Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver. The overall 5-year survival rate without any treatment is less than 5%.9 HCC is less frequent in Western countries than in the East or Southeast Asia. The incidence of HCC, however, is rising in Europe and North America.5, 38 In a recent study, the incidence of HCC in the United States increased from 1.4 per 100,000 between 1976 and 1980 to 2.4 per 100,000 between 1991 and 1995.9 Men are affected three times as often as women, and blacks twice as often as whites.9 The age-specific incidence of HCC has progressively shifted toward the younger population, reaching its peak at about 80 to 84 years of age between 1981 and 1985 and dropping to 75 to 79 years of age between 1991 and 1995.9

Cirrhosis is present in 90% of patients with HCC.41 In addition to HCC, the cirrhotic liver often contains regenerative and dysplastic nodules. By understanding the transition from benign to dysplastic to malignant nodules, one can more easily make sense of the complex nodularity depicted in cirrhotic livers on multiple MR imaging pulse sequences.2, 18, 26

During the last two decades, MR imaging has emerged as an important imaging modality for assessing cirrhosis and its complications, such as HCC.27 First, the introduction of fast sequences allows imaging of the entire liver in a single breath-hold. Second, the use of timing bolus sequences as well as automated contrast detection methods (for instance, SmartPrep [GE Medical Systems, Milwaukee, Wisconsin]) allows capture of the arterial phase, which is crucial for the detection and characterization of liver lesions such as HCC. Finally, the availability of dedicated work stations allows postprocessing of large imaging data sets in relatively short times.

In this review, MR imaging features of HCCs are described. To understand better the MR imaging features of HCC, recent progress regarding its etiology, treatment, carcinogenesis, histologic grading, and gross pathology will be described first.

ETIOLOGY OF HCC

HCC occasionally arises in individuals without any preexisting hepatic abnormalities. However, in North America, HCC usually arises in a previously damaged liver.35
Damage to the liver, which often leads to fibrosis and cirrhosis, can be caused by several factors, including toxic agents, metabolic disorders, obesity, alcoholism, and viral infections.34

Aflatoxin, a product of the fungus Aspergillus flavus, which grows on improperly stored grain and nuts (including peanuts), is toxic to liver cells. Aflatoxin is considered an important cause of HCC in areas endemic to aflatoxin, such as Africa and Asia.

Metabolic and genetic disorders, including hemochromatosis (increased hepatocellular iron deposition), Wilson's disease (increased hepatocellular copper deposition), and α1-antitrypsin deficiency, can lead to cirrhosis and HCC. The exact mechanism of the liver injury in the latter condition is unknown.

In developed countries, obesity often results from an increased intake of dietary fat and carbohydrates (high-calorie diets). Alcohol can directly damage the liver cells, but it also impairs the uptake as well as the oxidation of fatty acids in the hepatocellular mitochondria.33 Excess dietary fat and carbohydrates are stored as fatty acids and triglycerides in the hepatocytes. In addition, damaged liver cells lose their ability to efficiently remove triglycerides from the liver. Therefore, obesity, diabetes (type II), and alcoholism can lead to fatty infiltration of the liver (steatosis), which is reversible in early stages. Long-standing steatosis, however, can lead to steatohepatitis, which may progress to fibrosis, and eventually to cirrhosis.34

Viral hepatitis, mainly caused by hepatitis B (HBV) and C (HCV) viruses, is the most important etiologic factor leading to liver fibrosis and cirrhosis in North America.9 In about 85% of adults infected with HCV and 5% of those infected with HBV, the infection becomes chronic.9 Once cirrhosis is established, HCC develops at a rate of 1% to 4% per year. This means that after 20 years HCC will develop in 1.9% to 6.7% of all patients with chronic HCV infection.5 These projections are important because 3.9 million people in the United States are infected with HCV. In contrast, 1 to 1.25 million people are infected with HBV, and the annual probability of HCC is 0.5% and 2.4% in HBV-related chronic hepatitis and cirrhosis, respectively.5,9

This illustrates that HCC is an important health problem in North America, and its severity is expected to increase in the following decades.9 Apart from the mode of treatment, the most important factors influencing the survival of patients with HCC are the size of the tumor at the time of the diagnosis and the severity of the underlying cirrhosis.42 To improve the survival rates, improved diagnostic and therapeutic strategies are necessary.

**TREATMENT OF HCC**

A number of treatments for HCC are available. These include orthotopic liver transplantation, partial resection, and minimally invasive treatment. Liver transplantation may be the most appropriate mode of treatment in patients with HCCs because the procedure can cure both the tumor and the underlying cirrhosis and can reduce the incidence of additional HCCs.42

One study showed that liver transplant is effective in patients with a single tumor (≤5 cm) or no more than three tumors, each 3 cm or less in diameter. In this study, the overall and recurrence-free survival at 4 years was 75% and 83%, respectively. The results of this study also suggested that the total bulk of the tumor tissue rather than the number of tumors determines recurrence.24 Not all patients with HCC can receive a liver transplant because the number of donor organs and the number of medical centers with sufficient expertise are limited.

