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**Recent advances in non-invasive magnetic resonance imaging assessment of hepatocellular carcinoma**

Ippolito D *et al*. Advances in magnetic resonance liver

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**Abstract**

magnetic resonance imaging of the liver is an important tool in terms of detection and characterization of focal liver lesions and for assessment of diffuse liver disease, having several intrinsic characteristics, represented by high soft tissue contrast, avoidance of ionizing radiation or iodinated contrast media, and more recently, by application of several functional imaging technique (*i.e.*, diffusion-weighted sequences, hepatobiliary contrast agents, perfusion imaging, magnetic resonance (MR)-elastography and radiomics analysis). MR functional imaging techniques are extensively used both in routinely practice or in the field of clinical and pre-clinical research, because through a qualitative rather than quantitative approach they could offer valuable information about tumour tissue and tissue architecture, as cellularity biomarker related to the hepatocellular functions, or as tissue vascularizations profile related to tumour and tissue biology. This kind of approach offers *in-vivo* physiological parameters, capable in evaluating physiological and pathological modifications of tissues, by the analysis of quantitative data that could be used in tumour detection, characterisation, treatment selection and follow-up, in addition to those obtained from standard morphological imaging. In this review we provide an overview of recent advanced techniques in MR for diagnosis and staging of hepatocellular carcinoma, and their role in the assessment of response treatment evaluation.

**Key words:** Hepatocellular carcinoma; Magnetic Resonance; Liver; Cirrhosis; Transarterial chemoembolization; Contrast media

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**Core tip:** Magnetic resonance (MR) of the liver is an important diagnostic option for detection and characterization of focal liver lesions. To date, beside the standard morphological sequences, new functional imaging tools (*i.e.*, diffusion-weighted sequences, hepatobiliary contrast agents, perfusion imaging, MR-elastography or radiomics analysis) have been introduced in clinical practice. The aim of functional imaging is to provide an *in-vivo* quantitative complementary functional data related to the tissue or tumour modifications, offering useful comprehensive informations about the biology, behaviour and prognosis of hepatocellular carcinoma lesions. This functional approach may help the clinicians in the correct management of cirrhotic patients, also after therapeutic treatment.

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**INTRODUCTION**

Liver cancer is the fifth most frequently diagnosed malignancy among men and the ninth among women. In the last years, it has risen from the third to the second cause of death from cancer, accounting for nearly 746000 deaths in 2012. In some regions like Eastern and South-Eastern Asia, mortality almost equals incidence with an overall ratio of 0.95[1]. The most common histological subtype of liver cancer is hepatocellular carcinoma (HCC), representing more than 90% of cases. The incidence of HCC increases with advanced age reaching a peak at 70 years, at least in developed countries[2]. In up to 90% of cases, HCC occurs in the setting of liver cirrhosis and overall, one-third of cirrhotic patients will develop HCC during their lifetime[3].

The primary risk factor for HCC is still represented by chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection[[4]](https://paperpile.com/c/XJSxgM/6M6p), with a prevalence of virus B infection in Eastern countries and a prevalence of virus C infection in Western countries. Other causes of cirrhosis comprise alcohol abuse, non-alcoholic fatty liver disease (NAFLD) and less frequent disorders such as hemochromatosis. All aetiologies could lead to cirrhosis and may be complicated by tumor formation, but the risk is higher in patients with hepatitis infection. In the next years, the diffusion of new antiviral agents for HCV[[5]](https://paperpile.com/c/XJSxgM/3xpK+b02w), vaccination and therapy for HBV[[6]](https://paperpile.com/c/XJSxgM/5Lsn) and prevention campaigns are expected to reduce the burden of chronic viral liver disease and its complications, including hepatocellular carcinoma[7]. On the other side, the widespread epidemic of obesity is expected to induce a significant increase in incidence of NAFLD, and its complications such as NASH, cirrhosis and hepatocellular carcinoma[[](https://paperpile.com/c/XJSxgM/ZjLn+5kRj+KDfe+kNA1+pMHj)8,9[]](https://paperpile.com/c/XJSxgM/ZjLn+5kRj+KDfe+kNA1+pMHj).

