Chapter 4
Imaging in Hepatocellular Carcinoma: Radiologic Assessment

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Abstract In the context of Predictive, Preventive and Personalized Medicine (PPPM), radiologists play an essential role in patient management throughout the different phases of hepatocellular carcinoma (HCC). This includes diagnosis, staging, treatment planning, and evaluation of response to treatment. This chapter provides an in-depth examination of the fundamental pathophysiologic mechanisms underlying the radiologic diagnosis and assessment of HCC. Observations made in contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI), in conjunction with alpha-fetoprotein (AFP) can allow the diagnosis of HCC to be made with confidence without the need for biopsy, in many cases. Treatment decisions and prognosis are strongly influenced by the tumor extension, the number and size of lesions, tumor location, biliary dilatation, ascites, and the presence of macrovascular invasion and extrahepatic tumor spread. In addition, radiologic assessment of co-morbidities and response to previous treatments must be included in the overall assessment. The patient-specific findings from diagnostic imaging and interventional radiology identified in this chapter will be designated as Information Entities (IEs) in later chapters. These IEs will ultimately be used in the generation of Digital Patient Models (DPMs) to facilitate diagnosis, prognosis, and treatment selection, i.e. Model Guided Therapy (MGT) and PPPM.

Keywords Personalized medicine · Hepatocellular carcinoma · Diagnosis · Screening · Imaging · Staging · Computed tomography · Ultrasound · Contrast-enhanced ultrasound · Magnetic Resonance Imaging · Diffusion-weighted imaging · MR contrast agents · Treatment evaluation

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4.1 Introduction

In the setting of a multidisciplinary clinical liver cancer center, radiologists play an essential role in the different phases of hepatocellular carcinoma (HCC) patients' management, including diagnosis, staging, treatment planning, and evaluation of response to treatment.

According to the Barcelona Clinic for Liver Cancer (BCLC) staging system [1], treatment decisions and prognosis are strongly influenced by the tumor extension, in terms of lesions' number and size, presence of macrovascular invasion, and extrahepatic tumor spread; precise tumor identification is therefore mandatory for proper patient allocation. Moreover, treatment is often determined by other parameters that are not specifically addressed in the BCLC algorithm, such as tumor location, biliary dilatation, ascites, co-morbidities, and radiological response to previous treatments. Therefore, in clinical practice, clinical data need to be fully integrated to an entire spectrum of radiological parameters.

4.1.1 Diagnosis of HCC

The development of a neoplasm in cirrhosis is a long-lasting process. Many cellular changes occur along the pathway from normal hepatocytes to neoplastic cells so that different types of nodules can be detected in a cirrhotic liver, ranging from regenerative nodules to low-grade dysplastic nodules (LGDNs) and high-grade dysplastic nodules (HGDNs), early HCC and, finally, overt HCC.

HGDN nodules and early HCC are considered as premalignant and early malignant nodules. Foci of HCC can be found inside HGDNs, while in early HCC cells degeneration is not usually already associated to all the typical vascular changes found in overt HCC [2, 3]. These vascular alterations include the reduction of portal venous supply and the development of unpaired arteries and arterio-venous shunts [3].

These typical vascular changes account for the pathological background for current non-invasive diagnosis of HCC at dynamic contrast-enhanced imaging, based on the so-called "typical vascular pattern", characterized by wash-in in the arterial phase and wash-out in the portal venous/late phases. This pattern has shown up to 100 % specificity for HCC nodules > 1 cm in size, in the setting of a cirrhotic liver [4–6]. Therefore, according to current guidelines, the detection of the typical vascular pattern at multidetector computer tomography (MDCT) or magnetic resonance (MR) is considered sufficient for the diagnosis of HCC in patients with cirrhosis [7–9]. It should be noted that none of the guidelines reports which cross-sectional imaging modality between MDCT and MR should be performed to evaluate a nodule detected during ultrasound (US) surveillance. In fact, MR and MDCT show similar sensitivity in the detection of the typical vascular pattern, ranging between 44–62 % and between 44–53 %, respectively, although MR has been proven to be superior especially in nodules < 2 cm [10, 11].