If liver transplantation is not possible, partial resection is the next best option.42 In these patients, the remainder of the liver should have a sufficient functional reserve. The overall survival rates after partial resection are much lower compared with those after transplantation, probably because of progression of cirrhosis and because of new tumors that arise in the remaining liver tissue.42

Minimal invasive treatment (MIT) has become an alternative to partial resection. Image-guided MIT procedures include laser-
Table 1. TNM STAGING SYSTEM FOR LIVER TUMORS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Solitary tumor &lt;2 cm without vascular invasion</td>
</tr>
<tr>
<td>T2</td>
<td>Solitary tumor &lt;2 cm with vascular invasion, or multiple tumors in one lobe, none &gt;2 cm without vascular invasion, or a solitary tumor &gt;2 cm without vascular invasion</td>
</tr>
<tr>
<td>T3</td>
<td>Solitary tumor &gt;2 cm with vascular invasion, or multiple tumors in one lobe, none &gt;2 cm, with vascular invasion, or multiple tumors in one lobe, any &gt;2 cm, with or without vascular invasion</td>
</tr>
<tr>
<td>T4</td>
<td>Multiple tumors in more than one lobe, or tumors involving a major branch of the portal or hepatic vein(s)</td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
<tr>
<td>MX</td>
<td>Presence of distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

Stage grouping

| I     | T1N0M0 |
| II    | T2N0M0 |
| III   | T1N1M0 |
|       | T2N1M0 |
|       | T3anyNM0 |
| IVA   | T4anyNM0 |
| IVB   | T4anyNM1 |

CARCINOGENESIS OF HCC

New Terminology of Hepatocellular Nodular Lesions

In 1995, an International Working Party, sponsored by the World Congresses of Gastroenterology, recommended a new terminology for nodular hepatocellular lesions. The new nomenclature categorizes lesions using two main sets of criteria (1) regenerative or dysplastic nature of the cells, and (2) anatomic characteristics of the adjacent hepatic stroma. According to the new nomenclature, there are only two types of hepatocellular nodular lesions: the regenerative and the dysplastic or neoplastic lesions.

Regenerative Nodules

Regenerative nodules result from a localized proliferation of hepatocytes and their supporting stroma. Regenerative lesions include monoacinar regenerative nodules, multicentric regenerative nodules, cirrhotic nodules, lobar or segmental hyperplasia, and focal nodular hyperplasia (FNH). FNH and lobular or segmental hyperplasia have been described elsewhere in this issue.

A monoacinar or multicentric regenerative nodule is a well-defined region of parenchyma that has enlarged in response to necrosis, altered circulation, or other stimuli. It may contain one (monoacinar) or more than one (multicentric) portal tracts. The diameter of the monoacinar nodules is usually between 0.1 and 10 mm, and that of the multicentric nodules should be at least 2 mm. Large multicentric nodules are usually between 5 and 15 mm in diameter; rarely they are larger (≥ 5 cm).

Cirrhotic nodules are regenerative nodules that are largely or completely surrounded by fibrous septa. Cirrhotic nodules can be mono- or multicentric. Although not strictly comparable to the mono- and multicentric subtypes the terms micronodular and macronodular (> 3 mm) cirrhosis have been ap-
proved by the International Working Party, especially when histology is not available.

Dysplastic or Neoplastic Lesions

Dysplastic or neoplastic lesions are composed of hepatocytes that show histologic characteristics of abnormal growth caused by presumed or proven genetic alteration. Because the genetic criteria are not yet generally available, dysplastic or neoplastic nodules are defined histologically by (1) the presence of cytoplasmic or nuclear variations and (2) topographic clustering of such variations to form recognizable subpopulations of cells. Dysplastic or neoplastic nodules include hepatocellular adenoma, dysplastic focus, dysplastic nodule, and HCC. Dysplastic focus is defined as a cluster of hepatocytes less than 1 mm in diameter with dysplasia but without definite histologic criteria of malignancy. Dysplasia indicates the presence of nuclear and cytoplasmic changes, such as minimal to severe nuclear atypia and an increased amount of cytoplasmic fat or glycogen, within the cluster of cells that compose the focus. Dysplastic foci are common in cirrhosis and uncommon in noncirrhotic livers.

Dysplastic nodule is a nodular region of hepatocytes at least 1 mm in diameter with dysplasia but without definite histologic criteria of malignancy. These nodules are usually found in cirrhotic livers. Dysplastic nodules can be low- or high-grade. Low-grade dysplastic nodules often show clonelike cell populations, whereas high-grade dysplastic nodules can additionally show a number of nuclear and cytoplasmic aberrations.

