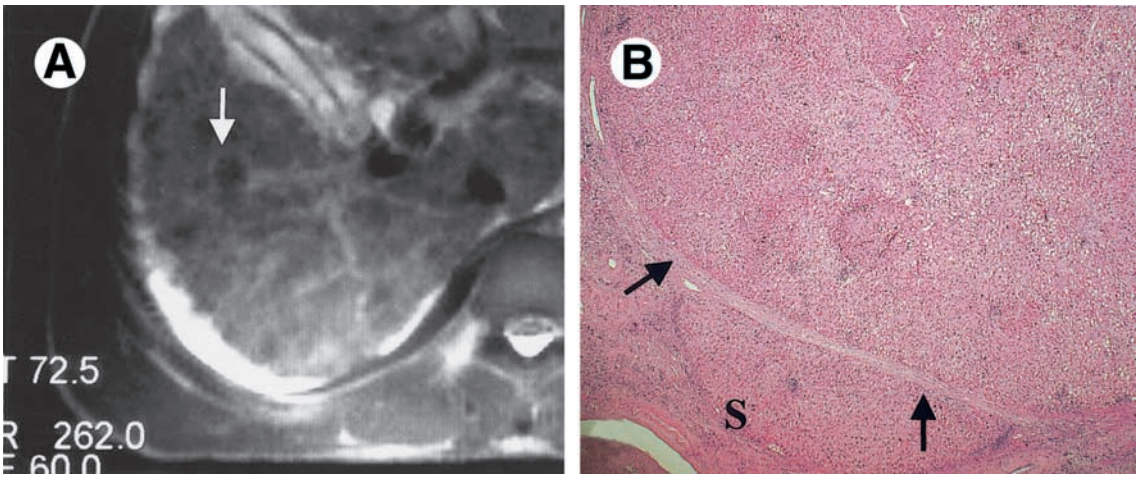

Figure 9. (A) A hypointense nodular lesion on the T2-weighted contrast-enhanced MR image. The lesion was correctly diagnosed as a DN. (B) The corresponding LGDN in the cirrhotic explant liver (arrows) is steatotic and paler than the surrounding regenerative nodules (S) and has a diameter of 1 cm. (Original magnification: [B] ×25.)

lesions that were hyperintense on T1-weighted images, isointense to hypointense on T2-weighted images, and not enhanced during the arterial phase were interpreted as DNs. Nodular lesions that showed variable intensity on T1-weighted images, hyperintensity on T2-weighted images, and/or enhancement during the arterial phase were diagnosed as HCCs (Figs. 8 through 10).

At first, this seems to represent a weakness of our study. However, we wanted to determine the accuracy of imaging techniques as they are performed in routine daily practice in our academic tertiary-care medical center, not in the specific setting of a study in which the radiologist most likely would unintentionally have taken more time and effort to interpret imaging results. Retrospective (re)interpretation of results of imaging examinations by one or more radiologists[19,21,30] includes a similar bias that most likely would lead to greater accuracy than is the case in routine daily practice.

Only reports of imaging examinations performed inside our institution within 6 months before transplantation were used. We selected 6 months as the longest interval between imaging and pathological examination to minimize the occurrence of incorrect false-negative imaging diagnoses because of growth and new development of focal lesions in this interval.[31,32] If the same type of imaging examination was performed more than once in this period, only the most recent report was used.

Based on the reported size and segmental localization according to Couinaud,[24] all radiologically detected focal

