Diagnostic Imaging of Hepatocellular Carcinoma in Patients With Cirrhosis Before Liver Transplantation

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Key Concepts:
1. The lack of whole-liver explant correlation has led to an overestimation of the sensitivity of imaging tests for the diagnosis of HCC in the radiological literature.
2. Ultrasound is insensitive for the diagnosis of HCC in the cirrhotic liver and should not be used for the detection of focal liver lesions in this setting.
3. Although magnetic resonance (MR) imaging is more sensitive than multidetector 3-phase computed tomography (CT) for the diagnosis of regenerative and dysplastic nodules it is probably no better than CT for detection of HCC and has a lower false-positive rate.
4. Approximately 10-30% of nodules measuring <2 cm seen only on the hepatic arterial phase at CT or MR imaging represent small HCC and vigilant surveillance imaging is required as interval growth is the best indicator of malignancy.

Hepatocellular carcinoma (HCC) is the most common primary liver neoplasm, the fifth most common cancer in the world and is responsible for up to 1 million deaths annually worldwide.1 Over the last 20 years, the incidence of finding HCC by ultrasound (US) has increased from 1.4 to 2.4 per 100,000, with a concomitant 41% increase in overall mortality rate.2 The 5-year survival rate for untreated, symptomatic HCC is less than 5%.2 In contrast, the 5-year survival rate in patients with cirrhosis following transplantation of small (≤2 cm) HCC is 80%.3 The detection of small HCC is clearly critical to patient outcome.3

Morphologic distinction of HCC from other liver nodules can be difficult (Fig. 1). Cirrhotic livers frequently contain numerous regenerative nodules that are benign. Small HCC, and their precursors, premalignant dysplastic nodules (DN) can often be histologically distinguished from background cirrhotic regenerative nodules by cellular atypia and stromal microinvasion at pathologic examination. However, by noninvasive imaging tools, the distinction between malignant and benign nodules is limited and relies primarily on their different vascular supply.4-8 Regenerative nodules, like underlying liver parenchyma, have a portal venous blood supply, whereas high-grade DN and HCC demonstrate neo-arteriogenesis with an increased number of nontriadal or unpaired arteries.7-10

There are several differences in both the pathological and imaging findings in livers from patients who undergo transplantation from those that do not. Explanted livers from patients with viral or alcoholic cirrhosis tend to demonstrate a more advanced disease state than those seen in Asia from partial hepatectomy specimens. This is because most patients who undergo orthotopic liver transplantation are often Child class C, whereas only Child class A or B patients can tolerate an extended hepatic resection. In addition, Asian hepatopathologists have recognized DN (formerly adenomatous hyperplasia) from hepatectomy specimens far earlier than the American and European transplant centers; it wasn’t until the early to mid 1990’s that these centers began to report these lesions. Early studies from North America by computed tomography (CT) failed to even comment on the presence or absence of DN.11,12 Finally, the interobserver variability between high-grade DN and early HCC is large, reflecting the differences in experience between hepatopathologists across the globe.

Although many CT and magnetic resonance (MR) im-
Aging studies have reported high diagnostic accuracy for HCC and DN in patients with cirrhosis, most of these have been limited by study design, incomplete pathologic correlation and suboptimal imaging techniques. Because HCC and DN are frequently multifocal in the setting of cirrhosis, whole-liver explant studies are required to determine the true accuracy of imaging modalities. The lack of whole-liver explant correlation has led to an overestimation of the sensitivity of sonography for detection of HCC and DN in the cirrhotic liver results from the presence of fibrosis, fatty infiltration altering background liver echogenicity and the presence of nonneoplastic regenerative nodules. The alterations in background hepatic parenchymal echogenicity make infiltrating tumors particularly difficult to detect.

In the largest study performed to date that used US with explant correlation, Bennett et al.\(^20\) demonstrated a sensitivity of only 21% for detection of HCC and 5% for DN in 200 patients with end-stage cirrhosis. Specificity was high (96%) as essentially all lesions detected were HCC and DN. Limitations in this study include a retrospective study design, and a wide range of skills of the physicians who performed the studies. Rode et al.\(^21\) reported a sensitivity of 46.2% for detection of HCC (6 of 13 lesions), 33.3% for “borderline nodules” (2 of 6 lesions) and 2% for macrorregenerative (dysplastic) nodules (1 of 50) in a study of 46 patients. In a study by Kim et al.,\(^22\) 6 of 18 HCC and 0 of 20 DN were detected in 52 patients with advanced cirrhosis, for a sensitivity of 33% and 0%, respectively. By use of color Doppler US in 46 patients with cirrhosis who underwent imaging and transplantation within 6 months, Libbrecht et al.\(^23\) demonstrated a per-patient sensitivity of 40% for HCC and 0% for DN, respectively. Nevertheless, the specificity of US in the setting of cirrhosis remains high and all lesions seen should be considered HCC until proven otherwise.