HCC is a malignant neoplasm composed of cells with hepatocellular differentiation. A small HCC is defined as measuring ≤2 cm in diameter. According to the International Working Party, the use of terms such as early HCC, early advanced HCC, malignant hepatoma, and hepatocarcinoma should be discontinued. The criteria used to distinguish HCC from high-grade dysplastic nodules are not clearly defined. Criteria in favor of malignancy include prominent nuclear atypia, high nuclear–cytoplasmic ratio with nuclear density twice that of normal, plates three or more cells thick, numerous unaccompanied arteries, mitoses in moderate numbers, and invasion of stroma or portal tracts. Small HCCs are usually well differentiated. Plates more than three cells thick and necrosis are features of moderately or poorly differentiated HCC. Most small HCCs cannot be distinguished histologically from dysplastic nodules. Invasion of the stroma or portal tracts is highly suggestive of malignancy, although invasion may be difficult to diagnose with confidence. In addition, foci of carcinoma have been found in one third of otherwise benign dysplastic nodules. These and other findings support the theory of stepwise carcinogenesis of HCC, especially in patients with pre-existing liver disease.

Stepwise and de Novo Pathways of Carcinogenesis of HCC

On the basis of a detailed examination of 58 small surgically resected hepatocellular lesions, Sakamoto and colleagues proposed a stepwise carcinogenesis of HCC. In their series, the authors found a gradually increasing size and cellular density among the following lesions: adenomatous hyperplasia (AH), atypical AH (AAH), early HCC (eHCC I), and early advanced HCC (eHCC II). Later on, regenerative nodules (RN) were considered precursors of adenomatous hyperplasia. The International Working Group discourages the use of the term adenomatous hyperplasia. According to the new terminology, the previously mentioned stepwise sequence of events (RN → AH → AAH → eHCC I → eHCC II) can be translated as follows: regenerative nodule, low-grade dysplastic nodule, high-grade dysplastic nodule, small HCC, and large HCC (Fig. 1). In contrast to the recognized stepwise carcinogenesis of colon carcinomas, the exact genetic alterations that probably form the basis for the stepwise carcinogenesis of HCC are not fully known. Although at least some HCCs clearly develop within dysplastic nodules, several authors have pro-
Figure 1. Step-wise pathway for the carcinogenesis of hepatocellular carcinoma (HCC). A cirrhotic liver often contains numerous regenerative nodules. One or more regenerative nodules may show signs of atypia and change into dysplastic nodules. Atypia within dysplastic nodules can progress and can give rise to well-differentiated, moderately differentiated, and poorly differentiated hepatocellular carcinomas.

Figure 2. De novo pathway of the carcinogenesis of HCC. Within a non-cirrhotic liver or in non-regenerative liver tissue within a cirrhotic liver one or more foci of HCCs may occur and develop into large well differentiated, moderately differentiated, or poorly differentiated HCCs.
Grading System.\(^8, 17\) Recently, Kanai and colleagues proposed a modified grading system consisting of Edmondson grades I through IV.\(^7\) Depending on tumor differentiation, one hepatocellular lesion may contain one or more clonelike cell populations, and these cell populations can be graded between I and IV. Small well-differentiated HCC usually contains components of Edmondson grades I and II. Edmondson grade I–like cell populations, however, can be seen in high-grade dysplastic nodules as well.\(^13, 17\) Therefore, high-grade dysplastic lesions can resemble very-well-differentiated HCC histologically.\(^13\) Moderately differentiated tumors mainly contain grade II and grade III, and poorly differentiated lesions usually contain grade III and IV cell populations.\(^17\) Originally, Edmondson and Steiner characterized grade II lesions as composed of adult or mature cells and grade III and IV lesions as composed of embryonal or immature cells.\(^8\)

### Gross Pathology of HCC

The classic macroscopic classification of HCC by Eggle has been used since 1901.\(^17\) On the basis of this classification, Edmondson and colleagues categorized 70 HCCs in their series as nodular (81%), massive (23%), and diffuse (3%).\(^8\) This classification, however, is not suitable for small HCC because only Eggle’s “nodular” type can be found in small lesions.\(^17\) In 1987, Kanai and co-workers presented a new classification for small HCC. They divided the lesions into (1) type 1: single nodular type; (2) type 2: single nodular type with extranodular growth; (3) type 3: contiguous multinodular type; (4) type 4: poorly demarcated nodular type; and (5) early HCC (<12 mm): a lesion that does not destroy the underlying liver structure. According to Kanai and colleagues, type 1 and 2 lesions are more likely to show an expanding growth, whereas types 3 and 4 and early HCC predominantly display a replacing growth. Elevated α-fetoprotein, portal vein thrombosis, intrahepatic metastases, and multiple recurrences are more common with type 2 and 3 lesions, whereas type 1 lesions show remark-