Liver cirrhosis is the underlying and common condition associated with hepatocarcinogenesis. Cirrhosis develops after a long period of chronic liver disease when the risk of HCC is still low. The nodules that could be potentially find in a cirrhotic liver comprise: small and large regenerative nodule (RN), low-grade dysplastic nodule (LGDN), high-grade dysplastic nodule (HGDN), early HCC, well-differentiated HCC and moderately-poorly differentiated HCC. Hepatocarcinogenesis is a multistep event during which cell density increase, Kuppfer cells decrease, nodules enlarge and hemodynamics changes occur. In the initial phase, normal arterial supply decrease but portal perfusion is still present. Later, intranodular arterial vascularity increases due to the appearance of unpaired arteries (capillarization) while portal blood supplies progressively decrease[10]. At the same time organic anionic transporting polypeptide (OATP), transporters of bile salts, simultaneously and gradually decrease. OATP expression levels are high in RNs and LGDNs and lower in many HGDNs, early HCCs, and progressed HCCs. The hemodynamic changes are well depicted during dynamic multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) and both European and American guidelines have endorsed this techniques for the diagnosis of HCC > 1 cm, based on the typical hallmarks of hypervascularity in arterial phase with wash-out in portal phase, avoiding liver biopsy[11,12].

However, there is still a high rate of false negative, ranging from 25%-30%, in particular for nodules < 2 cm[13,14], which actually are the more often encountered focal liver lesions, thanks to the widespread of surveillance programs. In these small nodules, hemodynamic changes of hepatocarcinogenesis are in an early step since neoangiogenesis is incomplete and they are still mainly filled by portal vessels, in contrast to progressed HCC. MRI in part overcomes these limits. It has been recently demonstrated that this diagnostic technique has a higher diagnostic performance over computed tomography (CT), in the detection of high-risk nodules[15]. This is due to its high contrast resolution and to its multiparametric characteristics. In fact, it is known that hyperintensity on T2 weighted sequences and restricted diffusion in diffuse weighted images (DWI), are features of malignancy[16]. Moreover the recent introduction of hepatospecific MRI contrast agent gadolinium-ethoxybenzyl-dieth-ylenetriamine pentaacetic acid (Gd-EOB-DTPA, Primovist ®; Bayer Schering Pharma, Berlin, Germany) which gives information not only on vascular changes but also on hepatocyte function, raises the sensitivity for the detection of early HCC to 91%-93%[17]. Based on this features Kim BR and colleagues[16] demonstrated that readers had significantly higher detection sensitivity for early HCCs with MRI than with multidetector CT (78.6% *vs* 52.4%, *P* = 0.001; 71.4% *vs* 50.0%, *P* = 0.011; and 73.8% *vs* 50.0%, *P* = 0.001], respectively), by the meaning of 30 more LI-RADS category 4 early HCCs identified at MRI.

The correct characterization of all nodules possibly encountered in a cirrhotic liver is of paramount importance because of their completely different management. In fact while regenerative and dysplastic nodules deserve a strict follow-up, HCC should be treated with the more suitable therapeutic option, according its stage. This is clearly defined by the Barcelona Clinic Liver Cancer (BCLC) staging system, adopted in all Western countries, and endorsed by both American and European guidelines.

In this context, beside traditional radiological techniques, new functional imaging tools have been introduced in clinical practice in order to provide not only morphological information but also functional data information. Functional magnetic resonance imaging encompasses a wide range of advanced techniques capable in evaluating physiological and pathological modifications of tissues, by the analysis of quantitative data, in addition to those obtained from standard morphological imaging. These techniques may include diffusion-weighted sequences, hepatobiliary contrast agents, perfusion imaging, MR-elastography and more recently radiomics analysis. In particular, perfusion imaging (related to vascular profile) and diffusion imaging (related to cellular profile) (Figure 1) techniques have been extensively studied during various steps of HCC evolution, from initial assessment of vascular modifications in cirrhotic liver through its progression in tumor lesion, and finally to its follow-up after treatment. Hence, in this review we provide an overview of recent advances and techniques in MR studies for the diagnosis and the staging of hepatocellular carcinoma.