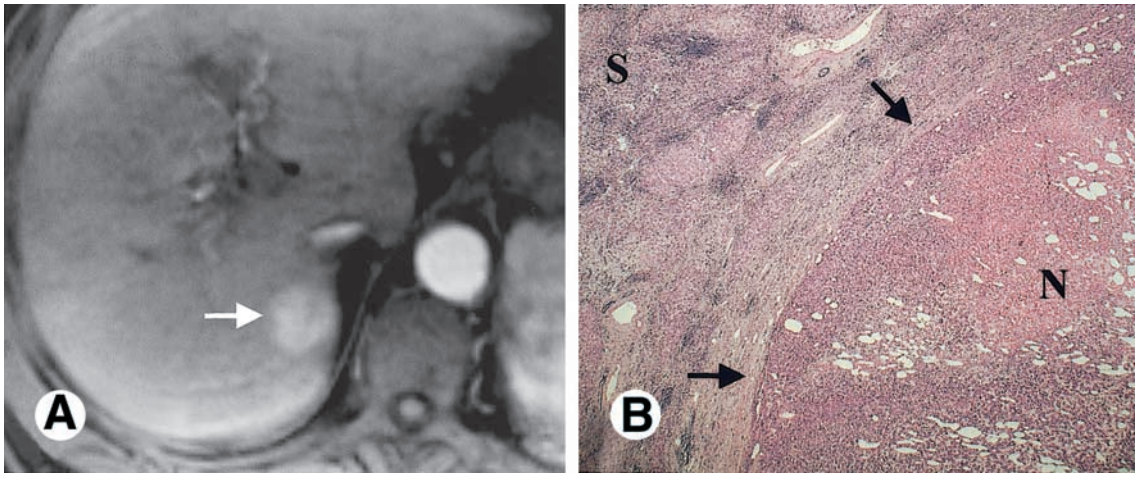

Figure 10. (A) A nodular lesion that enhances on the arterial phase of a contrast-enhanced MR image (arrow). The lesion was correctly diagnosed as an HCC. (B) The corresponding HCC in the cirrhotic explant liver (arrows) show areas of necrosis (N) and has a diameter of 2 cm. (Original magnification: [B] ×25.)

lesions were correlated on a one-by-one basis with focal lesions detected during pathological examination of the cirrhotic explant liver.

Imaging Techniques

Standard US was performed using broadband frequency probes of 3.5 MHz with harmonic imaging (Sequoia 512; Acuson Siemens, Erlangen, Germany; or Sonoline Elegra; Siemens, Erlangen, Germany), completed with color and power Doppler.

Helical CT was performed using either a single-slice Somatom Plus 4 (Siemens) or multislice Somatom Volume Zoom (Siemens). Scans were obtained through the liver from dome to base during one breath hold. Single-slice technique parameters were as follows: slice thickness, 5 mm; table feed, 4 mm; and pitch, 1.5. Multislice technique parameters were as follows: slice thickness, 5 mm; collimation, 2.5 mm; reconstruction interval, 5 mm; and pitch, 4. Dynamic contrast examinations were performed in the arterial and portal phase after scanning the liver without contrast. Scans were performed 15 to 20 seconds and 70 to 80 seconds after the delivery of 125 mL of nonionic iodinated contrast material (Omnipaque 350; Nycomed Amersham, Brussels, Belgium; or Iomeron 350; Byk Belga, Brussels, Belgium) at 2.5 to 4 mL/s using a power injector through an antecubital vein.

MR imaging was performed using a Magnetom Vision 1.5 Tesla (Siemens) or an Intera 1.5 Tesla (Philips, Best, The Netherlands). Standard T1- and T2-weighted images were performed using T1 gradient echo with inversion recovery (Turbo FLASH) in the axial plane (6-mm slice thickness, 8-mm interval) and T2 turbo spin echo (HASTE) in the axial plane (6-mm slice thickness, 8-mm interval). For dynamic contrast series of the liver, a spoiled gradient echo sequence was used (two-dimensional FLASH; 8-mm slice thickness, 8-mm interval). As on CT, these were performed without and after intravenous contrast injection in both the arterial phase and portal venous phase (20 mL of dimeglumine gadopentetate (Magnevist; Schering, Diegem, Belgium) or meglumine gadoterate (Dotarem; Codali, Brussels, Belgium) at 1.5 to 2 mL/s.

Statistical Analysis

The significance of correlations or differences was calculated using Fisher's exact test, Chi-square test, or Wilcoxon's rank-sum test, when appropriate. For all tests, significance was accepted for $P < .05$. Continuous data were expressed as mean ± SD. Statistical analyses were performed using Statview, version 5.0.1 (SAS Institute, Cary, NC).

