The diagnosis of hepatocellular carcinoma (HCC) is based on imaging examinations in combination with clinical and laboratory findings. Despite technological advances, imaging cirrhotic patients remains a challenging issue because nonmalignant hepatocellular lesions, such as dysplastic nodules, mimic a small HCC. One of the key pathologic factors for differential diagnosis that is reflected in imaging appearances is the vascular supply to the lesion. It is accepted that imaging techniques may establish the diagnosis of HCC in nodules larger than 2 cm showing characteristic arterial hypervascularization. In lesions ranging from 1 to 2 cm, biopsy is still recommended, although a negative response can never be used to rule out malignancy completely. Although ultrasonography is widely accepted for HCC surveillance, spiral computed tomography (CT) or dynamic magnetic resonance imaging is required for diagnostic confirmation and intrahepatic tumor staging. These examinations have replaced invasive procedures, such as lipiodol CT, but remain relatively insensitive for the detection of tiny HCC lesions and tumor vascular invasion into peripheral portal vein branches.

**KEYWORDS:** Ultrasonography, computed tomography, magnetic resonance imaging, percutaneous biopsy

**Objectives:** Upon completion of this article, the reader will be able to (1) recognize and characterize imaging findings of hepatocellular carcinoma and dysplastic nodules in cirrhosis, (2) discuss advantages and limitations of current imaging techniques for intrahepatic tumor staging, and (3) select the most appropriate diagnostic work-up for patients with suspected hepatocellular carcinoma.

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**Credit:** TUSM designates this educational activity for a maximum of 1 Category 1 credit toward the AMA Physicians Recognition Award. Each physician should claim only those credits that he/she actually spent in the educational activity.

Diagnostic confirmation and assessment of disease extent are crucial for proper clinical management of patients with hepatocellular carcinoma (HCC). For years, the diagnosis of HCC was based on percutaneous biopsy, and intrahepatic tumor staging required invasive procedures, such as angiography and lipiodol computed tomography (CT). Currently, owing to advances in imaging techniques, a reliable diagnostic assessment can be based in most instances on noninvasive examinations in combination with clinical and laboratory findings. Nevertheless, imaging cirrhotic patients with suspected HCC is a challenging issue. HCC shows a variety of imaging features that reflect the variable gross and microscopic characteristics of this malignancy. In addition, pathologic changes inherent in cirrhosis—such
as large regenerative nodules and dysplastic nodules (DNs)—may be indistinguishable from a small HCC. One of the key pathologic factors for differential diagnosis that is reflected in imaging appearances is the vascular supply to the lesion. Through the progression from regenerative nodule, to low-grade DN, to high-grade DN, to frank HCC, one sees loss of visualization of portal tracts and development of new arterial vessels, termed nontriadal arteries, which become the dominant blood supply in overt HCC lesions. It is this neovascularity that allows HCC to be diagnosed and is the key for imaging cirrhotic patients.2,3

Although ultrasonography (US) is widely accepted for HCC surveillance, spiral CT or dynamic magnetic resonance (MR) imaging is required for diagnostic confirmation and intrahepatic tumor staging. However, despite recent technological advances, CT and MR imaging remain relatively insensitive for the detection of tiny satellite lesions and tumor vascular invasion into peripheral portal vein branches.

ULTRASONOGRAPHY
US is the imaging technique most commonly used worldwide for early detection of HCC in surveillance programs.1 US enables a rapid and noninvasive evaluation of liver parenchyma, although a comprehensive assessment may be impossible because of patient’s body habitus or colonic interposition. In fact, when careful imaging–pathologic correlation was performed, the sensitivity of US in the detection of small HCC lesions was shown to be much lower than previously estimated. In seven series that reported the correlation between pre-transplantation US and pathologic examination of explanted liver, lesion sensitivity ranged from 20 to 72% (Table 1).4–10 The ability to detect the emergence of a small HCC is highly dependent on the expertise of the operator performing the examination. Of interest, no improvement in sensitivity was observed over the past decade despite the advances in US technology (Table 1).