**CONTRAST MEDIA: EXTRACELLULAR AND HEPATOBILIARY AGENTS**

Gadolinium is a paramagnetic ion which shorten T1 relaxation time in tissues and therefore produces an increase of signal intensity[18]. Based on bio-distribution, there are 3 categories of gadolinium-based contrast agents: Extracellular fluid agents (ECFAs), blood pool agents (BPCAs) and targeted and organ-specific contrast agents such as hepatocyte-specific contrast agents (HCAs). ECFAs and HCAs are the most commonly used in liver imaging. ECFAs consist of gadolinium chelated to an organic compound such as DTPA[19]. They are further divided in standard relaxivity macrocyclic agents, standard relaxivity linear agents and high relativity linear agents (Table 1). The details regarding the advantages and disadvantages of each contrast category is beyond the scope of this article, but in general, there is little clinical difference[20]. The standard dose is 0.1 mmol/kg typically injected intravenously at a rate of 2 mL/s followed by a normal saline “flush” of 20 to 50 mL. After the injection, ECFAs are rapidly cleared from the intravascular space through the capillaries into the extracellular space. They are mainly eliminated by renal excretion and have imaging dynamics comparable to the extracellular iodinated contrast media used in CT. However, MRI is more sensitive to the effects of gadolinium than CT is to the effects of iodine, because Gadolinium has an amplification effect due to the number of adjacent water protons relaxed by a single gadolinium atom[19,21]. In summary, ECFAs enter into the liver through the hepatic artery and portal vein and are freely redistributed into the interstitial space; they demonstrate vascular perfusion by distributing and allow the evaluation of liver lesions based on assessment of vascularity. The combination of arterial phase hyperenhancement followed by washout appearance in the portal venous and/or delayed phase is the key diagnostic feature of HCC[11,12] (Figure 2).

The pathophysiologic basis for arterial phase hyperenhancement in HCC is related to the increasing of intranodular arterial supply during hepatocarcinogenesis[22]. The mechanisms underlying washout appearance in HCC depending on a range of factors: early venous drainage of contrast material from the tumour, progressive enhancement of background liver, reduced intranodular portal venous blood supply, tumour hypercellularity with corresponding reduction in extracellular volume and intrinsic hypoattenuation/hypointensity[23]. In cirrhotic patients, this enhancement pattern has approximately 100% specificity for lesions larger than 2 cm and approximately 90% specificity for those of 1-2 cm[24]. However, the main limitation with ECFAs for diagnosis and staging HCCs is low per-lesion sensitivity, because an atypical vascular behaviour is quite common in small (< 2 cm) nodule and approximately one-third of these are malignant (‘‘the one-third rule’’)[25]. Indeed, the intranodular hemodynamic changes during carcinogenesis starts with an arterial hypovascularity with portal perfusion still present, followed by a decrease of both arterial and portal blood supply and, subsequently, by an increase in arterial vascularity to isovascular and, finally, to a hypervascular pattern[12].