Although the typical hallmarks of HCC at dynamic imaging are recognized by all current guidelines, diagnostic algorithms differ in the suggested management of

the detected nodules according to their size. European Society for the Study of the Liver (EASL) guidelines suggest that a single imaging modality is sufficient for HCC diagnosis in nodules > 2 cm, while smaller nodules (between 1–2 cm) should be investigated by two imaging modalities if not performed in centers of excellence with 'high-end radiological equipment' [7]. On the contrary, the American Association for the Study of Liver Diseases (AASLD) guidelines suggest that the detection of the typical enhancement pattern at one single imaging modality in nodules > 1 cm can be considered as sufficient to formulate a diagnosis of neoplasm [8]. Finally, EASL guidelines disregard the dimensions of the nodules, because the diagnosis of malignancy can be assessed even in lesions < 1 cm in the case of a typical enhancement pattern [9].

Only two-thirds of HCCs are reported to show a typical vascular pattern, and diagnosis of atypical HCC nodules remains a controversial issue, with differences in their suggested management according to the available guidelines [12]. While both EASL and AASLD guidelines suggest biopsy for all atypical nodules > 1 cm [7, 8], the Asian Pacific guidelines suggest the use of new diagnostic tools, such as MR using reticulo-endothelial system (RES)- or hepatocyte-specific contrast agents, or contrast enhanced ultrasound (CEUS) using Sonazoid [9], while biopsy should be performed in case of inconclusive findings.

The role of biopsy as a solving problem tool is again controversial. In fact, it should be kept in mind that sampling errors can occur (such as insufficient tissue or samplings not representative of the entire lesions) and that pathological interpretation can be challenging on a specimen obtained from needle biopsy, with inability of evaluating all the criteria suggesting malignancy (especially stromal invasion) [12, 13].

4.1.2 New Diagnostic Tools

Despite being very specific, the diagnosis of HCC based solely on the detection of neoangiogenesis has a low sensitivity. Thus, the role of different diagnostic elements is under evaluation [4]. In this setting, MR seems to provide some advantages compared to MDCT, due to its intrinsic capability of identifying other intracellular components, such as glycogen, hemorrhage, water, and metals, and defining other parameters, such as diffusivity and biliary function [14–16].

4.1.2.1 Diffusion-Weighted Imaging (DWI)

Diffusion-weighted imaging (DWI) is a dedicated MR sequence that allows for the evaluation of the random motion (related to thermal effects) of water molecules ('Brownian motion') within biological tissues. Recently, DWI has been introduced in liver MR protocols, as several studies have reported its usefulness in improving detection and characterization of focal liver lesions, by measuring their apparent diffusion coefficient [17, 18], providing an adjunctive tool in the differential diagnosis between benign and malignant lesions.

4.1.2.2 Hepatospecific Contrast Agents for MR

During carcinogenesis, together with neoangiogenesis, progressive loss of biliary polarization of the hepatocyte and derangement of its microscopic, secretory structure are observed. Recent studies have described modifications of membrane carriers (such as organic anionic transporter protein [OATP] and multidrug-resistance protein [MRP]) that are involved in bilirubin metabolism in neoplastic nodules.

The recent introduction of hepatobiliary contrast agents in MR studies, especially of the highly lipophilic compound Gd-EOB-DTPA, has provided an additional tool for the assessment of the metabolic function of nodules. In fact, due to a competitive binding to bilirubin transporters, these agents provide information regarding the residual performance of cellular membrane proteins and intracellular metabolic activities [19, 20].

Moreover, these agents enable the evaluation of both dynamic vascular and metabolic nodular functions in a single session study since the contrast is taken up within functioning hepatocytes, and then, excreted at the level of the biliary pole at the end of the intravascular phase. This metabolic phase occurs 20–40 min after the injection.

In recent studies, the lack of contrast agent uptake in the hepatobiliary phase has been found in premalignant HGDNs, as well as cases of malignant degeneration (early/overt HCC), even in the absence of the typical vascular pattern [4, 5, 21]. Thus, the use of hepatobiliary contrast agents might increase MR sensitivity in identifying malignant and premalignant lesions. Accordingly, recent studies have demonstrated that the combination of DWI and MR with hepatospecific contrast agents can provide information regarding the risk of premalignant lesions evolving into overt HCC [15, 16].

4.1.3 Therapeutic Algorithm and Treatment Planning

The BCLC staging classification stratifies HCC patients into five major categories (very early, early, intermediate, advanced, and terminal stages) on the basis of tumor extension, liver function, and performance status [1]. For each stage, different prognostic variables are identified, life expectancy is estimated, and the most proper treatment option is suggested.

