Chapter 1
Hepatocellular Carcinoma

Eric C. Ehman, Michael S. Torbenson, Christopher L. Hallemeier, Julie K. Heimbach, and Lewis R. Roberts

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cell cancer. HCC is one of the most common causes of death from cancer worldwide, variably ranking between second and fourth in annual number of deaths and years of life lost from cancer, after lung cancer and essentially tied with gastric cancer and colorectal cancer for the number 2 position [1, 2]. The majority of liver cancers occurring worldwide develop in the context of chronic injury and inflammation of the liver, which results in exhausted liver regeneration and an aberrant healing response with fibrosis leading to cirrhosis. The major etiologies of HCC are chronic hepatitis B

E. C. Ehman (✉)
Department of Radiology, Mayo Clinic, Rochester, MN, USA
e-mail: ehman.eric@mayo.edu

M. S. Torbenson
Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
e-mail: torbenson.michael@mayo.edu

C. L. Hallemeier
Department of Radiation Oncology, Mayo Clinic, Rochester, MN, USA
e-mail: hallemeier.christopher@mayo.edu

J. K. Heimbach
Department of Transplantation Surgery, Mayo Clinic, Rochester, MN, USA
e-mail: heimbach.julie@mayo.edu

L. R. Roberts
Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA
e-mail: roberts.lewis@mayo.edu

L. R. Roberts et al. (eds.), *Evaluation and Management of Liver Masses*,
https://doi.org/10.1007/978-3-030-46699-2_1

and C virus infections, alcoholic liver disease, and nonalcoholic fatty liver disease. Other less common causes of liver inflammation and cirrhosis, including hereditary hemochromatosis, primary biliary cirrhosis, and autoimmune hepatitis, are also associated with increased risk of HCC.

The inflammatory microenvironment induced by the different causes of liver injury is characterized by a high concentration of reactive oxygen species that react with hepatocyte genomic DNA to induce DNA mutations and chromosomal aberrations that lead to induction of tumor oncogenes and loss of tumor suppressor function, thus enhancing liver cell growth and inhibiting apoptosis. The inflammatory and fibrotic microenvironment also mediates other tumorigenic processes, including angiogenesis and inhibition of natural antitumor immune responses. In many parts of the world, dietary exposure to mutagenic compounds such as fungal aflatoxins or plant-derived aristolochic acid significantly enhances the risk of HCC, acting synergistically with other etiologic factors such as chronic viral hepatitis [3]. Chronic hepatitis B virus infection and adeno-associated virus 2 infection uniquely cause HCC by viral integration into the host genomic DNA, leading to increased expression of oncogenic proteins.

Imaging techniques have played a central role in improvements in the diagnosis and care of patients with HCC over the past several decades. The use of ultrasound and multiphasic contrast CT to identify new masses developing in patients with liver cirrhosis followed by advancements in angiographic technique and the use of embolization, either bland or with chemotherapy drugs (transarterial chemoembolization, TACE), led to rapid change in the diagnostic and treatment paradigm for HCC. In 2002, two randomized trials showed that chemoembolization was superior to best supportive care in the management of patients with unresectable intermediate stage HCC [4, 5]. TACE is now complemented by transarterial radioembolization (TARE), which uses Yttrium-90 (Y-90) impregnated glass or resin beads to deliver high-activity β-particle radiation to the arterial distribution of HCCs. TARE has been shown to achieve better tumor control and equivalent survival in comparison to TACE for patients with Barcelona Clinic Liver Cancer (BCLC) stages A or B HCC and Child Pugh Class A or B cirrhosis [6].

The next major advances in the use of imaging in HCC were the recognition that multiphasic CT and MRI of the liver could be used for noninvasive diagnosis of newly developing HCC in the cirrhotic liver. At a time when there was concern about the risk of tumor seeding driving recurrence after biopsy, percutaneous ablation, or liver transplantation with posttransplant immunosuppression, the ability to make a noninvasive diagnosis of HCC with high specificity was a substantial advance, as it provided assurance of a lower risk of recurrence for those patients who were eligible for potentially curative ablation or surgical treatment. Further, the arterial vascular enhancement, portal and late venous washout, and other ancillary features characteristic of viable tumor could also be applied to the assessment of treatment response and tumor recurrence, becoming codified as the modified-Response Evaluation Criteria in Solid Tumors (m-RECIST) criteria for HCC [7]. Most recently, expanded evaluation of the diagnostic criteria for

liver masses has resulted in the development of the Liver Imaging Reporting and Data System (LI-RADS), which provides a more systematic classification of liver lesions by imaging [8].

In this chapter, we discuss the current role of liver imaging in the diagnosis and treatment of HCC, including the imaging-intensive treatment modalities of ablation, transarterial chemoembolization (TACE), transarterial radioembolization (TARE), stereotactic body radiation therapy (SBRT), and proton beam therapy. There is a large variability in phenotypic presentation of HCC, ranging from single nodules between 1 and >20 cm in size, to oligonodular tumors with only two or three nodules that may be located in the same segment of the liver, in different segments of the same, right or left, lobe of the liver, or in a bilateral, multilobar distribution, to multinodular tumors presenting with three to ten or more nodules, and then to the extreme end of the spectrum, where there is diffuse involvement of the liver with small, almost miliary nodules or alternatively with a diffusely infiltrative nearly confluent mass of tumor. Consequently, although general principles of care can be produced in guidelines, the optimal treatment of each patient with HCC must be personalized based on the specific presentation.

Knowledge of the spatial geography of tumor nodules within the liver as determined by cross-sectional imaging is critical for making optimal treatment decisions. For example, whether a 2 cm HCC is best treated by liver transplantation, surgical resection, microwave ablation, or transarterial radioembolization depends on its peripheral or central location within the liver and the proximity of large blood vessels or bile ducts, complemented by an assessment of the severity of the underlying liver cirrhosis, loss of liver synthetic function, and associated portal hypertension, and also of the patient's age and comorbidities that may preclude surgical treatment.

Optimal integration of these different factors in treatment selection requires a multidisciplinary team approach including specialists in diagnostic and interventional radiology, pathology, hepatology, medical oncology, radiation oncology, hepatobiliary surgery and liver transplant surgery, and palliative care. Further, since the varying phenotypic presentations almost certainly reflect the underlying biology of the tumors, it is imperative to develop a deeper understanding of the specific biologic determinants of HCC tumor phenotype and outcomes, as these may be directly linked to the response of specific tumors to local, locoregional, targeted, or immune modulatory treatments.

An additional consideration in the care of patients with HCC is the concept of tumor heterogeneity. During the development and progression of liver cancer, once the key molecular alterations needed for the cancer phenotype are established, the malignant clone continues to acquire additional alterations and potentially additional phenotypic characteristics. This may result in HCCs developing a more aggressive, invasive, and metastatic phenotype over time. From an imaging perspective, phenotypic changes acquired by tumors during their growth can often be discerned by differences in their imaging appearances. Perhaps the most well-known imaging proof of tumor progression is the nodule-in-nodule appearance seen when well-differentiated tumors transition into a less well-differentiated

histology, with the more aggressive clone pushing the earlier, less aggressive tumor to the edges of the nodule. Tumor heterogeneity is important in part because the additional changes in tumor biology that occur during tumor progression may be associated with increased resistance to physical, chemical, or systemic anticancer therapies.

Pathologic Features of Hepatocellular Carcinoma

HCC are composed of malignant epithelial cells with hepatocellular differentiation. A tissue proven diagnosis of HCC is based on H&E findings supplemented with immunohistochemical stains. HCC show a number of important architectural changes that help distinguish them from benign liver lesions. They show abnormal arterialization of the hepatic lobules, loss of portal tracts, and abnormal growth patterns (Fig. 1.1), which can include thickened hepatic cords (normally 1–2 cells thick), pseudoglandular structures, and loss of the normal reticulin framework. These architectural changes can be accompanied by cytological abnormalities such as increased nuclear to cytoplasmic ratios, nuclear atypia including hyperchromasia, and prominent nucleoli. Some HCC also develop distinctive cytoplasmic inclusions, including hyaline bodies, Mallory-Denk bodies, or pale bodies.