### MR Imaging Features of HCC

During the process of stepwise carcinogenesis of HCC, the formation of new tumor vessels takes place, which facilitates the development of regenerative nodules into dysplastic nodules and HCC (Fig. 1).\(^12, 13, 23, 31, 33\) Abundant neovascularity within HCC can be used for early detection and characterization of these lesions with contrast-enhanced imaging.\(^23\) By understanding the events of the stepwise carcinogenesis of HCC and taking advantage of the abundant neovascularity of HCC, one can more easily make sense of the complex nodularity depicted in cirrhotic livers on multiple MR imaging pulse sequences.\(^2, 19, 27\)

### HCC Versus Regenerative and Dysplastic Nodules

Typically, HCC is a focal liver lesion with a high signal intensity on T2-weighted images and a variable signal intensity on T1-weighted MR images. It shows intense enhancement during the arterial phase, usually isointensity during the portal phase, and washout of contrast material during the delayed phase of dynamic gadolinium-enhanced MR images (Fig. 3). In an MR imaging study of 47 HCCs from 1989, 94% of the lesions were hyperintense on T2-weighted images and a variable signal intensity on T1-weighted MR images. It shows intense enhancement during the arterial phase, usually isointensity during the portal phase, and washout of contrast material during the delayed phase of dynamic gadolinium-enhanced MR images (Fig. 3).

In an MR imaging study of 47 HCCs from 1989, 94% of the lesions were hyperintense on T2-weighted images.\(^22\) Later studies reported that the signal intensity of HCC can be variable and more lesions could be iso- or even hypointense on T2-weighted MR images compared with the surrounding liver.\(^6, 23\) This is especially the case in small well-differentiated HCC (Edmondson grade I) or (high-grade) dysplastic nodules.\(^6, 30\) On T1-weighted images, HCC can be isointense, hyperintense, or hypointense to the surrounding liver. Most high-grade dysplastic lesions (formerly adenomatous hyperplasia) and well-differentiated HCC (Edmondson grade I or II) have
Figure 3. Typical HCC. A, T2-weighted fast spin-echo (FSE) image shows a HCC (arrow) which is predominantly bright compared to the surrounding liver. On the T1-weighted sequence (not shown), the lesion was isointense to the liver. B, On arterial phase of the dynamic gadolinium-enhanced T1-weighted spoiled gradient echo (GRE) image, HCC (arrow) shows intense heterogeneous enhancement. C, On portal-phase, the enhancement of the lesion (arrow) is more heterogeneous. D, On the delayed fat-saturated gadolinium-enhanced T1-weighted spoiled GRE image, most of the lesion shows washout with enhancement of a tumor capsule (arrow).

high signal intensity on T1-weighted MR images (Figs. 4 and 5). Muramatsu and colleagues found fatty changes in most HCCs with high signal intensity on T1-weighted images. In a recent study, HCC with high signal intensity on T1-weighted images demonstrated higher copper content than did the surrounding hepatic parenchyma. In addition, this study found that HCCs with higher signal intensity on T1-weighted and T2-weighted images than the surrounding liver were related to a higher and a lower degree of histologic differentiation, respectively. Regenerative nodules, especially with iron deposition (siderotic nodules), are usually hypointense on T2-weighted images (see Fig. 4). Most recent literature clearly indicates that high signal intensity on T1-weighted images is correlated with the presence of an increased amount of copper in the lesion. Fatty change is generally present in no more than 10% of HCCs.

The overlapping signal intensities of regenerative nodules, dysplastic nodules, and HCC on T1- and T2-weighted MR images necessitate the use of contrast media. Several investigators have applied tissue-specific MR contrast media for the diagnosis of HCC.
Figure 4. HCC versus regenerative nodules. A, T2-weighted fat saturated FSE image shows a hyperintense HCC (long arrow) and multiple hypointense regenerative nodules (short arrow). B, On T1-weighted spoiled GRE image, HCC (arrow) as well as most of the regenerative nodules are isointense to the liver. C, On arterial phase of the fat-saturated dynamic gadolinium-enhanced three-dimensional (3-D)-enhanced fast GRE image, a part of the HCC (arrow) shows intense enhancement. D, On delayed phase of the dynamic gadolinium-enhanced study, the entire lesion (arrow) shows washout of contrast with enhancement of the tumor capsule (arrow).
Figure 5. High-grade dysplastic nodule. A, T2-weighted fat-saturated FSE image shows a low signal intensity nodule (arrow). B, On T1-weighted spoiled GRE image, the nodule (arrow) has a higher signal intensity compared to the liver. C, On the arterial phase of the dynamic gadolinium-enhanced 3D fat-saturated enhanced fast GRE image, most of the lesion (straight arrow) shows intense enhancement. The enhancement of the hepatic artery (solid curved arrow) and the inhomogeneous enhancement of the spleen (open curved arrow) are typical for the arterial phase. D, On delayed phase of the dynamic gadolinium-enhanced image, the lesion shows washout with enhancement of a tumor capsule (arrow). Note the enhancement of the portal vessels (curved arrows).
Very-well-differentiated HCC may contain functioning hepatocytes and Kupffer’s cells, which take up hepatobiliary agents such as manganese-based and superparamagnetic iron oxide (SPIO) contrast media.\textsuperscript{12, 29} MR imaging findings with these contrast media of HCC can overlap with other hepatic lesions, such as regenerative or dysplastic nodules, focal nodular hyperplasia, and adenoma. This can lower the diagnostic accuracy of MR imaging for HCC.\textsuperscript{37} Recently, a combination of gadolinium and SPIO was found to improve the diagnostic capability of MR imaging for HCC.\textsuperscript{41}