4.1.3.1 Very Early Stage

The very early stage (stage 0) is composed of patients with single nodule <2 cm in a well-compensated cirrhotic liver without portal hypertension. These patients can benefit from resection with estimated 5-year survival rates exceeding 90%. Livraghi and colleagues have demonstrated that similar clinical outcomes can be obtained also by percutaneous radiofrequency ablation (RFA), with lower costs

and periprocedural risks [22]. Thus, when technically feasible according to lesion location, percutaneous ablation may represent a valid treatment option, although according to the AASLD Practice Guidelines ablation should currently be limited to patients not eligible for surgical resection [8]. Also, lesion location requiring extensive resection could represent a parameter in favor for RFA.

4.1.3.2 Early Stage

The early stage (stage A) is composed of patients in good clinical conditions with a single nodule or less than 3 nodules < 3 cm in size each. These patients can benefit from curative treatments, such as liver transplantation (LT), resection or percutaneous ablation, with estimated 5-year survival rates of approximately 50–75 %.

LT is able to cure both the tumor and the underlying liver disease. Its success is strongly related to the adopted inclusion criteria and to the waiting time. Strict inclusion criteria have been proposed in 1996 by Mazzaferro et al., the Milan criteria, defined as the presence of a single nodule < 5 cm in size, or no more than three nodules each < 3 cm in size [23]; therefore, precise tumor identification is mandatory to set indications for LT. Cautiously expanded criteria have been subsequently proposed [24, 25], with acceptable 5-year survival rates. Some authors have proposed the use of locoregional treatments for tumor down-staging in highly selected patients [26–28], for whom the identification of a radiological complete tumor response after treatment could even represent a marker of favorable biological tumor behavior allowing LT [29, 30]. Locoregional treatments, such transarterial chemoembolization (TACE) and percutaneous ablation, are also extensively used in T2-stage HCC patients waiting for LT and in patients with an expected waiting time > 6 months, to reduce the risks of dropout for tumor progression [31, 32].

There are several clinical factors that contraindicate LT even in patients within Milan criteria such as age, co-morbidities, and alcohol abuse. In this setting, RFA and resection are regarded as treatment options with curative intent.

Exclusion criteria for resection vary from site to site, although several authors agree in excluding patients with portal hypertension. In this scenario, imaging may play a role in identifying signs of portal hypertension such as hepatofugal shunts, varices, and splenomegaly. After resection, residual liver function represents the strongest predictor of survival [1, 33], while pathological findings, such as vascular invasion, satellites, and tumor differentiation, are risk factors for tumor recurrence.

Tumor location, size, and number may limit the indications for percutaneous ablation. In fact, the success of ablation is lower when more than two nodules are treated and in tumors > 3 cm in size [34–36]. For nodules between 3–5 cm in size, the combination of RFA and TACE has proven to be more effective compared to RFA alone [37, 38]. Moreover, technical feasibility and success of ablation are limited in the case of nodules located close to the gallbladder or to large vessels, or in subcaspular locations.

4.1.3.3 Intermediate Stage

The intermediate stage (stage B) of the disease includes a wide variety of patients, who are asymptomatic, with preserved liver function, but with a more extensive liver involvement. In these patients, TACE represents the treatment of choice, being able to improve survival compared to best supportive care [39, 40]. However, tumor relapse after TACE is a major issue, and the combination of TACE and sorafenib is under investigation, in the attempt to reduce tumor recurrence.

The intermediate stage is composed of a very heterogeneous population, ranging from patients with a single large nodule to patients with multifocal extensive bilobar involvement. Therefore, a better stratification of this group of patient is needed [41]. In clinical practice, there is wide variation in the management of these patients. Single large nodules can be treated effectively by surgical resection, downstaging followed by LT (in highly selected patients), or by combining TACE and RFA [42]. Alternatively, patients with extensive tumor involvement might not benefit from TACE and should be considered as advanced-stage HCC patients [43, 44].

4.1.3.4 Advanced Stage

In the advanced stage (stage C) of the disease, performance status is compromised and/or the tumor has spread into the vessels or outside the liver. Two multicenter, phase III, double-blind, placebo-controlled trials [45, 46] have demonstrated that in this stage sorafenib (an oral multikinase inhibitor of the vascular endothelial growth factor, the platelet-derived growth factor receptor and Raf) can prolong survival.