After a diagnosis is made, HCC are graded from well differentiated to poorly differentiated, based on how closely the tumor cells resemble normal hepatocytes (Fig. 1.2). Tumor grade predicts both patient survival and disease-free survival in all major clinical settings including resections in cirrhotic [9, 10] and non-cirrhotic livers [11], and after liver transplantation [12].

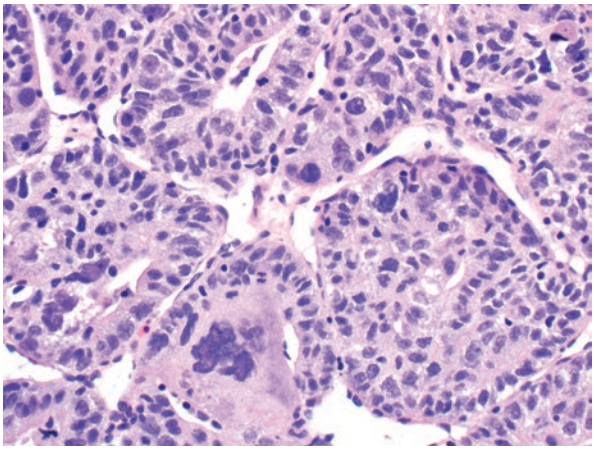

Fig. 1.1 Hepatocellular carcinoma. This hepatocellular carcinoma is growing with thick bulbous plates. The tumor cells show bizarre nuclei

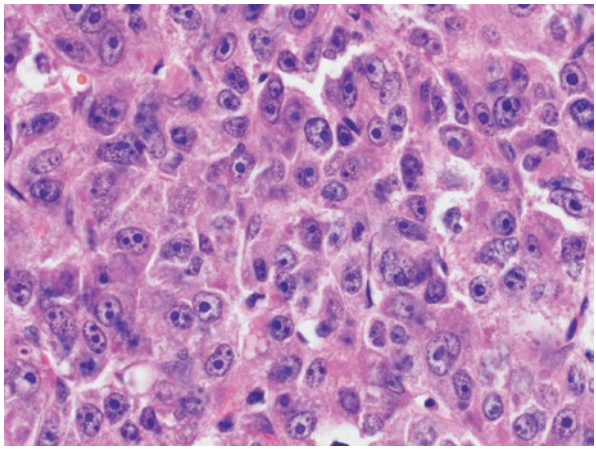

Fig. 1.2 Hepatocellular carcinoma, moderately differentiated. This hepatocellular carcinoma shows enough atypia to indicate that it is malignant, but at the same time shows evidence for hepatic differentiation, with moderately abundant eosinophilic cytoplasm

Histological Subtypes

Up to 35% of HCC can be further classified into histological subtypes or variants, which often have clinical and/or molecular correlates (Table 1.1). The subtypes also have their own potential diagnostic pitfalls, which depend on their morphology (Fig. 1.3). A subtype of HCC is defined by possessing these four key features [13], though all of the features will not be equally well developed when a subtype is first defined and may take many years to fully develop. The key features are the following: (1) unique H&E findings that are reproducibly identifiable and (2) can be confirmed by immunostains or other special studies. These findings in turn have (3) unique clinical correlates and (4) associated molecular findings.

Differential Diagnosis

The histological differential for HCC depends on the degree of differentiation within the tumor and on the presence or absence of cirrhosis in the background liver (Table 1.2). Immunohistochemical stains are used to distinguish between possibilities within the differential and are used in two distinct settings. First, they are used to separate benign hepatic lesions from hepatocellular carcinoma. Stains in this group are predominantly the reticulin stain (Fig. 1.4) and immunostains for glypican 3, glutamine synthetase, and Ki-67. Second, immunostains are used to show hepatocellular differentiation in cases where the differential includes non-hepatic lesions. The most common of these stains in current use are HepPar1 (Fig. 1.5), arginase, and glypican 3.

Table 1.1 Subtypes of hepatocellular carcinoma

Subtype	Frequency (%)	Prognosis[a]	Notes on subtype status
Steatohepatitic	5–20	Similar	Accepted subtype; may be genetically heterogeneous, with morphology reflecting underlying metabolic syndrome or alcohol use
Clear cell	7	Better	Accepted subtype; the percent of clear cell change required has not been well defined
Scirrhous	4	Variable, no strong consensus in literature	Accepted subtype
Chromophobe	3	Similar	Accepted subtype
Cirrhotomimetic	1	Worse	Probable subtype; currently only subtype defined by gross findings
Fibrolamellar carcinoma	1	Similar to HCC in noncirrhotic livers	Accepted subtype
Combined hepatocellular-cholangiocarcinoma	1–3	Worse	Accepted subtype
Combined hepatocellular and neuroendocrine carcinoma	<1	Worse	Accepted subtype
Carcinosarcoma	<1	Worse	Accepted subtype
Granulocyte-colony-stimulating-factor producing	<1	Worse	Accepted subtype
Sarcomatoid	<1	Worse	Accepted subtype
Lymphocyte rich	<1	Better	Accepted subtype
Lipid rich	<1	Unclear	Probable subtype, only a few cases reported

[a]As compared to conventional hepatocellular carcinoma

Pathology Staging and Other Tissue Prognostic Markers

Pathology staging is based on these findings: tumor size (maximum diameter), numbers of tumors, angiolymphatic invasion, and metastatic disease. Angiolymphatic invasion is divided into microscopic type and macrovascular type, where macrovascular invasion involves vessels (portal veins or hepatic veins) that are large enough to be recognized on gross examination or by imaging. The frequency of macrovascular invasion is generally low in resection specimens, because its presence on

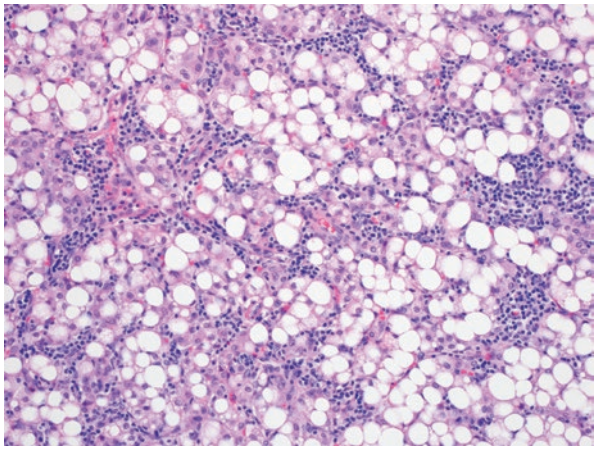

Fig. 1.3 Hepatocellular carcinoma, steatohepatitic subtype. This hepatocellular carcinoma shows fat, inflammation, and fibrosis, which are the key findings in steatohepatitis. This pattern of HCC can sometimes mimic benign liver tissue with steatohepatitis

Table 1.2 Differential for lesions in adult livers

	Well-differentiated hepatocytic lesion	Moderately or poorly differentiated hepatocytic tumor
Cirrhotic background liver	Focal nodular hyperplasia-like lesions[a] Macroregenerative nodule Dysplastic nodule Hepatocellular carcinoma	Hepatocellular carcinoma Cholangiocarcinoma Metastatic carcinoma
Non-cirrhotic background liver	Focal nodular hyperplasia Hepatic adenoma Hepatocellular carcinoma	Hepatocellular carcinoma Fibrolamellar carcinoma Cholangiocarcinoma Metastatic carcinoma

[a]Vascular shunting in cirrhotic livers can sometimes lead to lesions that share many similarities with a focal nodular hyperplasia in the non-cirrhotic liver

imaging is a deterrent to surgical resection. Microvascular invasion is defined as vascular involvement detected only microscopically and is present in about 30% of resected specimens (range from 15% to 60%) [14]. Overall, portal veins are about ten times more likely to be involved than central veins [15], and arterial invasion is even more rare.