With knowledge of the neovascularity of HCC, Mitchell and others have proposed the use of gadolinium in combination with breath-hold T1-weighted gradient-echo (GRE) imaging of the liver.\textsuperscript{26} In a study of 84 surgically confirmed HCCs and 25 adenomatous hyperplasias (AH) with CT, computed tomography during arterial portography (CTAP), CT hepatic angiography, Lipiodol (Guerbet S.A., Aulnay sous Bois, France) CT, and contrast-enhanced ultrasonography, Matsui and colleagues found that HCC had a greater arterial blood supply than the surrounding liver in 94% of cases, and AH in 6%.\textsuperscript{23} In a recent study of 72 HCC lesions with dynamic gadolinium-enhanced MR imaging, three enhancement patterns were observed. Pattern I was characterized by a peak enhancement within 60 seconds (arterial phase) followed by a rapid decrease. Pattern II depicted a linear increase of enhancement (no peak in arterial phase). Pattern III showed minimal or slight enhancement. Pattern I was observed in 63% of the lesions with striking neovascularity. Most tumors with pattern III (88%) were small (<2 cm), well-differentiated lesions with slight neovascularity. Pattern II was observed in the scirrhous type of HCC.\textsuperscript{44} Tang and colleagues found dynamic gadolinium-enhanced MR imaging superior to ferumoxides-enhanced MR imaging for the detection and characterization of HCC.\textsuperscript{37} In a comparative study of 72 small HCCs (<3 cm), receiver operative characteristic (ROC) analysis showed that the arterial phase of dynamic gadolinium-enhanced MR imaging was superior to that of helical CT for the detection of lesions in patients with chronic liver disease. In the arterial phase, the area under the ROC curve was 0.96 and 0.84 with MR imaging and helical CT, respectively.\textsuperscript{45}

The superiority of MR imaging is due to differences in techniques of data acquisition and contrast medium administration, in addition to inherently greater tissue contrast with MR imaging. First, in most centers, dynamic gadolinium-enhanced MR imaging is performed with multislice two-dimensional (2D) or three-dimensional (3D) GRE sequences. Such sequences have several intrinsic features that render them superior to CT.\textsuperscript{45} One of the advantages is that the central K-space profiles, which determine the image contrast in all individual slices, are acquired in less than half of the total duration of one breath-hold sequence (5 to 10 seconds). Second, fast MR imaging sequences allow the use of timing bolus or automated contrast detection techniques to determine the contrast arrival time within the aorta. Finally, in MR imaging, a small amount of contrast medium (15 mL to 20 mL of gadolinium) is injected. This allows a short injection time with a compact bolus.\textsuperscript{45} This facilitates the acquisition of truly distinct phases of dynamic contrast-enhanced MR imaging examination of the entire liver.

Small HCC

Recent advances in hepatic MR imaging techniques have facilitated the detection of small HCC (≤2 cm). The definition of small tumors has changed, from a solitary lesion less than 4.5 cm to a tumor less than or equal to 2 cm.\textsuperscript{2} High-grade dysplastic nodules and small HCC may have a nodule-within-a-nodule appearance on MR images, especially if a focus of HCC originates within a siderotic regenerative nodule.\textsuperscript{28} This appearance may be the result of the low intensity of a large nodule with one or more internal foci having a higher signal intensity on T2-weighted images (Fig. 6). On T1-weighted GRE images, such lesions typically show a markedly low intensity of a large nodule with internal foci that are isointense to the liver. At MR imaging, the recognition of small foci of carcinoma within a relatively benign cirrhotic nod-
nodule (nodule-within-nodule) is important because the average doubling time for the volume of such HCC is less than 3 months. Small HCC can also appear as small areas of slightly high signal intensity on T2-weighted images. On T1-weighted images, such areas can be isointense, hypointense, or hyperintense to the liver. On arterial-phase dynamic gadolinium-enhanced MR images, most small HCCs show intense enhancement (Fig. 7). The MR imaging appearance of such areas suggests a replacing, instead of an expanding, type of growth.

