



# Imaging of Hepatocellular Carcinoma

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## 5.1 Role of Ultrasound and Contrast-Enhanced Ultrasound

Ultrasound (US) every 6 months is universally recommended for hepatocellular carcinoma (HCC) surveillance in all guidelines [1, 2].

The detection of any new focal lesion during US surveillance should directly require a diagnostic “recall strategy” that varies according to the size of the lesion. Lesions <1 cm should be admitted into a non-enhanced follow-up program based on US repetition at 3–6 months; if the size remains stable over a 2-year period, the 6-month surveillance can be restored. The “recall strategy” for lesions  $\geq 1$  cm is based on contrast-enhanced imaging techniques with use of vascular contrast agent, such as computed tomography (CT) or magnetic resonance imaging (MRI).

Contrast-enhanced US (CEUS) has been observed to improve the characterization of focal liver lesions with enhancement patterns generally similar to CT and MRI and can be useful in the case of renal impairment. US contrast agents (microbubbles) comprise an albumen or phospholipid shell containing a stable perfluorocarbon or sulphur hexafluoride gas. CEUS is not recommended as a first-line imaging technique or for recall strategies in terms of cost-effectiveness, because CT or MRI will be needed for staging, but it can be utilized when both CT and MRI are contraindicated and/or inconclusive [1].

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## 5.2 Computed Tomography Technique

Contrast-enhanced CT (CECT) or contrast-enhanced MRI play an essential role in the diagnosis of HCC and do not require histopathologic confirmation. According to the Liver Imaging-Reporting and Data System (LI-RADS), the use of a multi-detector-row CT with a minimum of 8-detector rows is recommended, with an axial slice thickness  $\leq 5$  mm [3]. The scanning protocol should include an unenhanced phase (to detect hemorrhage/treatment sequelae) and three enhanced phases of study. For CECT, an extracellular intravenous iodinated contrast agent is used, possibly with moderate/high iodine concentration ( $\geq 350$  mgI/mL), administered at high injection rates ( $>3$  mL/s), with dose adjusted according to body size indexes [3]. According to LI-RADS v2018, the multiphase dynamic study of the liver consists of a first late hepatic arterial phase (25–30 s after contrast agent injection with bolus tracking), a portal venous phase (60–80 s after contrast agent injection) and an equilibrium phase (2–5 min after contrast agent injection) [3].

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## 5.3 Magnetic Resonance Imaging Technique and Contrast Agents

MRI improves the detection and characterization of focal hepatic lesions, in comparison to a CT scan. In addition, MRI performs better compared to CT in the detection of HCC in patients with liver cirrhosis, especially when a hepatobiliary phase (HBP) is added [4]. In particular, a HBP was found to be superior to CECT also in guiding the correct treatment decisions for HCC [5]. MRI of the liver is best performed at 1.5 T or higher field strength [3]. The MRI protocol includes T1-weighted in-/out-of-phase gradient echo (GRE) images, T2-weighted images without and with fat suppression, diffusion-weighted images with at least two b values acquired ( $0\text{--}50$  s/mm<sup>2</sup> and  $400\text{--}800$  s/mm<sup>2</sup>) [6]. The dynamic contrast-enhanced MRI scan can be performed both with gadolinium-based extracellular contrast agents or with hepatobiliary contrast agents [3]. The multiphasic MRI study is essential for identification of the typical imaging features and vascular hallmarks, which are defined according to LI-RADS v18 as “arterial phase hyperenhancement”, “washout appearance” and “enhancing capsule” [4, 6, 7]. Hepatobiliary contrast agents make it possible to investigate the vascular characteristics of HCC lesions and to assess hepatocellular function in a single examination [6]. The most commonly used hepatobiliary contrast agents include two gadolinium-based compounds: gadoxetate disodium (Gd-EOB-DTPA) and gadobenate dimeglumine (Gd-BOPTA).