A number of other biomarkers of tissue prognosis have been proposed, but to date, expression of CK19 in >5% of tumor cells, which is a negative prognostic indicator, is the most common tissue biomarker in clinical use, largely in Europe and Asia. The lack of underlying liver disease with advanced fibrosis imparts a better prognosis [16]. Targeted molecular-based therapies are also likely to depend on tissue biomarkers.

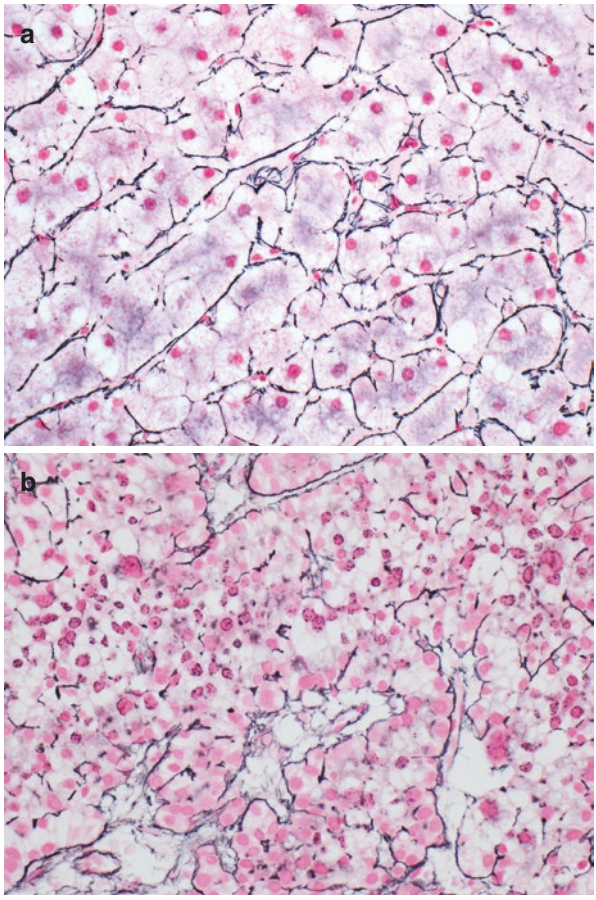

Fig. 1.4 Hepatocellular carcinoma, reticulin loss. The reticulin stain shows thin black lines that represent reticulin. In the normal liver, each hepatocyte is touching reticulin on at least one of its borders (panel **a**), but in hepatocellular carcinoma, many tumor cells are not touching reticulin fibers (panel **b**)

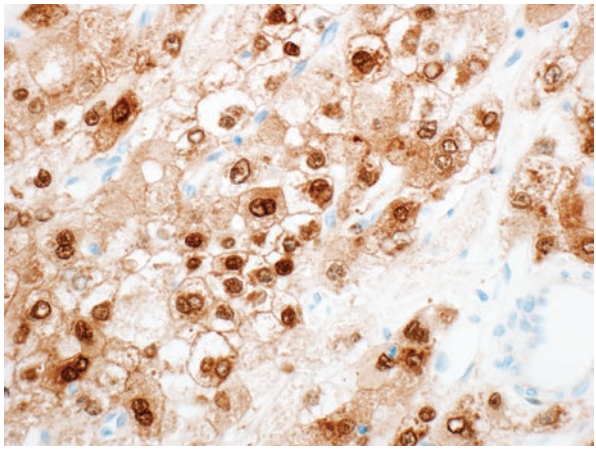

Fig. 1.5 Hepatocellular carcinoma, Arginase 1 stain. The arginase immunostain recognizes a key mitochondrial protein in hepatocytes. Like all immunostains, specificity requires correlation with the H&E findings, as rarely other tumors can also be arginase 1 positive

Imaging Features of Hepatocellular Carcinoma

HCC may be discovered incidentally during imaging for other indications or may be found on surveillance testing in at-risk patients. Historically, ultrasound has been used for surveillance, sometimes performed in an alternating fashion with other cross-sectional imaging including CT and MRI. Various nuclear medicine studies have been investigated, but in general are not being routinely used in the clinical setting. Most current consensus guidelines (American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Japan Society of Hepatology (JSH), Asia Pacific Association for the Study of the Liver (APASL), Korean Liver Cancer Society-National Cancer Center (KLCSG-NCC)) allow a diagnosis of HCC to be made by imaging alone, without the requirement for biopsy confirmation [17–21]. For this reason, it is important that imaging studies intended to diagnose HCC are both sensitive and specific for disease. The Liver Imaging and Reporting Data System (LI-RADS) provides a framework of nomenclature, imaging features, and guidelines to support this goal [8].

Ultrasound (US)

Ultrasound-based surveillance of high-risk patients is recommended by hepatology societies worldwide [17–21], typically every 6 months. Reported sensitivities for HCC in a surveillance population using US range between 47% and 89%, with specificities >90% [22–25]. HCCs have a variable appearance at unenhanced ultrasound, primarily due to the relative background appearance of the liver. In patients with normal liver parenchymal echogenicity, small lesions typically appear hypoechoic to background liver. Larger lesions may appear heterogeneous and have areas of increased or decreased echogenicity secondary to fibrosis, necrosis, internal fat/hemorrhage, or calcification (Fig. 1.6). Because of the variability in echogenicity of HCC, any lesion that is visible by US and cannot be definitely described as benign (cyst, hemangioma, etc.) should be deemed suspicious and follow-up considered. If the lesion is less than 1 cm in maximal diameter, short-term follow-up US is appropriate, but for larger lesions (≥1 cm), further evaluation with contrast-enhanced CT or MRI should be recommended [26].

The ability of US to visualize changes in blood flow using Doppler technique is particularly useful in the evaluation of HCC. Evidence of portal vein thrombus adjacent to a lesion is highly suspicious for HCC and warrants further evaluation with CT or MRI.

Contrast-enhanced ultrasound (CEUS) is an emerging technique in which US imaging is performed following the injection of an IV contrast agent consisting of small bubbles. Because images are obtained in real time as contrast is administered, it is nearly impossible to miss the arterial phase. CEUS is most useful for

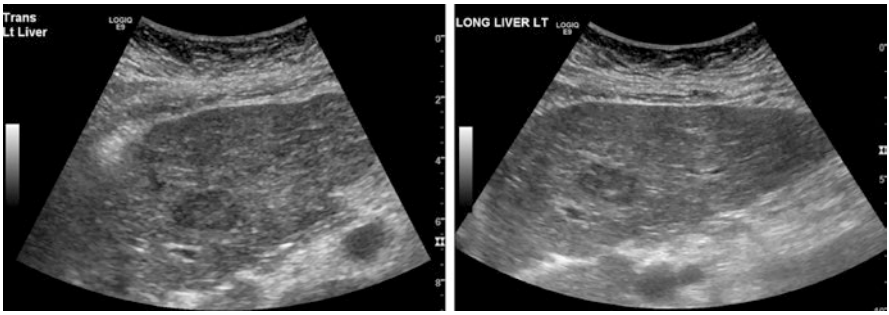

Fig. 1.6 A 72-year-old woman with cirrhosis secondary to primary biliary cirrhosis and autoimmune hepatitis. Gray scale ultrasound images demonstrate a predominantly hypoechoic lesion in the left hepatic lobe, with internal foci of increased echogenicity potentially reflecting internal blood products. No other lesions or venous involvement was seen. Finding is suspicious for hepatocellular carcinoma, and further evaluation with multiphase CT or MRI was recommended

problem-solving or interrogation of lesions seen on prior imaging such as gray scale ultrasound or lesions that are incompletely evaluated at multiphase CT or MRI. A maximum per study dose of IV microbubble contrast agent and a requirement to continuously observe each lesion during the imaging period limit the use of CEUS for whole liver staging. On CEUS, HCC will have non-rim arterial phase hyperenhancement with late (>60 seconds after injection) and mild washout. Care must be taken not to confuse rim-like arterial phase hyperenhancement or early (<60 seconds after injection) and marked washout, as these are features that indicate other types of malignancy such as cholangiocarcinoma or metastases [27]. Reported sensitivity and specificity for HCC using CEUS ranges are 72–94% and 62–69%, respectively [28].