**Large HCC**

Large HCC can have a number of characteristic features, such as mosaic pattern, tumor capsule, extracapsular extension with the formation of satellite nodule(s), vascular invasion, and extrahepatic dissemination, including lymph node and distant metastases. The *mosaic pattern* is a configuration of confluent small nodules separated by thin septa and necrotic areas within the tumor. This appearance most likely reflects the histopathology as well as the characteristic growth pattern of HCC. Kadoya and co-workers found a mosaic pattern in 36 of 72 (50%) lesions in their study. In this study, 88% of the lesions with a mosaic pattern were larger than 2 cm. The mosaic pattern is depicted more often on T2- than on T1-weighted images. On T1- and T2-weighted MR images, the mosaic pattern appears as areas of variable signal intensities, whereas on gadolinium-enhanced images the lesions enhance in a heterogeneous fashion during the arterial and later phases (Fig. 8).

*Tumor capsule*, a characteristic sign of HCC, is present in 60% to 82% of cases. In one study, 56 to 72 HCCs showed a capsule at histology, and 75% of the lesions with a capsule were larger than 2 cm (see Figs. 7 and 8). The tumor capsule becomes thicker with increasing tumor size. At histology, capsules are composed of two layers, an inner fibrous layer and an outer layer containing compressed vessels and bile ducts. The tumor capsule is hypointense on both T1- and T2-weighted images in most cases, although capsules with a thickness of more than 4 mm can have an outer hyperintense layer on T2-weighted images. Extracapsular extension of the tumor, with partial projections or the formation of satellite nodules in the immediate vicinity, is present in 43% to 77% of HCC (Fig. 9). In one study, 10 of 38 patients had an extracapsular invasion. Of these, 9 were detected with MR imaging, and only 5 were detected with CT. The presence of extracapsular invasion is one of the factors affecting recurrence after surgery.

Vascular invasion occurs frequently in HCC and can affect both the portal and the hepatic veins. In a recent study of 322 patients undergoing curative resection of HCC, 15.5% showed macroscopic and 59.0% microscopic venous invasion proved at histopathology. In this study, the lesions with vascular invasion were associated with a larger tumor size, a higher α-fetoprotein level, and less frequent encapsulation. In a meta-analysis of seven reports with 1,497 patients, portal vein invasion was found in 24% of the cases with HCC. With MR imaging, vascular invasion can be seen as a lack of signal void on multislice T1-weighted GRE and flow-compensated T2-weighted fast spin-echo images. With gadolinium-enhanced MR imaging, the tumor thrombus typically shows enhancement on images acquired during the arterial phase and a filling defect on images acquired during later phases (Figs. 10 and 11).

Extrahepatic dissemination of HCC occurred in 48% of 75 autopsy cases (Figs. 12 and 13). Recently, 37% of 403 patients with HCC studied consecutively had evidence of extrahepatic metastases on CT examinations. In both studies, most (55% to 58%) of patients had lung metastases, followed by lymph node metastases (53% to 55%). Distribution of sites of metastasis in 1,497 patients from seven reports showed lung metastases in 34% to 58% (mean, 44%) and lymph node metastases in 10% to 42% (mean, 27%). Metastases of HCC to other sites are less common. Edmondson and colleagues found the following frequencies: diaphragm (8%), peritoneum (5%), pleura (4%), adrenal gland (4%), bones (4%), and spleen (3%). At other
Figure 6. See legend on opposite page
Figure 7. Small HCC without a tumor capsule. A, On T2-weighted fat-saturated FSE image, a poorly demarcated area with faintly high signal intensity (arrow) is present. B, On opposed-phase T1-weighted spoiled GRE image, the lesion is not visible. C, On arterial phase of the dynamic gadolinium-enhanced 2-D spoiled GRE image, the lesion (arrow) shows intense enhancement. D, On fat-saturated delayed phase of the dynamic gadolinium-enhanced image, the lesion is difficult to distinguish from the surrounding hepatic parenchyma. Note the absence of a tumor capsule.