At US, small, nodular HCC usually appears as a round or oval mass lesion with sharp and smooth boundaries that may exhibit a hypoechoic, isoechoic, or hyperechoic appearance with respect to surrounding liver parenchyma. Nodular-type HCC with extranodular growth and contiguous multinodular-type HCC show a nodular configuration with irregular or blurred margins. The hyperechoic pattern of small HCC usually indicates fatty change or, less frequently, pseudoglandular arrangement of the cancer cells or peliotic changes of tumor vascular spaces. Small, nodular-type HCC is usually indistinguishable from a large regenerative nodule and DN. In addition, small hyperechoic HCC may be indistinguishable from hemangioma.11

Doppler US techniques have long been used in attempts to evaluate tumor vascularity of HCC. At color or power Doppler US, HCC is usually displayed as a vascular-rich lesion containing intratumoral flow signals with an arterial Doppler spectrum. A basket pattern, which is a fine blood flow network surrounding the nodule, and tumor vessels flowing into the lesion and branching within it are typically observed in large HCC. Doppler interrogation shows a pulsatile Doppler waveform with high frequency shifts and abnormally elevated resistive and pulsatility indexes. Because large regenerative nodules and DN usually do not show intratumoral arterial vessels, detection of neovascularity at Doppler US imaging supports the diagnosis of HCC.12 In small HCC lesions, however, the sensitivity of Doppler techniques in showing arterial hypervascularity is low, and a pulsatile flow with arterial waveform can be demonstrated in less than 50% of the lesions.12

The introduction of microbubble contrast agents and the development of contrast-specific scanning techniques have opened new prospects in liver US.13 Contrast-specific techniques produce images based on nonlinear acoustic effects of microbubbles and display enhancement in gray scale, with high contrast and spatial resolution. Over the past few years, several reports have shown that contrast-enhanced studies substantially increase the ability of US to characterize focal liver lesions.14–17 The advent of second-generation agents and low mechanical index real-time scanning techniques has been instrumental in improving the ease and reproducibility of the examination and has prompted the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) to define the indications and recommendations for the use of contrast agents in clinical practice.18

According to EFSUMB guidelines, performing a contrast-enhanced US study is recommended to characterize any lesion or suspect lesion detected at baseline US in the setting of liver cirrhosis.18 In fact, HCC typically shows strong intratumoral enhancement in the arterial phase (i.e., within 25 to 35 seconds after the start of contrast injection) followed by rapid washout with an isoechoic or hyperechoic appearance in the portal venous and delayed phases (Fig. 1). In contrast, large

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**Table 1  Sensitivity of Ultrasonography in the Detection of HCC in Series with Pathologic Examination of the Explanted Liver as Term of Reference**

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>No. of Patients</th>
<th>No. of Lesions</th>
<th>Lesion Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dodd et al, 1992⁴</td>
<td>200</td>
<td>80</td>
<td>36/80 (45%)</td>
</tr>
<tr>
<td>Shapiro et al, 1996⁵</td>
<td>21</td>
<td>40</td>
<td>21/40 (51%)</td>
</tr>
<tr>
<td>Kim et al, 2001⁶</td>
<td>52</td>
<td>18</td>
<td>6/18 (33%)</td>
</tr>
<tr>
<td>Rode et al, 2001⁷</td>
<td>43</td>
<td>13</td>
<td>6/13 (46%)</td>
</tr>
<tr>
<td>Bennett et al, 2002⁸</td>
<td>200</td>
<td>39</td>
<td>8/39 (20%)</td>
</tr>
<tr>
<td>Liu et al, 2003³</td>
<td>118</td>
<td>51</td>
<td>14/51 (27%)</td>
</tr>
<tr>
<td>Teefey et al, 2003¹⁰</td>
<td>25</td>
<td>18</td>
<td>13/18 (72%)</td>
</tr>
</tbody>
</table>
regenerative nodules and DNs usually do not show any early contrast uptake and resemble the enhancement pattern of liver parenchyma. In two series, selective arterial enhancement at contrast US was observed in 91 to 96% of HCC lesions, confirming that contrast US may be a tool to show arterial neoangiogenesis of HCC. Assuming findings at spiral CT as the “gold standard,” the sensitivity of contrast US in the detection of arterial hypervascularity was 97% in lesions larger than 3 cm, 92% in lesions ranging from 2 to 3 cm, 87% in lesions from 1 to 2 cm, and 67% in lesions smaller than 1 cm.