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

Noncontrast or single-phase CT or MRI is not sufficient for diagnosis of HCC. If a suspicious observation is made by noncontrast or single-phase imaging, dedicated multiphase imaging of the liver should be recommended.

HCC has a well-recognized temporal pattern of contrast enhancement at CT and MRI using extracellular contrast agents. Because of neovascularization and increased reliance on hepatic arterial supply to feed tumor cells, HCC enhances in an earlier phase of the contrast bolus compared to background liver and contrast washes out more quickly. Imaging diagnosis based on contrast enhancement pattern has been shown to have per lesion sensitivity of 44–78% while maintaining near 100% specificity even for small nodules measuring between 1 and 2 cm [29–32], with even higher sensitivity for larger lesions [33]. Other morphologic and

histologic features provide imaging features that are less frequently seen but may increase specificity for HCC when present.

A multiphase CT examination for HCC must include adequate late arterial phase images (35–40 seconds post injection) for maximum accuracy. Images can quickly be assessed for proper arterial timing by checking for contrast in both the hepatic arteries and the portal vein, without the presence of hepatic vein opacification. Lack of contrast within the portal vein indicates that the timing is too early, and there may be arterial contrast that has not yet reached hepatocytes, while the presence of hepatic veins indicates that the timing is too late, which decreases tumor enhancement to background contrast. A feature strongly associated with HCC is non-rim arterial hyperenhancement. This enhancement should be unequivocally more dense or intense than background liver and, for maximum specificity, should appear mass like or be associated with other imaging features such as visibility on other contrast-enhanced phases, mild T2 hyperintensity, or diffusion restriction [8].

CT and MRI exams should also include portal venous phase (70–80 seconds post injection) and delayed phase (3–5 minutes post injection) images. Adequacy of portal venous phase images can be confirmed by the presence of contrast in portal veins, hepatic veins, and hepatic parenchymal enhancement. Non-rim washout is a feature of HCC that is defined as the visual decrease in density or intensity between an earlier and a later phase of contrast using extracellular agents. This decreased signal may involve the entire observation or part of the observation and can be seen on either portal venous or delayed phase images. Another imaging feature that is strongly associated with HCC but is seen less frequently than are non-rim arterial phase hyperenhancement or non-rim washout is an enhancing "capsule." This feature must be seen on a more delayed phase of contrast (portal venous or true delayed phase) and must be unequivocally more dense/intense or thicker than fibrotic capsules surrounding other nodules. Figure 1.7 shows an example of a lesion demonstrating arterial phase hyperenhancement, washout, and capsule appearance.

Size and specifically an increase in size on consecutive exams is also a characteristic of HCC. Size should be measured as the maximal diameter on the imaging phase in which the observation is most visible, and if possible not on arterial phase images because perilesional enhancement may result in an artifactual increase or decrease in size. A change in size of greater than 50% in less than 6 months is highly suspicious for HCC (Fig. 1.8).

Minor Features and Special Circumstances

In addition to enhancement pattern and lesion growth, there are several additional imaging features that may either suggest HCC, malignancy in general, or a benign alternative. Features favoring HCC include a non-enhancing "capsule," a nodule-in-nodule appearance, mosaic architecture, intralesional hemorrhage, or intralesional fat. Features suggesting malignancy but not specific for HCC include US visibility as a discrete nodule, slow interval growth, restricted diffusion, mild–moderate T2

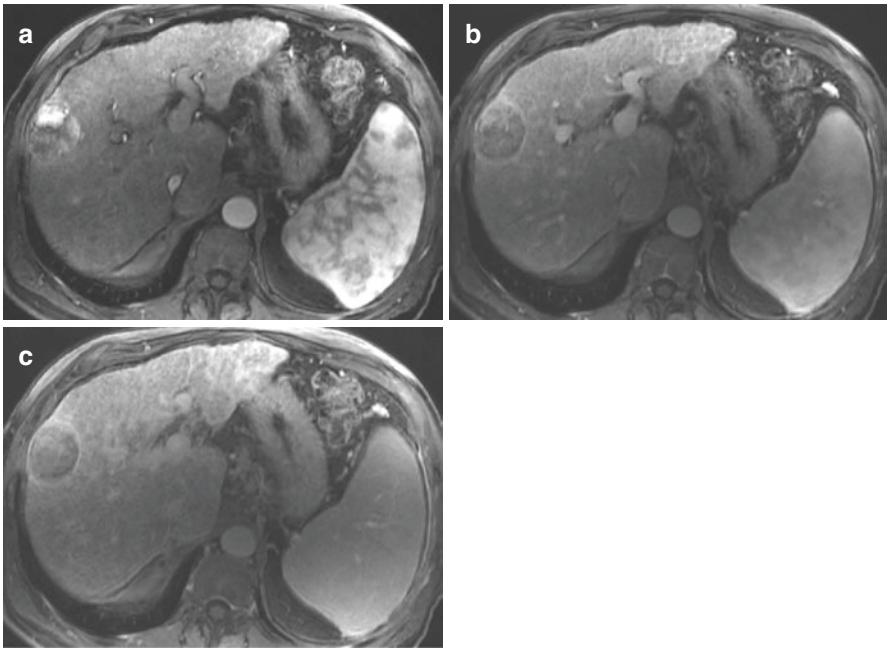

Fig. 1.7 A 69-year-old man with history of cirrhosis secondary to alcohol and steatohepatitis. MR of the liver using an extracellular contrast agent reveals a 5.1 cm lesion in the right hepatic lobe, which has arterial phase hyperenhancement (**a**), washout on both portal venous (**b**), and 5 minute delayed (**c**) phase images, as well as capsule appearance seen on portal venous and delayed phase images. Finding is compatible with a LI-RADS 5/OPTN class 5 lesion and therefore diagnostic of hepatocellular carcinoma

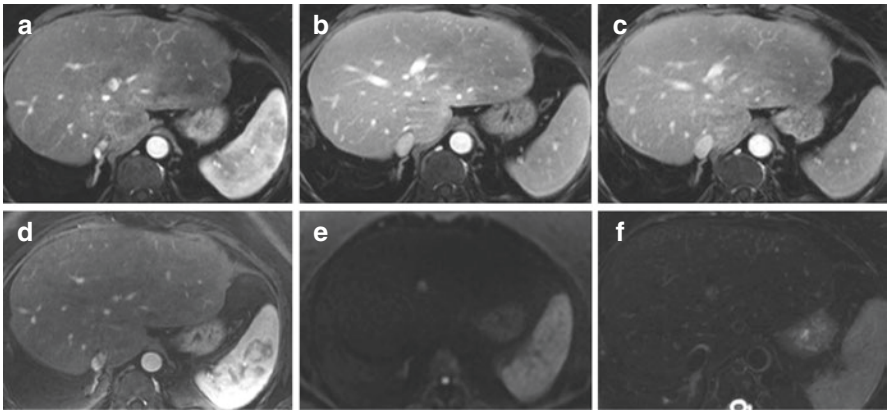

Fig. 1.8 A 53-year-old man with history of HCC status post resection. Multiphase MR images demonstrate an arterially hyperenhancing (**a**) lesion adjacent to the left portal vein, which persists in the portal venous (**b**) and 5 minute delayed phases (**c**). This lesion has restricted diffusion (**e**) and intermediate T2 signal (**f**). MR obtained 4 months prior shows that the lesion has nearly doubled in diameter (from 6 to 11 mm) in the interval (**d**). Given arterial hyperenhancement and threshold growth, this lesion is considered a LI-RADS 5 lesion