Yttrium-90 (Y90) radioembolization (RE) (also known as selective internal radiation therapy [SIRT]) has been investigated in advanced stage, as well as in intermediate stage, HCC patients who have been excluded from, or have not responded to, TACE. The first phase II clinical study has demonstrated that in this clinical scenario Y90 RE is safe and effective, with promising clinical outcomes, particularly in patients with segmental portal vein thrombosis [47].

In fact, initial reports regarding RE have demonstrated that even in the setting of the advanced stage HCC further efforts are needed for improved patients' stratification. It has been found that long-term survival is different for patients with metastasis compared to patients with HCC confined to the liver, as well for patients with segmental branch portal vein neoplastic thrombosis versus patients with main branch involvement [47–49].

4.1.4 Post-Treatment Evaluation

Response to previous treatment represents a key factor in determining a patient's prognosis and therapeutic management [44]. Traditionally, response is measured

in terms of tumor shrinkage using standard Response Evaluation Criteria in Solid Tumors (RECIST) [50, 51]. However, these criteria can be misleading when applied to molecular-targeted or locoregional therapies in HCC, since tumor necrosis may not always be paralleled by a reduction in tumor size [52]. For instance, a poor correlation was demonstrated between RECIST and clinical outcome of sorafenib treatment in HCC patients [46]. In 2001, EASL recommended measuring change in the area of tumor enhancement on contrast enhanced imaging as the optimal method to assess treatment response [53]. More recently, AASLD has proposed a formal amendment to RECIST that take into account variations in the degree of tumor arterial enhancement: modified RECIST (mRECIST) [54]. mRECIST has been validated in different clinical trials involving both locoregional therapies and systemic targeted agents [55, 56], and a correlation with pathological necrosis evaluated on the explanted liver has been demonstrated [57]. However, while RFA and TACE usually generate well-defined and easily measurable areas of necrosis, the extent of tumor necrosis is usually unpredictable and irregular following treatment with RE and sorafenib; these treatments might reduce tumor vascularization without necessarily creating areas of necrosis [58, 59]. Furthermore, patients with advanced-stage HCC, for whom sorafenib and RE are usually performed, often present with irregular and highly inhomogeneous lesions at baseline due to the infiltrative margins and the irregular perfusion caused by neoplastic portal vein thrombosis and previous locoregional treatments. Thus, mRECIST should be applied with caution when evaluating radiological response to sorafenib and RE.

The uncertainty in evaluating response to sorafenib with mRECIST is further emphasized in recent literature that focuses on the need to find new biological markers that are able to achieve early identification of patients responding to treatment. Some authors have pointed out the usefulness of monitoring AFP levels that might represent a more sensitive prognostic parameter compared to radiological criteria [60–62]. In addition, determination of response, based on changes in tumor density and perfusion parameters, has been proposed, using CEUS, perfusion CT, and/or MR spectral imaging [59, 63–68]. Finally, some authors have underlined the need for volumetric assessment of tumor variations to increase accuracy and reproducibility in assessing tumor response [69–71].

4.1.5 Electronic Medical Records and Radiological Data

As described in Chap. 2, comprehensive Digital Patient Models (DPMs) based on Multi-Entity Bayesian Networks (MEBNs) for patients with HCC may be constructed from electronic databases and repositories. Patient-specific findings of diagnostic imaging and interventional radiology that may be identified as Information Entities (IEs) will need to be integrated as clinical parameters in the MEBNs. Radiological findings that may be used to generate IEs are summarized in Table 4.1.

Table 4.1 Radiological features that may be employed as Information Entities

Clinical Task	Radiological findings
Preprocedural assessment	(a) number and size of HCC nodules; (b) number and size of nodules considered at risk for neoplastic degeneration; (c) presence and extension of portal vein neoplastic thrombosis; (d) presence of extrahepatic tumor spread; (e) radiological signs of cirrhosis (including varices and ascites); (f) biliary dilatations; (g) radiological signs of co-morbidities
Treatment planning	(a) features of nodules such as location, degree of vascularization, and presence of pseudocapsule; (b) vascular mapping; (c) technical details of previous treatments
Evaluation of previous treatment	(a) complications; (b) tolerability and compliance; (c) radiological response

Conclusion

It has been demonstrated that radiological imaging plays a critical role in the diagnosis and management of patients with HCC. The radiological features of HCC lesions provide information that is required to determine staging and prognosis, and to select the optimal treatment protocols.

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