US with injected contrast agents, though promising in some clinical settings,\(^24\) have not been evaluated in large numbers of patients with timely transplant correlation. Intraoperative laparoscopic US\(^25\) may increase lesion detection but is too invasive to be used for routine surveillance of HCC.

**MULTIDETECTOR ROW CT (MDCT)**

Over the past few years, MDCT technology has been introduced into clinical practice. MDCT uses 4, 16, or 64 contiguous detectors to decrease scanning time, without consequent loss of spatial resolution along the axis of scanning. These scanners allow thin sections in a single breath-hold, with greatly improved speed and longitudinal resolution, which results in nearly isotropic image acquisition and subsequent high-resolution multiplanar reformations. In addition, whereas MDCT technology allows faster scanning of the liver in less than 5-10 sec. (compared to approximately 20 sec for single-detector helical CT), with the possibility of acquiring 2 separate arterial phase images within the time accepted as the hepatic arterial dominant phase in single-detector helical CT. The early arterial phase (angio-

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**Figure 1.** Very high risk patient with hepatitis C cirrhosis and multiple large nodules (arrows) hyperintense on unenhanced T1-weighted gradient echo (A) and hypointense on fat-suppressed T2-weighted (B) MR imaging. The lesions did not enhance during the hepatic arterial phase (not shown) and may represent large regenerative nodules, dysplastic nodules, or, less likely, small hypovascular HCC. The pattern of large nodules with T1 hyperintensity and T2 hypointensity (but without hepatic arterial phase enhancement) has been reported to represent dysplastic nodules, but in fact is more commonly seen in large regenerative nodules at explantation.
graphic phase) could be used to define the vascular supply of the tumor and the liver.

CT has been widely used to evaluate the cirrhotic liver for HCC since the early 1980’s. The examination requires intravenous iodinated contrast material and exposes the patient to ionizing radiation. In the setting of mild or early cirrhosis, the examination is readily performed as patients usually have normal renal function. However, some patients who await explantation develop decompensated cirrhosis and markedly abnormal renal function due to the hepatorenal syndrome. In addition, to minimize cold ischemia times of the procured liver allograft, there is little justification for performing an emergent CT before transplantation. Therefore, the number of published papers with timely explant correlation is limited. However, as live liver donation is now performed worldwide, many patients are transplanted before development of renal impairment providing more optimal radiological-pathological correlation with multiphase, multidetector CT.

Multidetector helical CT is typically performed slightly after peak hepatic arterial enhancement (hepatic arterial dominant phase) and repeated during peak portal venous enhancement following an injection of iodinated contrast material. The sensitivity of dual-phase helical CT for the detection of small HCC and DN with whole-explant correlation is variable. In large part, this is due to limited temporal resolution of the arterial phase, which is particularly challenging given the intravenous injections of contrast material and variable circulation times.

In the largest study to date, Peterson et al. detected 430 patients with cirrhosis with either dual-phase (noncontrast and portal venous phase) or triple phase (addition of hepatic arterial phase) helical or incremental single-slice CT. The mean time between CT and transplantation ranged from 1-671 days (mean 107) for 59 patients with HCC. By use of only patients who underwent helical triphasic CT imaging, the prospective sensitivity for the detection of HCC on a nodule by nodule basis was 37%. On retrospective review the sensitivity increased to 44%. No mention was made of DN. An earlier study from the same institution used incremental biphasic CT in 200 patients with cirrhosis who were transplanted within 223 days of imaging and demonstrated a sensitivity of 68% for detection of HCC.

In a smaller study of 41 patients who underwent triphasic CT and transplantation within 100 days (mean 75), Lim et al. detected 71% of HCC and 39% of DN. By use of triphasic CT in 43 patients with cirrhosis before transplantation, Rode et al. detected 2% of DN and 54% of HCC; the interval between imaging and transplantation was not provided. In a smaller study of 34 patients who underwent transplantation and triphasic CT within a mean time of 44 days demonstrated a sensitivity of 52% for HCC and 0% of DN, respectively.