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## 5.4 Imaging Features of Hepatocellular Carcinoma

HCCs are generally arterial hypervascular tumors. However, hyperenhancement (“wash-in”) in the arterial phase alone is poorly specific for HCC. When hypoenhancement in the portal venous or delayed phases (“wash-out”) is added, both the



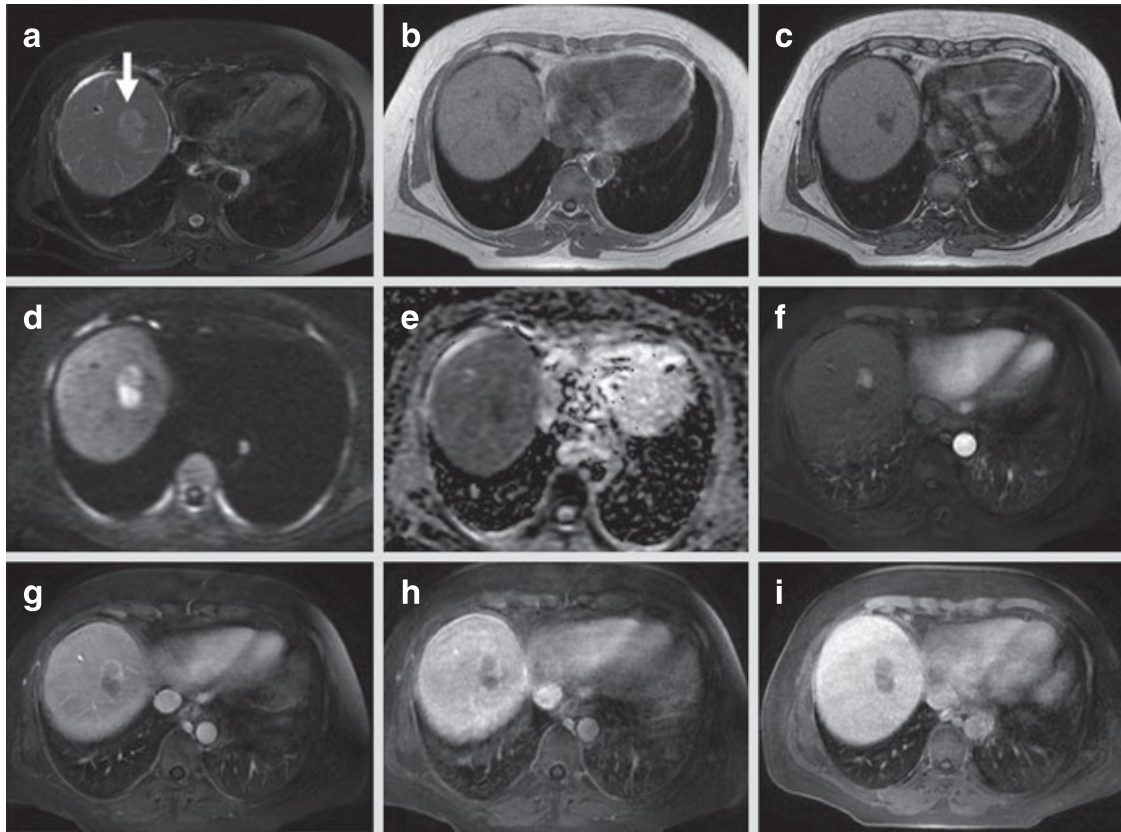
**Fig. 5.1** Typical CT imaging features for hepatocellular carcinoma. (a) Axial plane, arterial phase CT scan demonstrates arterial wash-in associated with afferent arteriole on maximum intensity projection reconstruction. (b, c) Portal and delayed phases respectively show the progressive wash-out of the lesion. The figure is published with the patient’s authorization

specificity and sensitivity increase (Fig. 5.1) [8]. Early HCCs are, however, characterized by a hypo- or isoenhancement in arterial phase imaging, due to their incomplete neoangiogenesis [7]. Another characteristic imaging feature included by LI-RADS among the major criteria for HCC diagnosis is the presence of a peripheral “capsule appearance”, histologically composed also by fibrous tissue, which explains its late enhancement due to retention of gadolinium in the extracellular interstitial spaces [6, 9]. Another characteristic feature of HCC, included in the “ancillary criteria” of LI-RADS, is the “nodule-in-nodule” appearance (Fig. 5.2) [10]. Vascular invasion is more frequent in progressed HCC. It can be microvascular, if it is only appreciable on microscopy, or macrovascular (Figs. 5.3 and 5.4) which refers to macroscopically visible tumor in vein (LR-TIV) [11]. Both of them are indicators of a poor overall survival and an aggressive biologic behavior [6]. The presence of intralesional fat is very specific for HCC and this is well evaluable on MRI T1-weighted GRE dual-echo sequences, with loss of signal in the out-of-phase images (Fig. 5.5) [10].