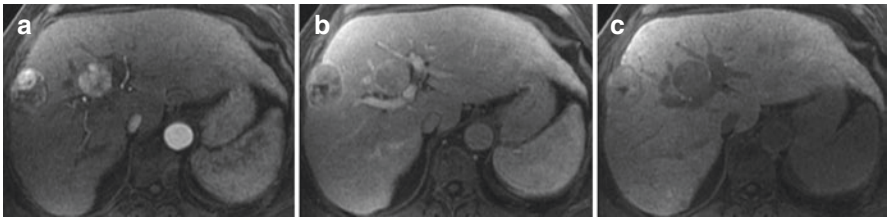

Fig. 1.9 A 68-year-old man with chronic hepatitis C and multiple hepatocellular carcinomas. MRI of the liver performed with a hepatobiliary contrast agent demonstrates two lesions in the right liver. Both lesions show arterial hyperenhancement (**a**), washout, and capsule appearance (**b**). The more lateral lesion shows moderate hepatobiliary contrast agent on 20-minute hepatobiliary phase images (**c**) while the more medial lesion shows no uptake. Both lesions also show a hepatobiliary phase hypointense rim (**c**). Based on imaging appearance, both lesions are LI-RADS 5/OPTN class 5 lesions

hyperintensity at MRI, corona enhancement, focal fatty sparing within a solid mass, focal iron sparing within a solid mass and transitional or hepatobiliary phase hypointensity when using hepatobiliary contrast agents. Features favoring benignity include size stability or reduction, contrast enhancement following blood pool, lack of vessel distortion, iron in mass greater than in liver, marked T2 hyperintensity, and isointensity on the hepatobiliary phase.

There is increased evidence that MRI hepatobiliary contrast agents such as gadoxetate disodium and gadobenate dimeglumine may be useful in the detection and characterization of HCC, providing an increase in per-lesion sensitivity over extracellular contrast-enhanced MRI of 6–15% [34–36]. In general, more poorly differentiated tumors will have decreased expression of the OATP transporter, which normally facilitates hepatobiliary contrast uptake, resulting in hypointensity of these lesions on hepatobiliary phase images. There is the potential for false negatives in lesions which remain well differentiated enough to have adequate OATP expression, and thereby remain hyperintense or isointense to background liver on hepatobiliary phase images (Fig. 1.9). Use of hepatobiliary agents is also limited in patients with severe hepatic dysfunction (total bilirubin >3 mg/dL) due to decreased hepatic uptake of contrast. Further work will be required to identify the most appropriate role for these agents in the evaluation of HCC.

Nuclear Medicine (PET, Scintigraphy)

Currently, the role of positron emission tomography (PET) and single photon emission computed tomography (SPECT) in the evaluation of HCC is limited. 18F-fludeoxyglucose (FDG) is the most commonly used tracer for whole-body PET/CT and is a marker of cellular metabolism. Prior studies have shown that sensitivity using FDG PET/CT is limited with only 50–70% of HCC having FDG uptake beyond background liver [37]. In general, more poorly differentiated HCCs have a greater degree of FDG uptake and are more likely to metastasize; therefore,

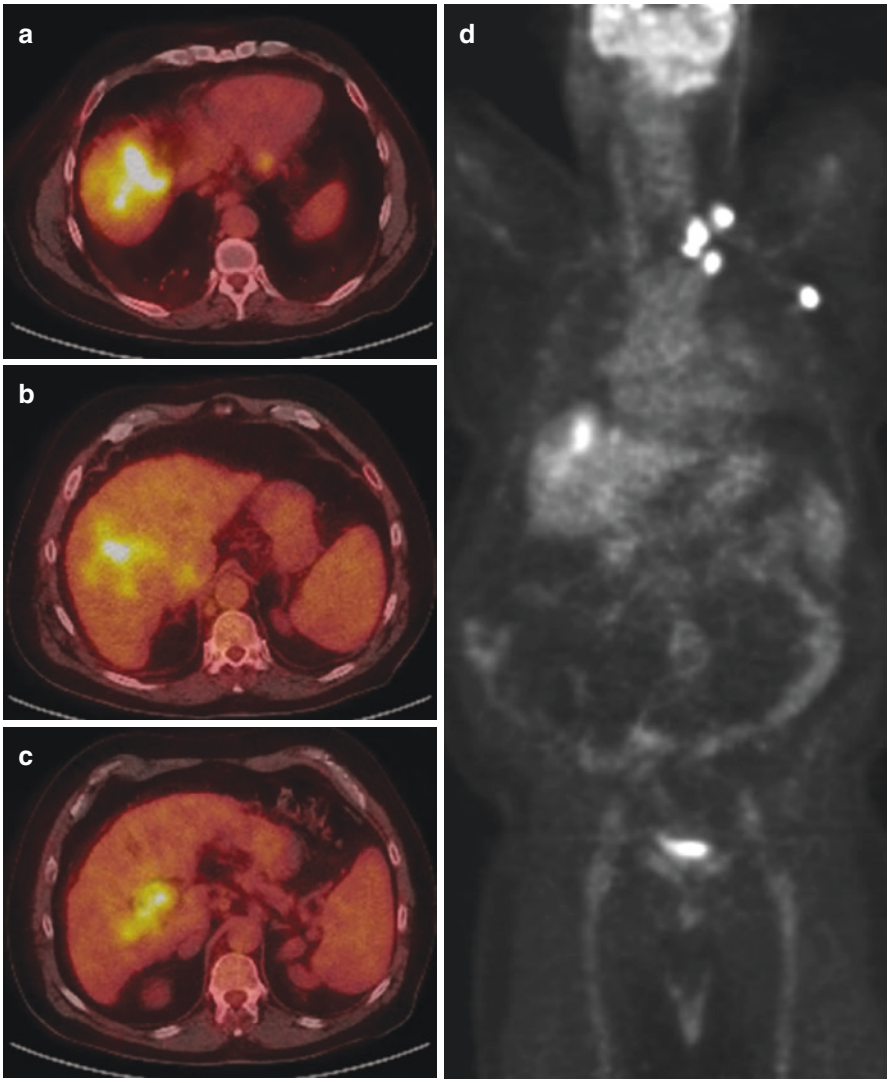

Fig. 1.10 A 66-year-old man with history of hepatitis C found to have a hepatic mass on ultrasound. Biopsy proved hepatocellular carcinoma. Fused FDG PET/CT images (**a**–**c**) show an FDG avid mass in the dome of the liver with extension of abnormal FDG uptake into the portal vein. Coronal PET image (**d**) shows metastatic left supraclavicular and axillary lymphadenopathy, which is also FDG avid

there may be a role for PET/CT in the detection of metastatic disease [38] or in the prognostication of patients at risk for advanced disease [39]. An example of FDG avid metastatic disease is shown in Fig. 1.10.

No reliable SPECT tracer for the detection of HCC exists, but Tc-99 m macroaggregated albumin (MAA) scans are used prior to treatment with Y-90

radioembolization to determine lung shunt fraction and to confirm tumor arterial supply. Bremsstrahlung scanning can be performed immediately after treatment with Y-90 to confirm in-tumor deposition of radioactive particles and absence of nontarget embolization.

Catheter Angiography

Infrequently used for the de novo diagnosis of HCC, catheter angiography typically takes place as a part of catheter-directed therapies including bland embolization, chemoembolization, and radioembolization. Angiographic evaluation of HCC is useful to determine the presence of arterial blood supply to the tumor, the location of the lesion, and whether applied treatment has successfully altered the arterial blood supply to the tumor. Cone-beam CT, which can be performed during catheter-based procedures and allows for 3D reconstruction and display of angiographic images (Fig. 1.11), has been shown to further improve diagnosis and treatment in many HCC lesions [40, 41].