Figure 6. Small HCC with a nodule within a nodule appearance. A, On T2-weighted fat-saturated FSE image, a smaller high signal intensity nodule is visible within a low signal intensity nodule (arrow). Note the ghost artifacts (open arrows) caused by the aorta. B, On in phase T1-weighted spoiled GRE image, the nodule is isointense to the liver. Note the ghost artifacts (arrows) caused by the aorta. C, On opposed-phase T1-weighted spoiled GRE image, the nodule becomes hypointense to the liver, most likely due to fatty infiltration at least in a part of the lesion (arrow). D, On arterial phase of the dynamic gadolinium-enhanced two-dimensional (2-D) spoiled GRE image, the lesion (arrow) shows intense heterogeneous enhancement. E, On fat-saturated delayed phase of the dynamic gadolinium-enhanced image, the lesion shows washout with enhancement of a tumor capsule (arrow). Note the enhancement of the portal vessels (curved arrow).
Figure 8. Large HCC with a mosaic pattern and a tumor capsule. A, On single-shot FSE image, a large HCC with areas of high and low signal intensity is visible (arrow). B, On in phase T1-weighted spoiled GRE image, the lesion is predominantly of high signal intensity to the liver with areas of low signal intensity. A thin hypointense tumor capsule surrounds the lesion (arrow). C, On opposed-phase T1-weighted spoiled GRE image, high signal intensity areas within the lesion (arrow) do not decrease in signal intensity, indicating that the high signal intensity is not caused by fatty infiltration.

Illustration continued on opposite page
Figure 8. (Continued). D, On arterial phase of the dynamic gadolinium-enhanced 2-D spoiled GRE image, the lesion (straight arrow) shows heterogeneous enhancement. Note the enhancement of the hepatic artery (curved arrow) and ghost artifact of the aorta (open arrow) projecting over the left lobe of the liver. E, On fat-saturated delayed phase of the dynamic gadolinium-enhanced image, most of the lesion shows washout with enhancement of a tumor capsule (straight arrow). Note the enhancement of the artery (long curved arrow) and the portal vein (short curved arrow).

Figure 9. Large HCC with an extracapsular nodular growth. A, T2-weighted fat-saturated FSE image shows a large tumor (long arrow) and a smaller satellite lesion (short arrow) with high signal intensity to the surrounding liver. B, On the delayed phase of the dynamic gadolinium-enhanced 3-D fat-saturated enhanced fast GRE image, both lesions show a heterogeneous enhancement. Note that the satellite lesion (short arrow) is located just outside the tumor capsule of the larger lesion (long arrow).
Figure 10. HCC with portal vein thrombosis. A, T2-weighted fat saturated FSE image shows a lesion (straight arrow) with high signal intensity as compared to the liver. Note that a part of the tumor projects into the left portal vein (curved arrow). B, On arterial phase of the dynamic gadolinium-enhanced 2-D GRE sequence, the tumor (straight arrow) is isointense to the liver and gives rise to a filling defect in the left portal vein (curved arrow). C, On the delayed phase, the lesion (straight arrow) shows washout of gadolinium. Note the improved conspicuity of the filling defect (long curved arrow). In this phase, the hepatic veins (short curved arrow) have also enhanced.
Figure 11. HCC with liver vein thrombosis. A, T2-weighted fat-saturated FSE image shows a predominantly bright large HCC with tumor extension into the middle liver vein (long curved arrow). The left liver vein shows the signal void (short curved arrow) normally present on this sequence in vessels that run perpendicular to the slice-selection direction. B, On arterial phase of the dynamic gadolinium-enhanced 2-D GRE sequence, the tumor and its extension into the middle liver vein (curved arrow) shows heterogeneous enhancement. Note the ghost artifact (open arrow) caused by the bright pulsating aorta. C, On the delayed phase, the tumor thrombus (long curved arrow) shows washout of gadolinium. Very bright signal in the lumen of the normal left liver vein (short curved arrow) is due to the synergistic effect of the inflow phenomenon as well as the enhancement caused by gadolinium.
Figure 12. HCC with a lymph node metastasis. A, Single shot T2-weighted FSE image shows the primary tumor (T) in the liver and a pathologically enlarged lymph node (N). Note the signal void in the hepatic artery (straight solid arrow), portal vein (curved arrow), and the inferior vena cava (open arrow). B, T2-weighted fat-saturated FSE image shows the tumor (T) as well as the lymph node (N) with higher signal intensity as compared to the single shot T2-weighted image without fat saturation in A. The hepatic artery (straight arrow) and the portal vein (curved arrow) remain visible with signal void. C, On arterial phase of the dynamic gadolinium-enhanced 2-D GRE sequence, the tumor (T) and the lymph node (N) show similar heterogeneous enhancement. Note the enhancement of the hepatic artery (arrow). D, On the delayed phase, the tumor (T) and the metastatic lymph node (N) become heterogeneous due to washout of contrast in some areas of the lesions. Note the enhancement of the portal vein (curved arrow) and the inferior vena cava (open arrow).
sites the percentages were lower. Katyal and co-workers found different frequencies: bone (28%), adrenal gland (11%), peritoneum and omentum (11%), and brain (2%). At other sites lower percentages were found. In this study, most (86% of 148) patients with extrahepatic HCC foci had intrahepatic stage III or IV A disease (see Table 1). Incidental extrahepatic lesions in patients with stage I and II intrahepatic HCC are unlikely to represent metastases of HCC.