SPIRAL COMPUTED TOMOGRAPHY

With the introduction of spiral scanners, the role of CT in liver imaging has dramatically changed. Because it is possible to scan the whole liver during a single breath-hold, a comprehensive evaluation of the hepatic parenchyma during the different phases of contrast enhancement has become feasible. The standard spiral CT examination protocol for detection and characterization of HCC should include unenhanced and contrast-enhanced images obtained in the arterial phase (scanning initiated at ~25 to 30 seconds after the start of contrast injection), the portal venous phase (scanning initiated at ~70 to 80 seconds after the start of contrast injection), and the delayed phase (scanning initiated at ~180 to 210 seconds after the start of contrast injection). Proper timing of arterial phase imaging is crucial to identify hypervascular nodules and requires the use of a test dose injection or a bolus track system to initiate the scanning at an optimal phase of opacification.

The coupling of multidetector-row scan technology with spiral image acquisition has further enhanced the performance of CT in liver imaging. Multidetector spiral CT offers a marked reduction in the time required for thin-section imaging of the entire liver relative to standard single-detector spiral CT. The resulting substantial improvement in spatial resolution was shown to increase CT sensitivity in the detection of hypervascular HCC. In addition, the increased temporal resolution permits hepatic imaging during two distinct arterial phases, the early arterial phase and the late arterial phase, acquired during the same breath-hold. Doubling the classic arterial phase of single-detector spiral CT may offer advantages. The early arterial phase, in fact, is a true CT arteriography and can be used to assess vascular anatomy. However, in most studies, acquiring a double arterial phase did not improve the detection rate of HCC with respect to late arterial phase imaging alone. A further evolution of the scanning protocol includes triple arterial phase scanning, with the middle arterial phase imaging claimed as the most sensitive for HCC detection.

Despite these substantial technological advances, CT remains relatively insensitive for the detection of tiny HCC lesions. In six series that reported careful lesion-
by-lesion imaging–pathologic correlations in explanted livers, the sensitivity of spiral CT in detection of HCC lesions ranged from 52 to 79% (Table 2).29–32 In particular, only 10 to 43% of lesions smaller than 1 cm and 44 to 65% of lesions of 1 to 2 cm were identified (Table 2).

Another important issue is the specificity of CT findings. It is accepted that overt HCC lesions show a hypervascular CT pattern, with clear-cut enhancement in the arterial phase and rapid washout in the portal venous and delayed phases (Fig. 2). In contrast, large regenerative nodules and DNs usually fail to exhibit this feature and appear isoenhancing or hypoattenuating to surrounding liver parenchyma.33,34 However, the positive predictive value of CT findings ranges from 59 to 88%, as nonmalignant lesions may show increased arterial blood supply and be indistinguishable from a small HCC. In one study, only 17 (24%) of 71 hypervascular hepatic nodules detected during arterial phase CT scans were confirmed as HCC at histopathology of explanted livers.35 Nonmalignant hepatocellular lesions—histologically diagnosed as large regenerative nodules or DNs—showed the following characteristics: 0.5 to 2 cm in diameter, distinct margins, internal homogeneity, and isoenhancement to surrounding liver on precontrast, portal venous, and delayed phase scanning.35