## 5.5 Liver Imaging Reporting and Data System (LI-RADS)

The LI-RADS system aims to standardize terminology, technique, interpretation, reporting and data collection in liver imaging for HCC surveillance and is promoted by the American College of Radiology and developed by an international committee of radiologists, hepatologists, pathologists and surgeons. US LI-RADS v2017 is limited to screening or surveillance in patients at risk for HCC, to identify HCC at an early stage, when it is potentially curable. CEUS LI-RADS v2017, as well as CT and MRI LI-RADS, should be applied in patients at high risk of HCC, including in this category adult cirrhotic patients, patients with chronic HBV, and patients with current or prior HCC.

The LI-RADS v2018 algorithm is articulated in successive diagnostic steps directed first to the identification of diagnoses other than HCC (LR-1, LR-2, LR-TIV, LR-M [malignancy other than HCC] or LR-NC [non-categorizable]) and

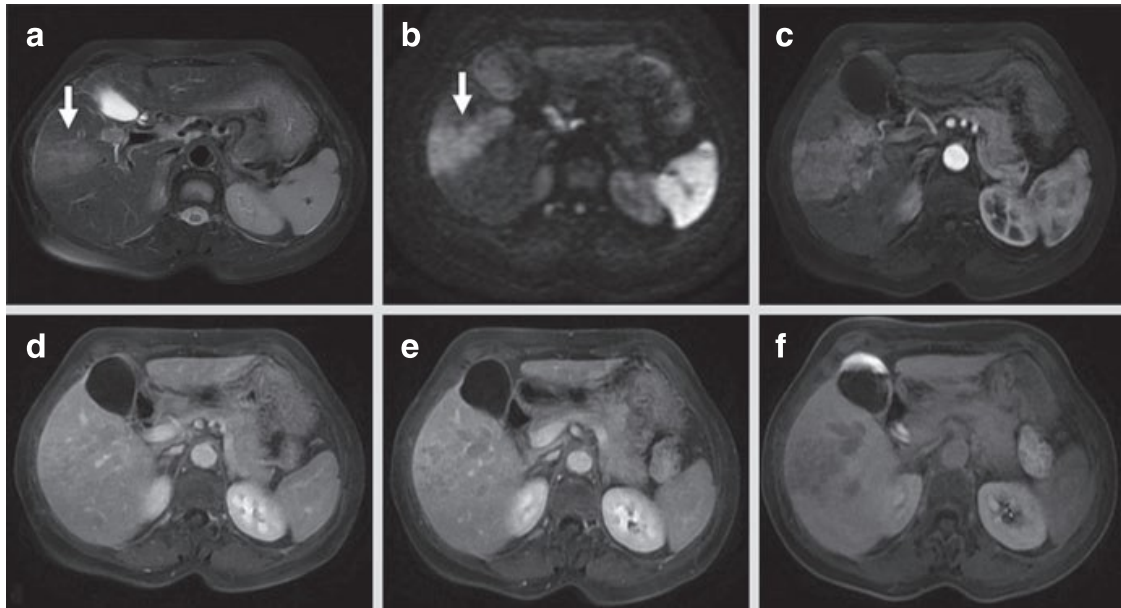


**Fig. 5.2** Small hepatocellular carcinoma nodule-in-nodule appearance. (a–c) A 3-cm nodule is appreciable on segment 8 (white arrow), mildly hyperintense on axial T2-weighted fat saturated (a), partially hyperintense on T1-weighted in-phase gradient echo (GRE) (b) with a partial signal drop-out on axial out-of-phase GRE (c) as expression intralesional fat. (d, e) Diffusion-weighted imaging (d), and apparent diffusion coefficient map (e) show lesion restriction related to hypercellularity. (f–i) Axial T1-weighted fat-saturated sequence in the arterial phase shows intense arterial wash-in of the upper portion of the nodule (f), with wash-out in the portal venous (g) and delayed (h) phases and lack of contrast agent uptake in the hepatobiliary phase (i). The figure is published with the patient’s authorization