On the other side, several recent studies demonstrated that the expression of organic anion-transporting polypeptide (OATP) diminishes during hepatocarcinogenesis[26]. Moreover, OATP 8 expression level decreases prior to complete neoangiogenesis, elevation of arterial flow and reduction of portal venous flow[27]. Thanks to their lipophilic characteristics HCAs, after the intravascular/interstitial distribution, are taken up by functioning hepatocytes, metabolized and excreted into the bile through the OATP 8: consequently, nodules with low or no OATP expression, as the majority of HCC, many early HCCs and some high-grade dysplastic nodule, do not uptake HCAs and appear hypointense in the hepatobiliary phase (HBP) (Figure 2). A recent meta-analysis has shown that the impact of HBP on a per-lesion sensitivity is significant, in particular the use of Gd-EOB-DTPA allowed a sensitivity of 87% *vs* 74% (*p* = 0.03) the one without HBP[28]. Based on these considerations, the current contrast agents applied in the study of the liver are the gadobenate dimeglumine (Gd-BOPTA/Dimeg, MultiHance®, Bracco, Milan, Italy), that is a chelate of the paramagnetic gadolinium ion salified with 2 molecules of meglumine, and gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA, Primovist®, Bayer Schering Pharma, Berlin, Germany), that is a highly water-soluble contrast agent with an ethobenzyl group attached to gadolinium diethylenetriamine pentaacetic acid[29]. The approved dose of Gd-BOPTA for hepatic imaging is 0.05 mmol/kg (0.1 ml/kg of a 0.5 mol/L solution)[30] and it should be administered undiluted followed by a normal saline “flush” of 20 to 50 mL. Hepatic uptake represents 2%-4% of the injected dose for Gd-BOPTA and the HBP is typically performed between 45 and 120 min after injection and is necessary in order to achieve sufficient enhancement.

The approved dose of Gd-EOB-DTPA is 0.025 mmol/kg, which is considered the minimum effective dose for the detection of liver lesions in the hepatobiliary phase. The modalities of gadoxetic acid administration were addressed in the ESGAR consensus statement[31] (flow-rate of 1-2 mL/s followed by a 20-mL saline flush at 1-2 mL/s using a bolus triggering technique). Hepatic uptake represents 50% for Gd-EOB-DTPA and the HBP reaches its maximum intensity approximately 20 min after injection with gadoxetate disodium, and persists for several hours[32]. The clinical use of liver-specific contrast agents allows the radiologist to obtain morphologic and vascular-related information, although an overlap between delayed phase and hepatocyte phase have to be considered during dynamic evaluation[33]. A recent meta-analysis[34] reported that in trials of MRI that directly compared test performance using different contrast agents, use of HCAs was associated with higher sensitivity than ECAs (difference of 13%), with no difference in specificity. The difference was somewhat greater for HCC lesions smaller than 2 cm (difference of 15%). These finding were stressed by the ESGAR consensus[31] who stated that a Gd-EOB-DTPA MR examination should be performed in order to characterize an undetermined focal liver lesion of 10 mm or larger in the cirrhotic liver. In summary, HCAs allow a comprehensive non-invasive imaging assessment of the liver parenchyma, intrahepatic lesions depiction or characterization, hepatic vasculature, and the biliary tree in a single examination. They have several advantages in evaluation of the cirrhotic liver including: (1) higher sensitivity for the diagnosis of HCC, in particular for lesions smaller than 2 cm[34]; (2) improved characterization of arterially enhancing lesions without definite washout on subsequent imaging[35]; (3) the possibility to differentiate arterially enhancing lesion *vs* pseudo­lesions[36]; and (4) detection of lesions with decrease uptake evidenced only in the HBP that are likely to be precancerous or borderline lesion[37].

**PERFUSION IMAGING**

Perfusion MRI in the assessment of HCC nowadays is focus on detection and characterization of lesions[38-40], in the evaluation of response to therapy[38,41-44] and prognosis[44,45] (Table 2).

The basis of dynamic contrast-enhanced (DCE)-perfusion MR imaging is the acquisition of multiple image sets, every few seconds, through the tumor or as much of the organ as possible, after gadolinium injection. The rate and pattern of contrast enhancement reflects the time evolution of the contrast agent within the tissue, which occurs as result of the microcirculatory pathophysiological changes. Perfusion MRI could extend the currently used qualitative assessment applied for the differential diagnosis of lesions, by applying quantitative metrics to describe their vascular behaviour.