False-positive interpretations can occasionally be caused by small (less than 1.5 cm) flash-filling hemangiomas, which may enhance homogeneously in the arterial phase.36 However, these lesions usually do not exhibit contrast washout and show attenuation equivalent to that of the aorta during portal venous and delayed phase CT imaging.37 Nontumorous arterioportal shunts can also be a cause of pseudolesions, although in most cases they have a typical wedge-shaped and homogeneous appearance (with or without internal linear branching structures representing early opacification of portal veins during the arterial phase) and are isoenhancing or slightly hyperattenuating during the portal venous phase.38

Identification of morphological features of HCC may support the diagnosis of HCC in questionable cases. The tumor capsule appears as a peripheral rim that is hypoattenuating on unenhanced and arterial phase images and hyperattenuating on delayed phase images. Unfortunately, the CT detection rate of the capsule is strongly dependent on lesion size and is low in small tumors because the capsule itself is thin and poorly developed.39 Internal mosaic architecture, with components showing variable attenuation index on CT images, is another typical feature of HCC that, however, is usually detected in large nodular lesions. Invasion of portal vein branches, with partial or complete neoplastic thrombosis, is quite frequent in advanced tumors and is best shown on portal venous phase images. Neoplastic thrombi, however, may enhance in the arterial phase, like the main tumor. Although invasion of main portal vein branches may be clearly detected by CT, identification of tumor spread into peripheral—segmental or subsegmental—branches remains a substantial limitation of the technique.40

MAGNETIC RESONANCE IMAGING
Over the past few years, MR imaging of the liver has progressed significantly. Technical advances in hardware and software have allowed the acquisition of images with excellent anatomic detail, largely free of artifacts secondary to respiratory motion. Fast sequences have reduced image acquisition time, thereby improving patients’ acceptance and allowing more efficient utilization of machine time. New volumetric sequences have enabled three-dimensional serial dynamic imaging of the liver with very high spatial and temporal resolution, reducing section misregistration and motion artifacts while improving multiplanar reformations.41 Several novel liver-specific contrast agents, including hepatocellular-specific agents, have been developed.42,43

Table 2  Sensitivity and Positive Predictive Value of Spiral CT in the Detection of HCC in Series with Pathologic Examination of the Explanted Liver as Term of Reference

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>No. of Patients/No. of Lesions</th>
<th>Overall Lesion Sensitivity</th>
<th>Sensitivity for lesions Lesions &lt; 1 cm</th>
<th>Sensitivity for lesions Lesions 1–2 cm</th>
<th>Sensitivity for lesions Lesions &gt; 2 cm</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim et al, 200029</td>
<td>41/21</td>
<td>15/21 (71%)</td>
<td>-</td>
<td>6/10 (60%)</td>
<td>9/11 (82%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Tode et al, 20017</td>
<td>43/13</td>
<td>7/13 (54%)</td>
<td>3/7 (43%)</td>
<td>3/5 (60%)</td>
<td>1/1 (100%)</td>
<td>N/A</td>
</tr>
<tr>
<td>de Ledinghen et al, 200220</td>
<td>34/54</td>
<td>28/54 (52%)</td>
<td>2/8 (25%)</td>
<td>15/34 (44%)</td>
<td>11/12 (92%)</td>
<td>28/37 (76%)</td>
</tr>
<tr>
<td>Burrel et al, 200231</td>
<td>50/76</td>
<td>43/70 (61%)</td>
<td>2/20 (10%)</td>
<td>17/26 (65%)</td>
<td>24/24 (100%)</td>
<td>43/49 (87%)</td>
</tr>
<tr>
<td>Teefey et al, 200310</td>
<td>25/18</td>
<td>13/18 (72%)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>13/22 (59%)</td>
</tr>
<tr>
<td>Valls et al, 200432</td>
<td>85/85</td>
<td>67/85 (79%)</td>
<td>-</td>
<td>23/38 (61%)</td>
<td>44/47 (94%)</td>
<td>67/76 (88%)</td>
</tr>
</tbody>
</table>

N/A, not available.
cyte-targeted and reticuloendothelial system (RES)-targeted compounds, have been developed, permitting manipulation of tissue signal in different ways, according to the relevant diagnostic issue.3