Posttreatment Follow-Up

Imaging following therapy for HCC has an evolving base of knowledge. Given that the range of available treatments includes transarterial embolic, percutaneous chemical and thermal ablation, external beam radiation, and surgical resection, the scope of appearances of treated lesions is broad. In general, treated lesions should no longer demonstrate the suspicious features of HCC, including arterial

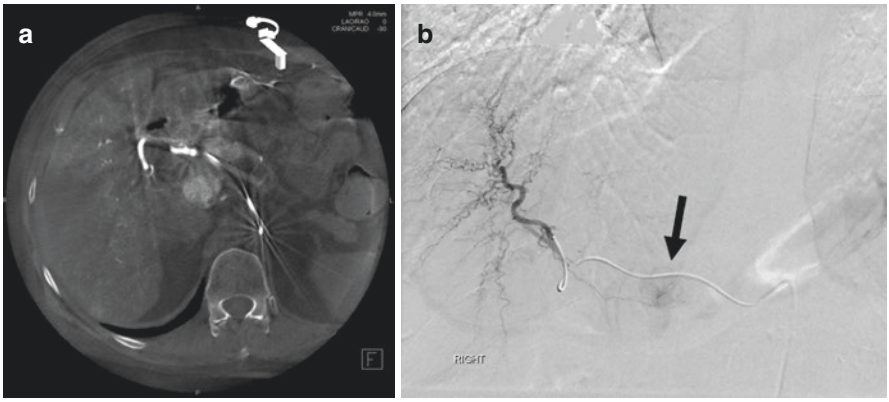

Fig. 1.11 A 63-year-old woman with cirrhosis secondary to nonalcoholic fatty liver disease. Hepatic angiogram (**a**) and cone-beam CT performed during a transarterial chemoembolization procedure (**b**) show an avidly enhancing tumor in the caudate lobe

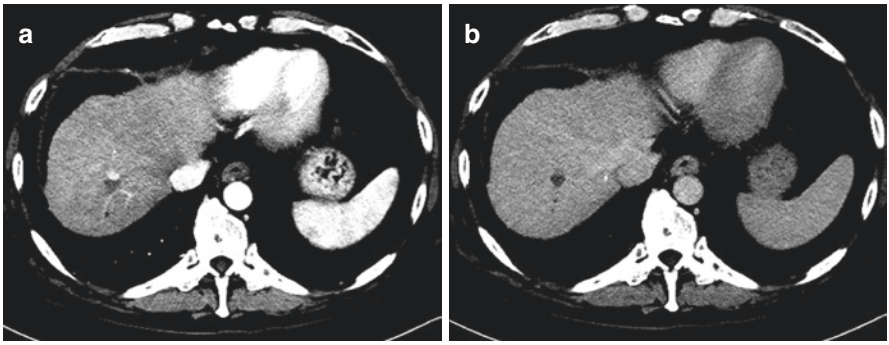

Fig. 1.12 A 61-year-old man with cirrhosis due to nonalcoholic fatty liver disease complicated by multifocal hepatocellular carcinoma. The patient underwent bland embolization to a tumor in the hepatic dome, but follow-up multiphase CT approximately 9 weeks later shows a nodule of residual arterial hyperenhancement (**a**) with washout on delayed phase images (**b**), suggesting residual viable disease

hyperenhancement, washout, or capsule appearance, nor should they enlarge significantly over time. Other features such as low-level progressive enhancement or slow enlargement may represent benign scar tissue or resolving necrosis at the site of treatment. Unfortunately, current imaging techniques are limited in the detection of small areas of viable tumor [42], and therefore any suspicious feature should be examined and followed very carefully (Fig. 1.12).

Imaging Scoring Systems (LI-RADS, OPTN)

The Liver Imaging Reporting and Data System (LI-RADS) is a system created by a multidisciplinary group of diagnostic and interventional radiologists, surgeons, hepatologists, and hepatopathologists and is intended to provide a comprehensive system for standardizing technique, interpretation, and reporting of liver imaging in order to improve communication, research, and ultimately patient care [8].

LI-RADS is a dynamic document that offers guidance for the evaluation of the liver at ultrasound surveillance, contrast-enhanced ultrasound and CT/MRI, as well as for the evaluation of treatment effects. Details of observation categorization and specifics of scoring are beyond the scope of this chapter, but up-to-date instructions may be found at the cited website. LI-RADS major and ancillary imaging features of HCC are listed in Table 1.3. LI-RADS categories range from 1 to 5 with increasing score increasing confidence in HCC and a LI-RADS 5 lesion having very high specificity for HCC.

Another important system for the evaluation of HCC are the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS)

Table 1.3 LI-RADS v2018 major and ancillary imaging features of HCC

Major features	Ancillary features
Determine primary categorization	*Allow adjustment of category after determining major features*
Used with lesion size to diagnose HCC	**Favoring malignancy**
Arterial phase hyperenhancement	US visibility as discrete nodule
Non-peripheral washout	Subthreshold growth
Enhancing capsule	Restricted diffusion
Threshold growth	Mild–moderate T2 hyperintensity
	Corona enhancement
	Fat sparing in solid mass
	Iron sparing in solid mass
	Transitional phase hypointensity
	Hepatobiliary phase hypointensity
	Favoring HCC in particular
	Non-enhancing capsule
	Nodule-in-nodule
	Mosaic architecture
	Blood products in mass
	Fat in mass, greater than adjacent liver

guidelines. The goal of this classification system is to recognize patients who would benefit from liver transplantation as a treatment for HCC in the absence of severe liver dysfunction, and thus grant them priority for allocation of deceased donor liver allografts. Because of the scarcity of donor livers, and lack of histologic confirmation in many cases, a high specificity for HCC is required in order to grant a patient MELD exception points. There is general agreement between the LI-RADS and the OPTN systems for the characteristics which are diagnostic of HCC (LI-RADS 5/OPTN class 5). The precise definitions of the UNOS/OPTN policy are again beyond the scope of this chapter, but are available for review in their most recently revised and published form [43]. In brief, for a nodule that is between 2 and 5 cm to be class 5, it must be hyperenhancing on arterial phase imaging and have washout or a pseudocapsule on delayed phase. Class 5 lesions between 1 and 2 cm are more stringently defined and require hyperenhancement on arterial phase imaging plus washout and a pseudocapsule. Hypervascular lesions which do not have washout or pseudocapsule must then meet specific interval growth criteria to be considered class 5. Biopsy may be considered for lesions that are highly suspicious but do not meet the OPTN class 5 requirements. For patients for whom transplantation may be an option, it is essential to establish the diagnosis of HCC before treating with liver-directed therapy.

Imaging for Liver Fibrosis, Cirrhosis, and Portal Hypertension

An important subclassification that needs to be made early in the evaluation of patients with suspected HCC is the distinction between those with and those without significant liver fibrosis or cirrhosis. Depending on the region of the world and the underlying etiology of liver disease, between 50% and 90% of patients with HCC will have underlying cirrhosis. These patients have two liver diseases, first the underlying etiologic cause of cirrhosis, which is most commonly chronic hepatitis B or C, alcoholic liver disease, or nonalcoholic fatty liver disease, and second, the growing hepatocellular carcinoma, which, if left unchecked, will replace the benign liver tissue and lead to liver failure.

Ultrasound, CT, and MRI Features of Cirrhosis

Liver cirrhosis is associated with the development of a number of characteristic imaging features, including nodularity of the liver, which may be micronodular or macronodular. Liver nodularity may be appreciated on ultrasound or cross-sectional CT or MRI studies as an irregular nodular outline of the liver, coarse echogenicity on ultrasound, or nodular heterogeneity on CT or MRI. Cirrhosis also leads to features of portal hypertension that are visible on imaging, including splenomegaly, patency of the umbilical vein, or the presence of paraumbilical varices, also termed the caput medusa, and upper abdominal or paraesophageal varices. Cirrhosis is also associated with a prothrombotic tendency that may lead to the development of portal vein thrombosis and with decreased liver synthetic function leading to hypoalbuminemia, and in conjunction with increased portal pressure due to increased fibrosis and stiffness of the liver, to the development of ascites.