Results

The 49 patients (17 women, 32 men) included in the study had a mean age of 53.4 ± 11.6 years. Causes of liver cirrhosis are listed in Table 1. In 13 patients (27%), the presence of HCC was suspected before transplantation based on alpha-fetoprotein levels and results of imaging examinations. No chemoembolization, radiofrequency thermal ablation, or other treatment for HCC was performed before liver transplantation. Based on imaging data, it also was considered that

Table 1. Cause of Liver Cirrhosis and Prevalence of HCCs, HGDNs, and LGDNs

Cause of Liver Cirrhosis	No. of Patients	HCC*	HGDN*	LGDN*
Chronic viral hepatitis	20	0 (50)	8 (40)	9 (45)
HBV	9	2	2	3
HCV	11	8	6	6
Cholestatic liver disease	8	0 (0)	0 (0)	0 (0)
PBC	2	0	0	0
PSC	6	0	0	0
Alcohol	12	3 (25)	2 (17)	4 (33)
Other or combination	9	2 (22)	1 (11)	1 (11)
Toxic	1	0	0	0
Caroli's disease	1	0	0	0
Cryptogenic	1	0	0	0
α_1-Antitrypsin deficiency	1	0	0	0
HCV and α_1-antitrypsin deficiency	1	0	0	0
HCV and alcohol	1	0	0	0
Hemochromatosis and alcohol	1	1	1	1
PBC and autoimmune hepatitis	1	1	0	0
HBV and Caroli's disease	1	0	0	0

NOTE. Values expressed as number (percent).
Abbreviations: HBV, hepatitis B virus; PSC, primary sclerosing cholangitis.
*Patients with at least one lesion.

the diameter of the HCC was 5 cm or less in patients with a single tumor or there were no more than three HCCs, each with a diameter of 3 cm or less, in patients with multiple tumors. It is the general policy at our institution to refrain from liver transplantation if this number or size limit is exceeded because patients with tumor(s) that exceed these limits have worse overall survival and more frequently experience recurrent HCC.[14] In the period during which the present study was performed, there have been a few exceptions to this rule. Three patients without chronic hepatitis C virus (HCV) infection for whom it was clear that their tumors exceeded the mentioned number and size limits received a donor liver from a patient with positive serological markers for HCV. These three patients were excluded from the study.

Within the 6 months before transplantation, US, contrast-enhanced CT, and contrast-enhanced MR imaging were performed in 46 (94%), 16 (33%), and 27 patients (55%), respectively. Mean intervals between imaging examination and transplantation were 70 ± 50 days (range, 2 to 166 days), 84 ± 43 days (range, 22 to 179 days), and 71 ± 48 days (range, 5 to 178 days), respectively.

HCCs, HGDNs, and LGDNs: Pathological and Imaging Data

Seventy-seven HCCs, 21 HGDNs, and 38 LGDNs were detected in 15 (31%), 11 (22%), and 14 patients (29%), respectively (Figs. 1 to 3). None of the 49 cirrhotic explant livers contained an incidental cholangiocarcinoma. The 59 DNs were present in 17 patients (35%). HCCs and DNs did not show a uniform macroscopic appearance. Mean numbers of HCCs, HGDNs, and LGDNs in these patients were 5.1 ± 8.4, 1.9 ± 0.7, and 2.7 ± 2.2, respectively. One explant liver contained 20 HCCs, and one liver contained 30 HCCs. Three of the 77 HCCs (4%) were located within an HGDN (so-called nodule-in-nodule lesions). The presence of at least one LGDN or HGDN was associated with the presence of at least one HCC ($P = .0012$ and $P < .0001$, respectively), and the presence of at least one LGDN was associated with the presence of at least one HGDN ($P = .0002$). Livers of 3 of 4 patients (75%) who had one or more HCCs, but no DNs, showed numerous foci of small-cell dysplasia. Mean diameters of HCCs, HGDNs, and LGDNs were 9.6 ± 8.9 mm (range, 2 to 40 mm), 6.5 ± 2.7 mm (range, 3 to 13 mm), and 6.2 ± 3.0 mm (range, 2 to 15 mm), respectively. There were no significant differences between these diameters, although DNs (LGDNs or HGDNs) tended to be smaller than HCCs ($P = .0959$). Fifty-five of 59 DNs (93%) and 61 of 77 HCCs (79%) were 1 cm or less in diameter ($P = .0144$). The segmental localization of (pre)malignant nodules is listed in Table 2. Only 1%, 5%, and 0% of all HCCs, HGDNs, and LGDNs were located in segment 1, respectively.