The standard examination protocol for the detection and characterization of HCC includes T1-weighted fast spoiled gradient-echo sequences with fat suppression, respiration-triggered or breath-hold T2-weighted fast spin-echo sequences with fat suppression, and serial dynamic T1-weighted fast spoiled gradient-echo sequences after bolus injection of a gadolinium chelate.3 Additional sequences, such as out-of-phase spoiled gradient-echo T1-weighted sequences, may be performed to provide comprehensive information or to solve specific diagnostic issues.42

HCC shows a variety of MR imaging features that reflect the variable characteristics of this malignancy in tumor architecture, grading, and stromal component as well as intracellular content of certain substances, such as fat, glycogen, or metal ions, that greatly affect the appearance of the lesion on baseline T1-weighted and T2-weighted MR images.3 The signal intensity may range from hypointensity to isointensity to hyperintensity on T1-weighted images and from isointensity to hyperintensity on T2-weighted images. Hyperintensity on T1-weighted images and isointensity on T2-weighted images are typical features of well-differentiated tumors, and hypointensity on T1-weighted images and hyperintensity on T2-weighted images are usually associated with moderately or poorly differentiated tumors.43 The signal intensity of HCC lesions may be inhomogeneous, reflecting the presence of areas with different degrees of differentiation. Lesion signal intensity on baseline T1-weighted and T2-weighted images may help differentiate HCC from a large regenerative nodule or DN, although considerable overlap exists.44

Dynamic contrast-enhanced MR imaging allows selective imaging of the entire liver in the arterial, portal venous, and delayed phases.45–49 The acquisition protocol should be optimized for proper timing of arterial phase imaging by using automated bolus-detection three-dimensional sequences and may include double or triple arterial phase imaging, as in multidetector CT.50,51 Dynamic MR imaging well demonstrates the typical vascular features of overt HCC, that is, arterial

Figure 2. Arterial phase multidetector CT (A) shows a tiny hypervascular lesion (arrow). The nodule (arrow) appears hypointensifying to liver parenchyma in the delayed phase (B). Histopanthologic examination of explanted liver confirms poorly differentiated HCC (C).
phase enhancement with portal venous phase washout. This feature enables differentiation of frank HCC from large regenerative nodules or DNs, which are usually not hypervascular.46 Nevertheless, as discussed for CT imaging, nonmalignant hepatocellular lesions—especially high-grade DNs—may show increased arterial blood supply and be indistinguishable from a small HCC. In addition, nontumorous arteriportal shunts may cause false-positive interpretations.52,53 In one study, 54 (52%) of 104 small (less than 2 cm), round or oval, early-enhancing hepatic lesions at serial contrast-enhanced dynamic MR imaging were not confirmed as HCC at follow-up.52

Despite technical improvements, MR imaging remains relatively insensitive for the detection of tiny HCC nodules and for the identification of tumor vascular invasion into peripheral portal vein branches. In series in which MR imaging findings were correlated with histopathologic results after thin-section slicing of the explanted liver, lesion-by-lesion analysis revealed a sensitivity of 33 to 78%, with positive predictive values ranging from 54 to 90% (Table 3).7,10,30,31,54,55 In particular, only 4 to 71% of lesions smaller than 1 cm and 52 to 92% of lesions of 1 to 2 cm were identified (Table 3). Nevertheless, state-of-the-art dynamic MR imaging outperforms single-detector spiral CT in the detection of small nodules: in one comparative study with explant correlation, the sensitivity for the identification of additional HCC lesions was significantly higher for MR imaging than for spiral CT in the range 1 to 2 cm.31