Noninvasive Assessment of Liver Fibrosis

A number of radiologic techniques have been developed for the assessment of the degree of liver stiffness; these include transient elastography (Fibroscan), ultrasound-based real-time tissue elastography or shear wave elastography, acoustic radiation force impulse imaging, and MR elastography. In those patients found to have underlying liver cirrhosis, the initial step in the treatment plan should be the evaluation and management of any of the sequelae of cirrhosis with portal hypertension, including ascites, esophageal or gastric varices, and hepatic encephalopathy. If not addressed, these sequelae will usually have a detrimental effect on the patient's performance status, often leading to the patient being considered ineligible for therapies that might otherwise be considered optimal.

Radiologic Assessment of Clinically Significant Portal Hypertension

Once the presence or absence of significant fibrosis or cirrhosis has been elucidated and any complications addressed, the next step in the determination of optimal therapy for HCC patients is making the distinction between those who have no cirrhosis and therefore have satisfactory liver synthetic function and the absence of clinically significant portal hypertension—typically defined clinically as patients with normal bilirubin, a platelet count above 120,000, and no varices - versus those with clinically significant portal hypertension, who are at risk for complications after surgical resection or interventions that result in significant decline in already tenuous liver function.

The hepatic venous pressure gradient (HVPG), which is the difference between the wedged (WHVP) and the free hepatic venous pressures, represents the gradient between pressures in the portal vein and the intra-abdominal portion of the inferior vena cava. The HVPG is measured angiographically, usually via a transjugular approach. Where the HVPG is routinely measured, patients with significant portal hypertension have gradients of 10 mmHg or greater. In centers where the Model for End-stage Liver Disease (MELD) score is routinely used, a MELD score of 9 or more has been shown to be associated with a higher risk of hepatic decompensation after surgical resection [44].

Surgical Treatments for Hepatocellular Carcinoma

Patients with a single HCC and a normal serum bilirubin and without clinically significant portal hypertension are usually candidates for consideration of surgical resection with curative intent regardless of the size of the primary tumor. In some patients for whom the remnant liver that would remain after surgical resection is felt to be marginal, portal vein embolization of the affected segment or lobe of the liver can be performed by angiographic techniques. This usually leads to compensatory hypertrophy of the unaffected liver over a 4- to 6-week period and can allow successful resection with a reduced risk of liver failure.

For patients with early stage HCC who have clinically significant portal hypertension and an elevated bilirubin, the most effective treatment currently available is liver transplantation, which has the advantage of removing the malignant tumor and also replacing the cirrhotic liver. The primary barrier to transplantation is the extreme shortage of available liver allografts. In addition, following transplant, patients need to be maintained on lifelong immunosuppression, which is associated with important side effects such as renal insufficiency and an increased risk of infection. While initially patients transplanted with HCC had dismal outcomes because of the high risk of recurrent disease, it was later established that patients with limited HCC disease or with relatively unaggressive, less invasive, and metastatic

features have excellent posttransplant survival and are appropriate candidates for liver transplantation. These were initially codified as the Milan criteria, including patients with a single lesion no more than 5 cm in size or with two or three lesions, each no more than 3 cm in size [45]. Typically, these are patients with a serum alpha fetoprotein (AFP) less than 500 ng/mL. Limited expansion of these criteria is allowed in patients who have favorable biology as demonstrated by response to locoregional or other treatments resulting in downstaging of the tumor to a size and number within the Milan criteria. The most popular extension of the Milan criteria are the University of California San Francisco (UCSF) criteria, which allow transplantation of patients with a solitary tumor smaller than 6.5 cm, or patients having three or fewer nodules, with the largest lesion being smaller than 4.5 cm or having a total tumor diameter less than 8.5 cm without vascular invasion [46].

Nonsurgical Treatment Algorithm for Hepatocellular Carcinoma, Including Radiological Methods

Patients with HCC who are not candidates for surgery and have 1–3 tumors, with the largest being no more than 3 cm in size, have been shown to have excellent results from treatment with local ablation techniques such as radiofrequency ablation or microwave ablation. Local ablation techniques that are less commonly used include irreversible electroporation, laser ablation, and percutaneous ethanol injection. Cryotherapy can be used in specific circumstances when there is a need for high-definition delineation of the extent of therapy such as in the treatment of pelvic metastases where the ability of CT/MRI to visualize the extent of the ice ball facilitates avoidance of injury to the pudendal nerves and other nerve roots.

Patients who are not candidates for treatment with curative intent using surgical resection, ablation, or liver transplantation are currently considered next for locoregional treatment with TACE.

Local Ablation

Local ablation methods typically use heat, cold, or chemical methods to induce necrosis or apoptosis of HCC nodules. The most commonly used methods are radiofrequency ablation and microwave ablation [47, 48]. Both techniques heat the tissue surrounding probes that are placed into the tumor nodule, resulting in coagulative necrosis of the tissue [49]. Microwave ablation is generally more popular than radiofrequency ablation where both are available, due to its similar effectiveness with shorter treatment times [50]. Both techniques rely on US- or CT-guided imaging for placement of the treatment probes, which can be performed percutaneously or surgically. The main contraindication for the use of heat-based ablation methods

is proximity of the tumor nodules to large blood vessels, which act as heat sinks and prevent the achievement of sufficiently high temperatures to effectively destroy the tumor tissue. Microwave ablation may be less susceptible to the heat sink effect than radiofrequency ablation [51]. When necessary, percutaneous ethanol injection can be used close to large vessels to supplement the effects of the heat-based ablative methods. Additional, less commonly used ablation methods include laser ablation, which can be applied with MR imaging, and irreversible electroporation.

Locoregional Transarterial Chemoembolization and Radioembolization

Locoregional treatment of HCC using catheter-based approaches has been in use since the late 1970s and early 1980s. The rationale for the technique is based on the observation that 95% or more of the vascular supply to HCCs is derived from the hepatic arterial branches. Consequently, delivery of absorbable gelatin sponge (Gelfoam) or nonabsorbable polyvinyl alcohol (Ivalon) beads was used to occlude the tumor vasculature, with initial positive results encouraging further development of the technique. The results of transarterial bland embolization (TAE) for HCC were first reported from Japan in 1983, followed by results of transarterial chemoembolization (TACE) using the anticancer agents mitomycin C or adriamycin suspended in Lipiodol in 1985. After a number of equivocal studies, two clinical trials completed in 2002 established the superiority of TACE over best supportive care in patients with intermediate stage HCC, and it subsequently became regarded as the standard of care [4, 5]. The use of TACE has been plagued by a lack of standardization of the techniques and chemotherapy agents used, leading to difficulty in determining the underlying reasons for variable results seen in different studies. More recently, attempts to standardize the administration of TACE have included the use of drug-eluting beads loaded with chemotherapy agents, typically doxorubicin/Adriamycin for HCC or irinotecan for colorectal cancer liver metastases. Increasing evidence suggests that TAE may achieve the same outcomes as TACE in patients with HCC [52, 53].

Transarterial radioembolization (TARE) is a modification of TACE in which glass (TheraSphere) or resin (SIR-Sphere) microspheres bearing Y-90 are infused into the hepatic artery branches supplying HCC nodules in a segment or segments of the liver. Y-90 microspheres are pure beta particle emitters, producing radiation with a mean human tissue penetrance of 2.4 mm and a half-life of 64.2 hours. Because of the limited depth of penetration and short half-life, Y-90 microspheres can be administered on an outpatient basis, and patients do not require special radiation shielding precautions after treatment [54].

TARE has been applied in a number of different circumstances for treatment of HCC. It can be used for “radiation segmentectomy,” in which relatively small regions of the liver are selectively catheterized and treated with very high radiation

doses per unit volume, resulting in complete radiation necrosis of the treated area. This approach can be used in patients with early stage disease, who are not candidates for surgical resection or for whom ablation is contraindicated or not considered an optimal treatment modality. TARE can also be used in place of portal vein embolization. Finally, TARE can be used in place of TACE for patients with intermediate stage disease, or instead of sorafenib or lenvatinib in patients with advanced stage HCC. For these latter indications, TARE has been shown to be capable of downstaging intermediate stage tumors to within criteria for liver transplantation and, in general, appears to be more effective than TACE in inducing tumor regression; however, the higher effectiveness in inducing tissue injury can also put patients at risk for either early or delayed radiation-induced liver injury [55–57]. It is therefore important to carefully assess liver remnant size and function when all but very limited regions of the liver will be treated with TARE.