Table 2. Segmental Localization of HCCs, HGDNs, and LGDNs

Segment	HCC	HGDN	LGDN
1	1 (1)	1 (5)	0 (0)
2	11 (14)	1 (5)	7 (18)
3	12 (16)	2 (10)	3 (8)
4	12 (16)	8 (38)	5 (13)
5	9 (11)	4 (19)	3 (8)
6	6 (8)	2 (9)	9 (24)
7	7 (9)	2 (9)	3 (8)
8	6 (8)	1 (5)	5 (13)
Overlap*	13 (17)	0 (0)	3 (8)

NOTE. Values expressed as number (percent) of lesions in the segment.
*Lesions localized in two segments (i.e., segments 2/3, 4/5, 5/6, 5/8, 6/7, and 7/8 for HCCs and segments 6/7 and 7/8 for LGDNs).

One or more HCCs, HGDNs, and LGDNs were present more frequently in cirrhosis of viral cause compared with cirrhosis of other or combined causes ($P = .0145$, $P = .0145$, and $P = .0351$, respectively). HCCs, HGDNs, and LGDNs were not present in livers with cirrhosis caused solely by cholestatic liver disease (Table 1). Patients with at least one HCC, HGDN, or LGDN were older than patients without the lesion (60.6 ± 8.5 *v* 50.3 ± 11.4 years, 61.3 ± 7.0 *v* 51.1 ± 11.7 years, and 56.8 ± 10.4 *v* 52.0 ± 11.9 years, respectively). This difference was significant for HCCs and HGDNs, but not for LGDNs ($P = .0008$, $P = .0042$, and $P = .1183$, respectively). No significant association was found between sex and the presence of one or more HCCs, HGDNs, or HCCs ($P = .8943$, $P = .8949$, and $P = .5691$, respectively).

The presence of one or more HCCs was confirmed in 9 of 13 patients (69%) who, based on imaging examinations, were suspected of having HCC before transplantation. In 3 patients, preoperatively diagnosed HCCs were other types of lesion, i.e., a focal nodular hyperplasia (FNH)-like nodule, two HGDNs, and foci of intrahepatic lithiasis. Pathological examination did not show a lesion correlating with the preoperatively diagnosed HCC in 1 patient. The number of HCCs exceeded the three-tumor limit in 4 of 9 patients (44%):

Table 3. Patient Sensitivity and Specificity for Each Type of Imaging Examination for HCC and DN

Imaging Technique	HCC	DN
US		
Sensitivity	6/15 (40)	0/16 (0)
Specificity	31/31 (100)	30/30 (100)
Contrast-enhanced CT		
Sensitivity	1/2 (50)	1/5 (20)
Specificity	11/14 (79)	11/11 (100)
Contrast-enhanced MR		
Sensitivity	7/10 (70)	3/11 (27)
Specificity	14/17 (82)	15/16 (94)

NOTE. Values expressed as number/total number (percent).

1 patient had 4 HCCs, 2 patients had 5 HCCs, and 1 patient had 30 HCCs.

An unsuspected HCC was present in six patients (12%). One of these patients had 20 HCCs, the other patients had 1 HCC, with a mean diameter of 8.8 ± 3.9 mm (range, 5 to 15 mm). Cause of cirrhosis was viral in three patients (50%), alcohol in two patients (33%), and primary biliary cirrhosis (PBC) and autoimmune hepatitis in one patient (17%). Patients with an unsuspected HCC were older than those without (63 ± 5 *v* 50 ± 12 years; $P = .0108$).

Patient sensitivity and specificity for each type of imaging examination for HCCs and DNs are listed in Table 3. US did not detect DNs. In one patient, a bile duct adenoma (BDA) was misdiagnosed as HCC on contrast-enhanced MR imaging. However, this patient had two HCCs elsewhere in the liver; therefore, in this case, there was no false positivity at the patient level.