Although the dynamic study performed by using gadolinium chelates is a currently a key part of the MR examination, a variety of liver-specific contrast agents have been used in attempts to improve the information provided by MR imaging in HCC detection and characterization.3 It has been shown that some well-differentiated HCCs may show positive enhancement after the administration of the hepatocyte-targeted agent manganese dipyridoxal diphosphate (Mn-DPDP) because of their affinity with normal hepatocytes. In one study, owing to this peculiar feature, early-stage tumors that were missed by spiral CT because of their immature neovascularity were detected.56 HCC conspicuity after the administration of RES-specific contrast agents depends on differences in the number of Kupffer cells within the nodule and the surrounding cirrhotic liver.57 Whereas moderately or poorly differentiated HCCs containing few or no Kupffer cells show a high contrast-to-noise ratio, well-differentiated HCCs have a Kupffer cell population that may not differ significantly from that of surrounding parenchyma, which results in a signal-to-noise ratio close to zero and, thus, in low detectability rates.57 Although in one series MR imaging with use of a RES-targeted agent was superior to spiral CT for the detection of HCC nodules,58 in comparative studies the sensitivity of MR imaging with use of either hepatocyte-targeted or RES-targeted contrast agents was shown to be inferior to dynamic MR imaging (Table 4).9–61 It has to be considered, however, that recently introduced liver-specific agents can deliver dynamic imaging in addition to the liver-specific phase.3

### Table 3 Sensitivity and Positive Predictive Value of Dynamic MR Imaging in the Detection of HCC in Series with Pathologic Examination of the Explanted Liver as Term of Reference

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>No. of Patients/No. of Lesions</th>
<th>Overall Lesion Sensitivity</th>
<th>Sensitivity for Lesions 1 cm</th>
<th>Sensitivity for Lesions 1–2 cm</th>
<th>Sensitivity for Lesions &gt; 2 cm</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rode et al, 2001</td>
<td>43/13</td>
<td>10/13 (77%)</td>
<td>5/7 (71%)</td>
<td>4/5 (80%)</td>
<td>1/1 (100%)</td>
<td>N/A</td>
</tr>
<tr>
<td>de Ledinghen et al, 2002</td>
<td>34/54</td>
<td>33/54 (61%)</td>
<td>2/8 (25%)</td>
<td>19/34 (56%)</td>
<td>12/12 (100%)</td>
<td>33/37 (89%)</td>
</tr>
<tr>
<td>Burrel et al, 2003</td>
<td>50/76</td>
<td>58/76 (76%)</td>
<td>8/23 (34%)</td>
<td>25/28 (89%)</td>
<td>25/25 (100%)</td>
<td>58/64 (90%)</td>
</tr>
<tr>
<td>Krinsky et al, 2002</td>
<td>24/118</td>
<td>39/118 (33%)</td>
<td>3/72 (4%)</td>
<td>11/21 (52%)</td>
<td>25/25 (100%)</td>
<td>39/45 (87%)</td>
</tr>
<tr>
<td>Teefey et al, 2003</td>
<td>22/18</td>
<td>14/18 (77%)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>14/19 (74%)</td>
</tr>
<tr>
<td>Bhartia et al, 2005</td>
<td>31/32</td>
<td>25/32 (78%)</td>
<td>3/8 (38%)</td>
<td>12/13 (92%)</td>
<td>10/11 (91%)</td>
<td>25/46 (54%)</td>
</tr>
</tbody>
</table>

*MR protocol included dynamic imaging plus liver-specific imaging after administration of a RES-targeted agent. N/A, not available.

### DIAGNOSTIC WORK-UP

Although the detection of a focal lesion in cirrhosis during US follow-up should always raise the suspicion of HCC, it has been shown by pathologic studies that many small nodules detected by US in cirrhotic livers do not correspond to HCC but rather correspond to nonneoplastic hepatocellular nodules, such as large regenerative nodules or DNs. The prevalence of HCC among US-detected nodules is strongly dependent on the size of the lesion: whereas half of the nodules less than 1 cm in size are not malignant, the large majority of the lesions exceeding 2 cm are true HCC or contain HCC foci.1 The differential diagnosis between small HCC and a large regenerative nodule or DN remains one of the greatest challenges in liver imaging. The diagnostic...
protocol, therefore, should be structured according to the actual risk of malignancy and the possibility to achieve a reliable diagnosis.