By use of triphasic CT in patients transplanted for HCC and cirrhosis, Zacherl et al. demonstrated a sensitivity of 75% for HCC and 40% for DN. In this study, intraoperative US performed better with a sensitivity of 92% for HCC and 60% for DN.

### MDCT Imaging Features of HCC

Imaging findings characteristic of small HCC on CT include hepatic arterial phase enhancement (Fig. 2) and decreased attenuation when compared to background liver on the portal venous phase. When the lesion is isodense to background liver on both the unenhanced and portal venous phase but demonstrates hepatic arterial phase enhancement it is indeterminate for HCC and options include MR imaging, follow-up CT in 3-6 months or biopsy. Approximately 10% of HCC nodules are not identified during the hepatic arterial phase and these lesions are usually diagnosed on the unenhanced or portal venous phase CT images (Fig. 3).

### MR Imaging with Gadolinium-Based Contrast Agents

Although many studies have been published regarding the sensitivity of MR imaging for detection of HCC and DN only a small number have had whole-explant correlation within 90 days of imaging. For MR imaging, a dual or triple-phase contrast-enhanced approach is typically used, where the first acquisition is timed for the hepatic arterial dominant phase. In addition, state-of-the-art MR imaging requires a 3-dimensional pulse sequence with an interpolated slice thickness of 2 mm. By use of this method in 71 patients with end-stage cirrhosis requiring transplantation (but without known HCC), Krinsky et al. demonstrated a sensitivity of 55% for detection of HCC and 15% for DN, respectively. Rode et al. demonstrated better results in 43 patients with a sensitivity of 77% for detection of HCC and 42% of DN. A smaller study of 34 patients also found slightly better results with a sensitivity of 61% and 27% for HCC and DN, respectively.
double dose of gadolinium chelates in 50 patients, Burrel et al.31 showed that MR was superior to triphasic CT on a per nodule basis; CT detected 61% and MR detected 76% of focal lesions. In particular, MR was markedly better than CT for nodules measuring between 1 and 2 cm.31

Among 24 patients transplanted specifically for HCC and cirrhosis, dynamic gadolinium-enhanced MR imaging detected only 39 of 118 HCC for a sensitivity of 33%.30 The lower sensitivity reflected smaller coexisting lesions that were diagnosed only by careful histopathologic sampling of the entire liver explant. When stratified by lesion size, only 4% of HCC measuring <1 cm were detected.30 Additionally, of the 9 who had diffuse HCC (all nodules <1 cm), none were detected before transplantation and 8 showed poor outcomes subsequently.30

DOUBLE-CONTRAST MR IMAGING

This technique uses 2 separate contrast agents (ferumoxides and gadolinium chelates) to maximize detection and characterization of focal liver lesions in the cirrhotic liver. The ferumoxide agent behaves as an iron particle that is taken up by Kupffer cells and markedly decreases the signal intensity of background liver on T2-weighted MR imaging. This increases the contrast between tumors without Kupffer cells (moderate and poorly differentiated HCC) and the background RN and DN resulting in increased lesion conspicuity. Sequential use of gadolinium chelates provides the additive information regarding lesion enhancement and vascularity.

By use of both gadolinium and ferumoxide MR agents, Bhartia et al.32 demonstrated a 78% sensitivity for detection of HCC in 31 patients transplanted between 3 and 245 days after MR imaging. The sensitivity dropped to 38% for lesions ≤ 1 cm. The authors did not evaluate DN.32

MR IMAGING FEATURES OF HCC

On T2-weighted MR images large HCC are classically hypointense whereas almost all dysplastic nodules are hypointense. Small HCC are hyperintense in about 60% of cases, whereas the remaining 40% are isointense (not seen) or hypointense to background liver (Fig. 4). Hepatic arterial phase enhancement with hypointensity in the portal venous phase and the presence of a pseudocapsule is diagnostic of HCC, regardless of the T2-weighted MR features (Fig. 4). Similar to CT, when a lesion is isointense to background liver on T1 and T2 weighted MR imaging but demonstrates hepatic arterial phase enhancement it is indeterminate for HCC and options include follow-up imaging in 3-6 months or biopsy.