Table 4 lists the number and size of detected and undetected HCCs and DNs for each type of imaging examination. The smallest lesion detected by US, contrast-enhanced CT, and MR imaging had a diameter of 10, 6, and 4 mm, respectively. All 5 DNs (100%) detected by contrast-enhanced CT were LGDNs, and 16 of 22 DNs (73%) detected by contrast-enhanced MR imaging were LGDNs. The three false-positive diagnoses of HCC on contrast-enhanced CT were caused by an FNH-like nodule, a hemangioma, and in one case, there was no correlating lesion. For contrast-enhanced MR imaging, the two false-positive diagnoses of DN were caused by an HCC and a focus of intrahepatic lithiasis, and the six false-positive diagnoses of HCC were caused by three HGDNs, a BDA, a focus of intrahepatic lithiasis, and, in one case, there was no correlating lesion.

Other Focal Lesions: Pathological and Imaging Data

FNH-like nodules. In the explant liver of four patients (8%) with cryptogenic cirrhosis (n = 1) and cirrhosis caused by HCV (n = 1) or alcohol (n = 2), we detected five nodules with a diameter of 6.4 ± 2.3 mm (range, 4 to 10 mm). These nodules were paler than the surrounding regenerative nodules, and two of the nodules had a central scar (Fig. 4A). Nodules were surrounded by a capsule and consisted of hepatocytes without atypia arranged in one- to two-cell thick plates separated by sinusoids. Nodules contained fibrous septa with numerous arteries and veins that subdivided the nodule into areas of different size. In contrast to the surrounding liver tissue, portal tracts with bile ducts were not present in nodules (Fig. 4B).

Additional histochemical and immunohistochemical stainings were performed on serial sections, as previously described.[33] Edges of septa showed reactive ductules positive for cytokeratin 7 and 19 and con-

Table 4. Number and Size of Detected and Undetected HCCs and DNs for Each Type of Imaging

Imaging Technique	Lesions Detected	Diameter of Detected Lesions (mm)	Diameter of Undetected Lesions (mm)	*P*
DNs				
US	0/57 (0)	NA	6.2 ± 2.6	NA
Contrast-enhanced CT	5/13 (38)	8.0 ± 1.5	5.5 ± 3.4	.1054
Contrast-enhanced MR	22/39 (56)	7.0 ± 2.5	6.5 ± 2.9	.2694
HCCs				
US	8/77 (10)	27.5 ± 12.5	7.6 ± 5.5	<.0001
Contrast-enhanced CT	2/33 (6)	27.5 ± 10.6	6.1 ± 5.4	.0326
Contrast-enhanced MR	10/20 (50)	26.0 ± 11.5	7.6 ± 2.5	.0002

NOTE. Values expressed as number/total (percent) or mean ± SD.
Abbreviation: NA, not available.

nected to cytokeratin 7–positive hepatocyte-like cells (data not shown). Stainings for α-smooth muscle actin and CD34 showed a high number of unpaired arteries and capillarized sinusoids radiating from edges of septa into the parenchyma (Fig. 4C).

Because these nodules are macroscopically, microscopically, and immunohistochemically virtually identical to FNH in noncirrhotic livers,[34-38] they were named FNH-like nodules in accordance with Sugihara et al.[39]

All four patients underwent US, which did not detect any of the FNH-like nodules. Contrast-enhanced CT was performed in two patients and detected the largest FNH-like nodule, with a diameter of 10 mm, on the arterial phase as an enhanced lesion, which led to the diagnosis of HCC (Fig. 8). Contrast-enhanced MR imaging in two patients did not detect FNH-like nodules.

Infarcted regenerative nodules. As described previously,[40-42] an infarcted regenerative nodule (IRN) is defined as a regenerative nodule showing extensive ischemic coagulative necrosis (Fig. 5). Confluence of several IRNs leads to larger lesions. In the explant liver of four patients (8%) who had cirrhosis caused by HCV (n = 2), hepatitis B virus (n = 1), and HCV and alcohol (n = 1), we detected five dark-red lesions consisting of one or more IRNs, with a mean diameter of 12.2 ± 10.0 mm (range, 7 to 30 mm).