External Beam Radiotherapy

External beam radiotherapy (EBRT) has been used for several decades for the treatment of HCC. It has long been recognized that the liver is a relatively radiosensitive organ, with whole liver doses of 30 Gy or higher associated with a high risk of radiation-induced liver disease (RILD), a syndrome characterized by anicteric hepatomegaly and ascites, followed by progressive liver failure and death [58]. In the 1970–1980s, the Radiation Therapy Oncology Group (RTOG) conducted several prospective clinical trials (RTOG trials 79-28, 83-01, 83-19, and 88-23) in the United States assessing the safety and efficacy of moderate dose (21–24 Gray) whole liver EBRT with concurrent radiosensitizing systemic chemotherapy for unresectable HCC. Results were not very promising; partial tumor response (>30% reduction) was seen in 22% of patients, and median survival was approximately 6 months [59]. Further attempts to intensify therapy using accelerated hyperfractionated radiotherapy, intra-arterial chemotherapy, and radioimmunotherapy were also unsuccessful. Therefore, EBRT was largely abandoned as a primary treatment for HCC in the United States, with use confined to palliation of local symptoms from metastatic disease.

Significant advances in diagnostic imaging and radiotherapy planning and delivery techniques have sparked renewed interest in the use of EBRT for HCC. Proton beam radiotherapy (PBT) and stereotactic body radiotherapy (SBRT) are advanced EBRT techniques, which allow delivery of high doses of focal radiation with relative sparing of surrounding normal tissues (Fig. 1.13). Furthermore, there is now better recognition of factors associated with increased risk of hepatotoxicity after partial liver radiotherapy, including severity of baseline liver dysfunction and radiotherapy dose-volume parameters for uninvolved liver [58]. Several retrospective and single-arm prospective studies have demonstrated promising safety and efficacy of PBT and SBRT for select patients with nonmetastatic HCC. A recent systematic

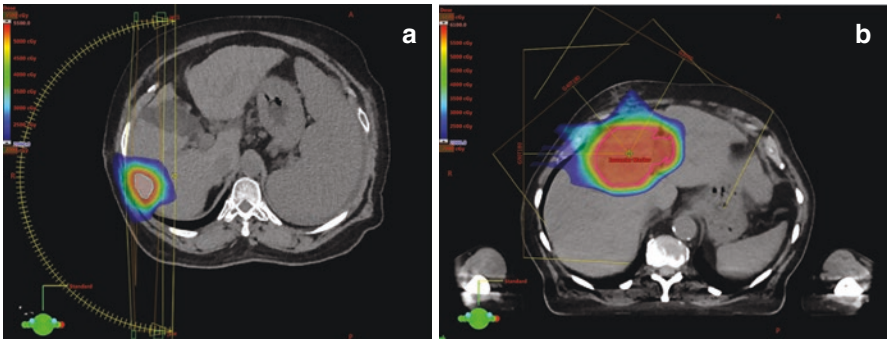

Fig. 1.13 (**a**) A patient with a 3 cm solitary hepatocellular carcinoma (blue outline) treated with stereotactic body radiotherapy (50 Gy in 5 fractions over 1 week) as "bridge to transplantation" therapy, following progression after previous hepatic arterial embolization. The blue indicates the volume receiving 20 Gy or higher, and the red indicates the volume receiving 50 Gy or higher. (**b**) A patient with a 7 cm hepatocellular carcinoma (pink outline) with contiguous left portal vein tumor thrombus treated with proton beam radiotherapy (58.05 Gy in 15 fractions over 3 weeks) as definitive therapy. The blue indicates the volume receiving 20 Gy or higher, and the red indicates the volume receiving 50 Gy or higher

review and meta-analysis found that PBT and SBRT were associated with greater efficacy and reduced toxicity compared to conventional radiotherapy techniques [60]. Ongoing studies will further define the role of EBRT for patients with localized HCC.

Systemic Therapy

For much of the early experience with systemic therapy for cancer, HCC was found not to be effectively treatable with chemotherapy. In particular, patients with cirrhosis often had cytopenias due to portal hypertension and splenomegaly that were exacerbated by treatment with cytotoxic chemotherapy, making them prone to chemotherapy-induced toxicity. In 2007, the first positive clinical trials of targeted therapy using the multikinase inhibitor sorafenib for patients with advanced HCC were reported. Sorafenib was shown to improve the median survival of patients with advanced HCC by 2–3 months [61, 62]. After an approximately 10-year period in which there was no progress in identifying new systemic treatments that significantly improve survival of patients with advanced HCC, several new therapies were approved in 2017 and 2018. Regorafenib was approved for HCC in the second line after progression or intolerance of sorafenib, followed by approval of the anti-PD-1 immune checkpoint inhibitor nivolumab following evidence from Phase I/II studies that nivolumab achieves a 15–20% response rate in advanced HCC. Subsequently, the multikinase inhibitor lenvatinib, an inhibitor

of VEGF receptors 1–3, FGF receptors 1-4, PDGF receptor α, RET, and KIT, was approved for use in the first line after a Phase III study showed non-inferiority to sorafenib in the first line [63–65]. Finally, the anti-PD-1 immune checkpoint inhibitor pembrolizumab was also approved for second-line treatment of HCC in late 2018 [66]. In 2018, two additional Phase III studies of cabozantinib, an inhibitor of MET, vascular endothelial growth factor receptor (VEGFR), and AXL for patients with advanced HCC progressing on sorafenib, and ramucirumab, an anti-VEGF antibody for HCC patients with high AFP levels ≥400 ng/mL, were reported as positive [67, 68]. On the basis of these results, the European Commission approved cabozantinib for treatment of advanced HCC in the second line after sorafenib in late 2018, and it was approved by the US FDA in January 2019. Ramucirumab was also approved for second-line treatment of patients with AFP ≥400 ng/mL, who have been previously treated with sorafenib in May 2019. Early results of combination treatment with immune checkpoint inhibitors and antiangiogenic agents were promising. In late 2018, combination therapy with the PD-L1 inhibitor atezolizumab and the VEGF inhibitor bevacizumab showed promising and durable antitumor activity in a phase Ib study of patients with advanced HCC, with an objective response rate of greater than 30% [69]. The results of the phase III trial comparing combination atezolizumab and bevacizumab to sorafenib in first-line treatment of HCC were reported in November 2019, showing clear superiority of the combination over sorafenib. The combination was approved by the US FDA for treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy in May 2020 [70]. After years of relative inaction, we are therefore now in a very exciting phase of development of effective systemic therapy for HCC.

Once patients are started on systemic therapy for HCC, close follow-up by cross-sectional imaging is warranted, typically every 3–4 months, in order to assess response to treatment and to identify progressive disease at the earliest possible stage, given the increased number of treatments now available in the first and second line, which can also potentially be administered in subsequent lines of treatment. The availability of additional therapeutic options is also stimulating the need for molecular and genetic analysis of biopsy tissue obtained from patients with intermediate and advanced stage HCC, with the goal of identifying the molecular characteristics that determine response of specific subgroups of HCCs to particular therapies. This trend toward routine biopsy of HCCs is further supported by evidence from large molecular and genetic profiling studies such as the Cancer Genome Atlas Project (TCGA) for HCC that showed that approximately 8% of HCCs that were phenotypically HCC by H&E staining had gene expression patterns typical of cholangiocarcinomas [71]. About 25% of these cholangiocarcinoma-like tumors also carried mutations in the isocitrate dehydrogenase 1 and 2 genes that are characteristic of intrahepatic cholangiocarcinomas.

To complement and potentially extend these predictive strategies, novel efforts are underway in the new field of imaging radiogenomics, using machine learning and artificial intelligence techniques to identify genomic subclasses of HCCs. These efforts represent an exciting new frontier in the use of imaging for determining the optimal systemic treatment for HCC.

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