HCC in a Noncirrhotic Liver

In patients without cirrhosis or other underlying liver disease, HCC is usually diagnosed at a very late stage. In a study of 68 patients with HCC in a noncirrhotic liver, the median tumor diameter was 8.8 cm. Seventy-two percent of these patients underwent partial resection, and 52% of them were alive 3 years after surgery. These patients can develop late recurrence, but aggressive surgery is still justified. In a recent study of 36 patients with HCC, including 11 with and 25 without cirrhosis, the MR imaging appearances were compared. The lesions in noncirrhotic livers were significantly larger, were more often solitary, and contained a central scar more frequently (Fig. 14). HCC arising in a cirrhotic liver is more likely to show invasion of the portal vein, and HCC originating in a noncirrhotic liver is more likely to involve lymph nodes.

DIFFERENTIAL DIAGNOSIS

Fibrolamellar carcinoma is a malignant hepatocellular tumor with distinct clinical and
Figure 14. Large HCC in a non cirrhotic liver. A, T2-weighted fat-saturated FSE image shows a predominantly bright large HCC (straight arrow) with brighter septa within the tumor that coalesce to form a central scar-like structure (curved arrow). B, On T1-weighted spoiled GRE image, the tumor (arrow) is hypointense relative to the liver. Note the ghost artifact (open arrow). C, On arterial phase of the dynamic gadolinium-enhanced 2-D spoiled GRE image, the tumor (solid arrow) show intense heterogeneous enhancement. Note the ghost artifacts (open arrow) caused by the pulsation of the bright aorta. D, On delayed phase, HCC (arrow) has become heterogeneous with some enhancement of the scar (curved arrow). The ghost artifact appears bright on this image (open arrow).

pathologic findings different from those of conventional HCC. Cirrhosis, hepatitis, alpha-fetoprotein, and other typical risk factors for HCC are usually absent. The tumors occur at a younger average age of 23 years (range, 5 to 69 years). Fibrolamellar carcinoma commonly presents as a large, well-demarcated, and lobulated mass, which is solitary in 80% to 90% of cases. Lesions have an average diameter of 13 cm (range, 3 cm to 27 cm). Most fibrolamellar carcinomas (65% to 75%) occur in the left lobe of the liver. In contrast, conventional HCCs occur predominantly in the right lobe of the liver. At histology, the lesions consist of large eosinophilic, polygonal neoplastic cells arranged in sheets, cords, or trabeculae separated by parallel sheets of fibrous tissue (i.e., lamellae). Vascular invasion occurs in less than 5% of cases. Regional adenopathy may be present in 50% to 70% of patients, and distant metastases are uncommon (20%).

At MR imaging, fibrolamellar carcinomas are typically hypointense on T1-weighted and hyperintense on T2-weighted images. In one study of 11 cases, 82% of the patients showed a central scar with radiating septa, which were hypointense on both T1- and T2-weighted images. Fibrolamellar carcinomas show heterogeneous enhancement on the arterial and portal phase of gadolinium-enhanced MR imaging. Central scar may show enhancement on delayed gadolinium-enhanced images. Experience with specific MR contrast media is limited. Well-differentiated fibrolamellar carcinoma, like HCC, can show
uptake of manganese-based contrast medium.\textsuperscript{10, 25}

Other hypervascular or primary focal liver lesions, such as FNH, liver adenoma, cholangiocarcinoma, metastases, and small hemangiomas, may show features that simulate HCC or fibrolamellar carcinoma. FNH and liver adenoma typically do not differ much in their signal intensity from the surrounding liver parenchyma on T1- and T2-weighted images. They show homogeneous enhancement on the arterial phase and fade to near isointensity on later phases of gadolinium-enhanced images. FNH usually has a central scar that is bright on T2-weighted images. The central scar and the radiating septa in FNH show enhancement on delayed images. The central scar in FNH is also smaller compared with that in fibrolamellar carcinomas.\textsuperscript{10} Patients with peripheral cholangiocarcinomas may have a history of primary sclerosing cholangitis and a lack of hypointense central scar on T2-weighted images. Liver metastases usually are similar in size, accompany a (known) primary malignancy, and affect the older population with normal levels of \(\alpha\)-fetoprotein and a lack of hepatic parenchymal disease.\textsuperscript{10} Hemangiomas are typically bright, well-circumscribed lesions on T2-weighted images and low in signal intensity on T1-weighted images. Most hemangiomas show a peripheral nodular enhancement, with filling in of the lesions on delayed images.\textsuperscript{36} Small hemangiomas may show intense homogeneous enhancement on the arterial phase of the dynamic gadolinium-enhanced images, but such lesions retain contrast on delayed images.\textsuperscript{15, 36} In such cases, in addition to the delayed gadolinium-enhanced images, T2-weighted image sequences with relatively short and long echo-time values may be useful for distinguishing benign from malignant lesions such as HCC.

\textbf{References}


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