US, contrast-enhanced CT, and contrast enhanced MR imaging did not detect any of the IRNs. These examinations were performed in 4, 2, and 2 patients with IRNs, respectively. One and two previous episodes of gastrointestinal bleeding from esophageal or gastric varices were documented in 1 and 3 patients, respectively. One or more previous episodes of gastrointestinal bleeding were documented in 12 of the other 44 patients (27%; $P = .0086$).

Biliary cysts. A biliary cyst is defined as a unilocular cyst lined by a flattened bile duct epithelium supported by a fibrous stroma.[38] We found 10 biliary cysts, with a mean diameter of 6.0 ± 2.6 mm (range, 4 to 12 mm), in explant livers of three patients (6%) who had cirrhosis caused by alcohol (n = 2) and PBC (n = 1).

The three patients underwent US that detected the largest biliary cyst of each patient as a circular and anechoic lesion. Two patients underwent contrast-enhanced CT, which detected all seven biliary cysts present in these patients as hypodense lesions that did not show enhancement in the arterial phase. The detected biliary cysts were correctly diagnosed on both US and contrast-enhanced CT.

Foci of intrahepatic lithiasis. In explant livers of two patients (4%) who had cirrhosis caused by PBC and primary sclerosing cholangitis, we detected one and three focal black lesions that consisted of small black stones and biliary sludge in intrahepatic bile ducts. The surrounding bile duct epithelium was focally absent and replaced by granulation tissue. These lesions correspond to foci of intrahepatic lithiasis (Fig. 6).[43] Mean diameter of these lesions was 4.0 ± 0.8 mm (range, 3 to 5 mm).

Contrast-enhanced CT and MR imaging performed in the patient with one focus of intrahepatic lithiasis did not detect the lesion. The patient with three foci of intrahepatic lithiasis located in the same area underwent US that did not detect the lesions. They were detected as an enhancing lesion on the arterial phase of contrast-enhanced MR imaging and were misdiagnosed as a single HCC.

In accordance with previous reports,[44,45] cystic dilation of large intrahepatic bile ducts was observed throughout the explant livers of the two patients with Caroli's disease. The largest cystically dilated bile ducts in these two patients had diameters of 30 and 35 mm, and the latter contained small black stones and biliary sludge.

One of these two patients underwent no imaging examinations within 6 months before transplantation. The other patient underwent US and contrast-enhanced MR imaging. The cystically dilated bile duct containing stones and biliary sludge was detected on contrast-enhanced MR examination. The lesion was hypointense on the T1-weighted image, slightly hyperintense on the T2-weighted image, but not enhanced on the arterial phase, which led to the diagnosis of DN.

BDAs. A BDA is defined as a nodule composed of a variable number of bile ductules with a narrow lumen organized in a tortuous configuration. Ductules are lined by small cuboidal cells and surrounded by a variable amount of connective tissue (Fig. 7).[38,46] Eight and two gray-white and firm BDAs were found in explant livers of two patients (4%) who had cirrhosis caused by HCV and alcohol, respectively. Only two BDAs were located under the capsule. BDAs had a mean diameter of 5.0 ± 3.3 mm (range, 3 to 14 mm).

US and contrast-enhanced CT were performed in two and one patients and did not detect BDAs, respectively. Contrast-enhanced MR imaging was performed in both patients and detected the largest BDA, with a diameter of 14 mm, but the lesion was misdiagnosed as HCC because the BDA was hyperintense on the T1-weighted image and enhanced on the arterial phase.

Cavernous hemangioma. The explant liver of one patient (2%) who had cirrhosis caused by alcohol contained a dark-red cavernous hemangioma, with a diameter of 5 mm, consisting of cavernous vascular spaces lined by flattened endothelium and separated by fibrous septa.[38]

The hemangioma was detected as an enhancing lesion on the arterial phase of a contrast-enhanced CT, which led to the diagnosis of HCC. On contrast-enhanced MR imaging, the hemangioma was correctly diagnosed and was hypointense on the T1-weighted image, hyperintense on the T2-weighted image, and showed enhancement on both the arterial and portal venous phases. US did not detect the hemangioma.