CATHETER ANGIOGRAPHY, CT DURING ARTERIAL PORTOGRAPHY, AND CT DURING HEPATIC ARTERIOGRAPHY

To date, only invasive studies (requiring catheter placement in the hepatic artery) have been used to directly evaluate the blood supply of cirrhotic nodules. By use of conventional catheter angiography in 40 patients with cirrhosis before transplantation, Spreafico et al.33 detected 67% of HCC; DN were not evaluated. By use of digital subtraction angiography (DSA) in 24 patients transplanted primarily for HCC and cirrhosis, Krinsky et al.34 detected only 18% of HCC ≤ 2 cm and no DN; this is likely due to the fact that DSA is a projectional, not a cross-sectional technique. A similar approach implemented with CT imaging during arterial portography (CTAP) and during hepatic portography (CTHA) can be used to compare arterial and portal venous phases of enhancement35 and may provides improved detection of HCC and DN over DSA. By use of CTAP only, Spreafico et al.33 detected 85% of HCC in patients transplanted for cirrhosis. More recently, Steingruber et al.36 evaluated 59 patients with cirrhosis with CTAP and DSA before explantation. Sensitivity and specificity...
were 75% and 60% for CTAP, 77% and 80% for DSA, and 84% and 81% for CTAP and DSA combined. However, these techniques are too invasive and costly to be used on a routine basis, may result in false negative diagnoses of HCC when arterial anatomy is aberrant and are subject to technical failure secondary to catheter position and operator error.

CT AFTER INJECTION OF INTRAARTERIAL LIPIODOL

Taourel et al. demonstrated a sensitivity of 53% for detection of HCC in 35 patients who underwent CT after Lipiodol; by use of a similar technique in 40 patients, Spreafico et al. demonstrated a 58% sensitivity for HCC. It appears that Lipiodol is selectively taken up by hypervascular HCC rather than hypovascular HCC, explaining its low sensitivity. In neither study was DN evaluated.

FATE OF LESION SEEN ONLY DURING HEPATIC ARTERIAL PHASE (HAP-ONLY LESIONS)

From an imaging standpoint, HAP-only lesions are problematic as they are common, usually cannot be biopsied and require costly follow-up imaging. Most nonneoplastic HAP-only nodules are arterioporal shunts that are common in the cirrhotic liver. These shunts cannot be seen when evaluating the explanted liver because they are only seen in vivo. Other causes of HAP-only lesions include dysplastic nodules, atypical hemangiomas, areas of focal fibrosis, focal nodular hyperplasmia, and aberrant venous drainage. By use of MRI with explant correlation in 46 patients transplanted with cirrhosis, Holland et al. demonstrated that 16 patients (35%) had 45 HAP-only lesions of which only 3 (7%) were neoplastic. In a MRI series by Jeong et al. 9 (13%) of 68 HAP-only lesions measuring up to 2 cm were HCC. In another study that used follow-up MR imaging, 158 small HAP-only lesions were detected in 75 (36%) of 208 patients on the initial MR images. Most lesions were not seen at follow-up imaging and 29 HAP-only lesions (18%) were HCC. By use of serial triphasic CT in 58 patients, O’Malley et al. followed 32 HAP-only nodules measuring between 1 and 2 cm of which 14 (44%) were stable, 9 (28%) decreased, and 9 (28%) increased in size. Eight HAP-only lesions (25%) were ultimately diagnosed as HCC. A reasonable strategy based on these studies would include a 6-month follow-up CT or MR for HAP-only lesions measuring <1 cm and 3-month serial imaging in lesions between 1 and 2 cm that are not amenable to biopsy (Fig. 5).

In conclusion, when the gold standard of imaging HCC and DN is whole-explant correlation, all modalities appear to be suboptimal for detection of small <2-cm lesions with US clearly performing the poorest. Further improvements in hardware, software and novel contrast agents will likely result in higher sensitivity for lesion detection in the cir-
rhotic liver with MR imaging showing the most promise. In addition, increased worldwide utilization of live-liver donation, with imaging and histopathologic correlation within 24 hours, will surely advance the science of radiology. Perfusion and diffusion weighted MR imaging appear particularly promising as does targeted molecular imaging with PET.

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Figure 5. Fate of the early enhancing lesion in a patient with viral cirrhosis demonstrating the importance of close interval follow-up imaging for indeterminate nodules. (A) A 16-slice MDCT hepatic arterial phase image in a patient with cirrhosis shows a 1.2-cm early enhancing lesion (arrow) in the right lobe. (B) The nodule was not seen during the portal venous phase and was thought to be suspicious for HCC. A 3-month follow-up MDCT was recommended because the nodule was not seen during attempted US-guided biopsy. (C) A 16-slice MDCT hepatic arterial phase image performed 3 months later shows interval growth to 2 cm (arrow). On the basis of rapid growth, the nodule was considered to be HCC, and chemoembolization was successfully performed.
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