The following work-up has been devised by a panel of experts of the European Association for the Study of the Liver and offers a guideline for the clinical management of suspected HCC lesions.1 In nodules smaller than 1 cm detected by US in a cirrhotic patient, in view of the high prevalence of nonmalignant lesions and the difficulties in achieving a final diagnosis of HCC, a reasonable protocol is to repeat US every 3 months until the lesion grows to more than 1 cm, at which point additional diagnostic techniques are applied. It has to be emphasized, however, that absence of growth during the follow-up period does not rule out the malignant nature of the nodule because even an early-stage HCC may take more than 1 year to increase in size.

When the nodule exceeds 1 cm in size, the lesion is more likely to be HCC and diagnostic confirmation should be pursued. If the nodule does not exceed 2 cm, biopsy of the nodule is still recommended because the imaging techniques do not seem to have sufficient accuracy to distinguish HCC from benign conditions and the α-fetoprotein concentration usually remains within normal values or is slightly elevated. Pathological confirmation may be best obtained by histology or combined cytology and histology sampling. The presence of an expert pathologist and the use of standardized interpretation criteria are crucial aspects of the technique. Nevertheless, a negative biopsy of a nodule in a cirrhotic liver can never be taken as a criterion to rule out malignancy. Hence, lesions in which malignancy is not confirmed should be carefully observed over time and additional diagnostic techniques must be applied in case of lesion growth.

For nodules above 2 cm, imaging techniques may confidently establish the diagnosis without needing confirmation with a positive biopsy even in patients with a normal α-fetoprotein value.1 Thus, in the setting of liver cirrhosis, HCC can be diagnosed by the coincident findings with at least two techniques (out of US, spiral CT, and MR imaging) showing characteristic features in a focal lesion larger than 2 cm. Imaging techniques should evidence characteristic arterial hypervascularization; on the strength of recent data, it appears that contrast-enhanced US could be usefully introduced in the diagnostic flow chart for this purpose. Nevertheless, multidetector CT and dynamic MR imaging provide a more comprehensive assessment of liver parenchyma with respect to contrast-enhanced US and are therefore required for intrahepatic tumor staging.

Table 4 Comparison of MR Imaging with Use of Liver-Specific Contrast Agents with Dynamic MR Imaging for the Detection of HCC

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>No. of Patients/No. of Lesions</th>
<th>Overall Lesion Sensitivity</th>
<th>Sensitivity for Lesions &lt; 1.5 cm</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pauleit et al, 2002</td>
<td>43/77</td>
<td>Fe-MRI 63/77 (82%)</td>
<td>Fe-MRI 19/31 (61%)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dy-MRI 69/77 (90%)</td>
<td>Dy-MRI 26/31 (84%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Youk et al, 2004</td>
<td>46/96</td>
<td>Mn-MRI 139/192 (72%)*</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dy-MRI 168/192 (87%)*</td>
<td>P &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Kwak et al, 2005</td>
<td>49/61</td>
<td>Fe-MRI 148/183 (81%)*</td>
<td>Fe-MRI 148/173 (85%)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dy-MRI 165/183 (90%)*</td>
<td>Dy-MRI 92/180 (85%)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = 0.03</td>
<td>P = 0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fe-MRI 148/173 (85%)*</td>
<td>Dy-MRI 165/188 (88%)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = N.S.</td>
<td></td>
</tr>
</tbody>
</table>

*Sum of observers with mean sensitivity and positive predictive values.
Dy-MRI, dynamic contrast-enhanced MR imaging; Fe-MRI, MR imaging with use of the RES-targeted contrast agent ferumoxide; Mn-MRI, MR imaging with use of the hepatocyte-targeted contrast agent Mn-DPDP; N/A, not available.

ABBREVIATIONS

CT = computed tomography
DN = dysplastic nodule
EFSUMB = European Federation of Societies for Ultrasound in Medicine and Biology
HCC = hepatocellular carcinoma
MR = magnetic resonance
RES = reticuloendothelial system
US = ultrasonography

REFERENCES