Discussion

One or more HCCs and DNs were present in 31% and 35% of the cirrhotic explant livers we investigated, respectively. That HCCs, HGDNs, and LGDNs were mutually associated corroborates the notion that LGDNs and HGDNs are distinct stages in the multistep process of hepatocarcinogenesis.[47]

The minimum diameter of DNs was not smaller than that of HCCs. However, we observed that the mean diameter of lesions increased from LGDN to HGDN to HCC, which suggests that progression through the stages of hepatocarcinogenesis is associated with an increase in diameter. The finding that a focal lesion larger than 1 cm is most likely an HCC, rather than a DN, may be useful in daily practice. That DNs and HCCs could be as small as a few millimeters contradicts the notion that all DNs (and HCCs) develop from large regenerative nodules.[48]

In view of the well-known epidemiological features of HCC,[3] it is no surprise that the prevalence of HCCs, HGDNs, and LGDNs was greater in patients with cirrhosis of viral cause and older patients.

Intriguingly, no LGDNs and only a very small proportion of HGDNs and HCCs were located in segment 1, known also as the caudate lobe. Yang et al[49] and Takayama et al[50] previously noted that only 1.5% and 0.5% of 411 and 386 patients undergoing partial hepatectomy for HCC had a tumor in the caudate lobe, respectively. Based on these and our findings, we conclude that the multistep process of hepatocarcinogenesis occurs rarely in the caudate lobe compared with other parts of the cirrhotic liver. In contrast to other segments, the caudate lobe is supplied by several portal vein branches coming from the two main portal veins and is drained into the inferior caval vein by a short hepatic vein independently of the major hepatic veins.[25,51] It is tempting to speculate that this peculiar vascularization has a role in the development of HCC because it is the only known factor that distinguishes the caudate lobe from other parts of the liver.

FNH is a lesion generally believed to occur only in noncirrhotic livers.[36,38] In contradiction to this widespread opinion, we detected five nodules in explant livers of four patients (8%) that were almost identical to FNH in noncirrhotic livers.[36,38] The only difference was that these FNH-like nodules had a capsule, whereas FNHs in noncirrhotic livers usually are not encapsulated.[36] Sugihara et al[39] previously reported an FNH-like nodule that was resected from a cirrhotic liver because the diagnosis of HCC was made on imaging examinations. Similarly, one of our FNH-like nodules was detected on contrast-enhanced CT and also misdiagnosed as an HCC.

It recently was reported that HGDNs and HCCs in cirrhotic liver have a unique vascular profile characterized by the diffuse presence of a high number of unpaired arteries and capillarized sinusoids compared with surrounding liver tissue. Conversely, atypical hepatocytes are distributed unevenly within these lesions.[7,52] These findings have led to the guideline that in a biopsy, a nodule with bland morphological characteristics and an increased number of unpaired arteries and/or capillarized sinusoids has to be diagnosed at least as an HGDN.[53,54] However, although cellular or structural atypia are not present in FNH-like nodules, they have a vascular profile similar to that of HGDNs and HCCs. Thus, (pre)malignancy should not be diagnosed without the presence of clear-cut atypical hepatocytes and/or architectural features. Application of this guideline to a needle biopsy specimen of an FNH-like nodule from a cirrhotic liver would erroneously lead to the diagnosis of HGDN or even HCC.

IRNs previously have been described in cirrhotic liver[40,42] and are seen mostly in patients who had one more periods of gastrointestinal bleeding.[40,41] This led to the hypothesis that IRNs develop because of hypoperfusion of the liver followed by ischemic necrosis of one or more regenerative nodules that are vulnerable to hypoxia.[41] This hypothesis is supported because one or more previous episodes of bleeding from esophageal or gastric varices were documented more frequently in patients with than without IRN. IRNs were present in 8% of patients, and this is the first report of their prevalence in patients with cirrhosis.