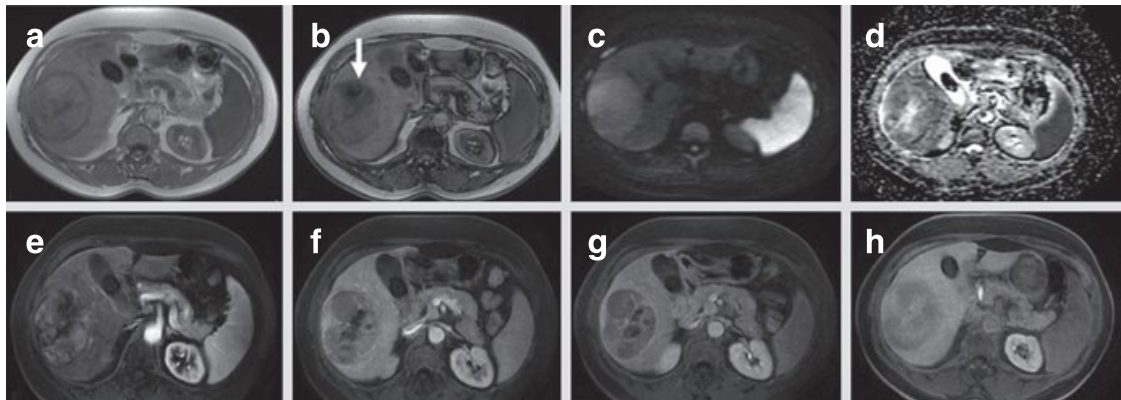


**Fig. 5.3** A voluminous lesion subverts the structure of the right liver, with imaging compatible with hepatocellular carcinoma appreciable on the CT axial images in the arterial (a), portal venous (b) and delayed (c) phases. Macrovascular invasion is observed with neoplastic thrombosis causing occlusion of the right portal vein, subocclusion of the left portal vein and the common portion of the mesenteric splenic confluence (black arrow). The figure is published with the patient’s authorization





**Fig. 5.4** Hepatocellular carcinoma with macrovascular invasion on MRI: between hepatic segments 5 and 6 a poorly defined mass associated with neoplastic thrombus in the anterior right portal vein branch. **(a)** Lesion with intermediate signal on the axial T2-weighted fat saturated image. **(b)** Restriction on diffusion-weighted imaging (white arrows). **(c)** Axial T1-weighted fat saturated image during the arterial phase with lesion wash-in. **(d, e)** Axial T1-weighted fat saturated images during the portal venous **(d)** and delayed **(e)** phases, with lesion wash-out. **(f)** Contrast-enhanced MRI axial T1-weighted fat suppressed image in the hepatobiliary phase with lesion hypointensity



**Fig. 5.5** Hepatocellular carcinoma with fat metaplasia at segment 5 and 6. **(a)** Axial T1-weighted gradient echo (GRE) in-phase sequence where the lesion is heterogeneously isointense to liver parenchyma. **(b)** Axial T1-weighted GRE out-of-phase sequence with signal drop-out due to intracellular fat component (white arrow). **(c)** Axial diffusion-weighted images with diffusion restriction of the lesion, **(d)** also appreciable on apparent diffusion coefficient map. **(e–g)** After contrast agent administration, the lesion shows slight hyperintensity on the axial T1-weighted fat saturated sequence in the arterial phase **(e)**, with progressive wash-out in the portal venous **(f)** and delayed **(g)** phases. **(h)** Hypointensity of the lesion on axial T1-weighted fat saturated sequence, in the hepatobiliary phase

then to a diagnostic table that helps to distinguish LR-3, LR-4 and LR-5 [7]. The classification from LR-1 to LR-5 is intended as growing probability of HCC malignancy, where LR-1 and LR-2 are considered respectively “certainly benign” and “probably benign”.

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## 5.6 Treatment Response: mRECIST and LI-RADS

Some HCC treatment strategies act by induction of tumor necrosis or reduction in vascularity, which is not necessarily accompanied by tumor reduction. The World Health Organization and Response Evaluation Criteria in Solid Tumors (RECIST) criteria do not address measures of antitumor activity other than tumor dimensional reduction [12]. In 2010, Lencioni et al. proposed a modified version of the RECIST (mRECIST) for HCC, in which tumor necrosis represents a treatment effect [13]. The mRECIST for HCC has introduced a classification in the determination of tumor response based on disappearance of tumoral arterial enhancement and changes in the sum of diameters of target lesions; it includes complete response, partial response, progressive disease, stable disease, or not evaluable disease.

### 5.6.1 LI-RADS Treatment Response Algorithm

The LI-RADS includes a treatment response algorithm that can be applied to patients with HCC treated by ablation, intra-arterial therapies, or external beam radiation therapy. The algorithm is based on the visual assessment of tumor viability defined as nodular, mass-like, or thick, irregular tissue in or along the treated lesion showing APHE or wash-out appearance. The LI-RADS algorithm expands on the mRECIST approach not only by defining viable disease but also by providing non-evaluable, equivocal, and nonviable treatment response categories. Unlike mRECIST, the LI-RADS treatment response categories are assigned on a lesion-by-lesion basis [7].

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