Intrahepatic lithiasis is seen predominantly in the Far East and is rare in the Western world. Stasis of bile and mucus caused by intrahepatic bile duct destruction and stricture is considered an important factor in the

pathogenesis of intrahepatic lithiasis.[43,55] Our results are in accordance with this hypothesis because all three patients with intrahepatic lithiasis (6%) had biliary cirrhosis caused by chronic destruction and stricture of intrahepatic bile ducts. There is only one previous report in which intrahepatic lithiasis in a cirrhotic liver is described.[56]

A BDA is usually detected as a coincidental finding during workup or abdominal surgery of patients with diseases that do not involve the liver. Classically, the BDA is singular and located subcapsularly in an otherwise normal liver.[38,46] In accordance with Krinsky et al,[23] we observed that BDAs also are present in 4% of patients with liver cirrhosis. We and others[57] show that, in contrast to BDAs in normal liver, BDAs in cirrhotic liver usually are multiple and diffusely distributed. This suggests that the cirrhotic process is involved in the pathogenesis of these BDAs.

Hemangiomas have been reported in 2%[58] and 4%[59] of patients with cirrhosis, similar to the prevalence of 2% in the present study.

In accordance with Krinsky et al,[58] we noted that the biliary cyst is the only type of benign focal lesion in cirrhotic liver that was always correctly diagnosed when detected on imaging examination. Although BDAs, IRNs, FNH-like nodules, hemangiomas, and foci of intrahepatic lithiasis do not occur in a high frequency in cirrhotic livers, they are clinically very important because we and a few other groups[39,41,60] show that these lesions are frequently interpreted as premalignant or malignant lesions on imaging examination before transplantation. The present study also shows that several of these benign focal lesions enhance on the arterial phase of contrast-enhanced CT or MR imaging, a feature generally considered highly suggestive of HCC.[27-29] Radiologists, pathologists, and clinicians have to be aware of the existence, features, and prevalence of these benign lesions in cirrhotic livers. A focal lesion detected in a cirrhotic liver should not a priori be considered (pre)malignant, even if the lesion shows enhancement on the arterial phase. In this respect, it is remarkable that in most previous studies in which cirrhotic explant livers were investigated by imaging and pathological examination, only (pre)malignant lesions were reported.[22,30,61-63]

We found that US had a poor patient sensitivity for HCC. Only the largest HCCs and none of the DNs were shown on US. Regular US examination of the liver is the classic tool used in surveillance for HCC in cirrhotic patients. The objective of surveillance for HCC is the detection of malignancy in an early stage, which results in a reduction in disease-specific mortality.[64] Our data suggest that a high proportion of small HCCs will be missed when surveillance is performed with US, and it therefore is possible that US is not the most cost-effective technique for surveillance of HCC in cirrhotic patients.

Contrast-enhanced CT and MR imaging had poor patient sensitivity, but good specificity for DN. Patient sensitivity and specificity of both imaging techniques for HCC were reasonable and good, respectively. These findings are in line with results of the two previous studies in which the so-called gold standard was used.[22,23] Contrast-enhanced CT and MR imaging were not able to detect the smallest (pre)malignant lesions, shown by the finding that undetected HCCs and DNs had smaller mean diameters than detected ones for both types of imaging techniques. Our findings indicate that the threshold beneath which these focal lesions are never shown is approximately 1 cm for US and 5 mm for contrast-enhanced CT and MR imaging.

Because of shortcomings of these imaging techniques used in pretransplantation evaluation, five patients (10%) underwent transplantation even though they exceeded the tumor number limit. We do not claim that transplantation was undeserved in all these patients, although the two patients with 20 and 30 HCCs most likely should not have undergone transplantation. Patients included in the present study will be followed up for a number of years to determine which patients will redevelop an HCC. Unsuspected HCCs were found most frequently in patients with cirrhosis caused by chronic viral hepatitis and older patients. Critical imaging and pathological investigations are clearly necessary in this subgroup. Conversely, no malignant lesion was found in the explant liver of four patients (8%) suspected of having an HCC. Our findings indicate that currently used imaging techniques cannot correctly determine the exact tumor burden in some cirrhotic patients evaluated for liver transplantation. As a consequence, selection of cirrhotic patients is suboptimal, regardless of tumor size and number limits used.

Based on findings of the present study, it seems warranted to perform regular (every 6 months) contrast-enhanced MR examination of cirrhotic patients who are evaluated for and placed on a liver transplant waiting list. In this way, (pre)malignant lesions can be detected as early and as small as possible. Nonsurgical procedures, such as thermal ablation or chemoembolization, may inhibit tumor growth while the patient is on the waiting list.

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