The main purpose of MRI perfusion is the quantification of vascular characteristics of HCC, because the growth and progression of histological malignancy of HCC are associated with new blood vessels formation[46] (angiogenesis). Moreover, the targets of anti-angiogenic drugs, recently used for HCC treatment, are represented by these new blood vessels and therefore the perfusion, as a functional imaging technique, may be suitable for evaluating patients treated with these agents[47-50].

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) provides non-invasive imaging biomarkers that can measure changes in tumour blood flow, vascular permeability, and interstitial and intravascular volumes[40,43,47] and can predict the survival outcome in patients with HCC[51-53]. Generally, DCE-MRI consists of acquisition of T1-weighted MR images before, during and after intravenous injection of a gadolinium-based contrast agent[40]. The contrast agent extravasates at level of tumour tissue, from intravascular to the extravascular extracellular space (EES) with increased T1-w signal[43,54,55]. This extravasation to EES in the tumour tissue depends on vessel leakiness (permeability) and blood flow (perfusion) and so the signal measured with DCE-MRI could be sensitive to alterations in vascular permeability, EES, and blood flow[43,54].

DCE-MRI signals can be quantified using a semi-quantitative (model free) or quantitative (model based) analysis[56]. Both analysis methods have several parameters related with tumor angiogenesis[54,57] and can give different information on liver and tumor perfusion[56]. Briefly, with the semi-quantitative analysis all perfusion parameters are extracted directly from time-signal intensity (SI) curves [*e.g.*, AUC, maximum SI or peak enhancement ratio, wash-in slope, mean transit time (MTT)], derived from different dynamic contrastographic sequences. Although widely used, semi-quantitative analysis is highly affected by the acquisition systems and comparison and quantification of these parameters can be difficult[56,57] because the true concentration of contrast agent in the tissues is not estimated (Figure 3).

Quantitative analysis depends on fitting the time SI curves with the changes in concentration of the contrast agent using pharmacokinetic techniques using several kinetics models based on different physiological assumptions made[56]. These kinetics models can be bi-compartmental models (taking into account vessels and EES) or mono-compartmental (taking into account the vascular space because of the typical architecture of the liver)[56], with a double or single input system (arterial and portal or arterial alone), conventional compartment (CC) models vs distributed parameters (DP) models[54,56].

Several parameters extracted with quantitative analysis are related to the influx of contrast agent from the intravascular space to the EES (K trans) and its reverse (Kep), the volume fraction of EES (Ve) which is an indirect expression of the cellular density of the tissue[43,54,56].

In comparison to the semi-quantitative analysis, these parameters are more time consuming because they generate parametric maps through a pixel-by-pixel curve fitting process. Although the histogram analysis and the heterogeneity of these parametric maps are more computationally demanding, they may also provide additional information[43,56]. Moreover, numerous pharmacokinetic models have been proposed by Tofts *et al*[58], Brix *et al*[59] and Larsson *et al*[60], using a single arterial input function[43]. Because hepatocellular carcinoma receives major blood supply from hepatic neo-arteries and often arise from a cirrhotic liver, the single input model (considering only the arterial input) and the dual compartment model (because of the alteration in the EES) are frequently both used in the literature[54,56].

However, because of numerous DCE-MRI–related limitations, parameters derived from these pharmacokinetic models may lack sufficient precision for clinical application[38], and there is no consensus regarding the pharmacokinetic model that should be used to quantify HCC perfusion parameters even if some studies demonstrated that some pharmacokinetic models can be equivalent in the results[40].

All these possibilities and differences in the field of DCE-MRI yielded the literature studies to different results.

In general, two recent studies demonstrated that HCC had significantly higher peak, slope, AUC, arterial fraction, and arterial flow but lower portal flow, distribution volume, and MTT than the liver[45]. HCCs with high peak are correlated to a longer overall survival (OS) in comparison with HCC with low peak[45] before systemic therapy. Secondary, high peak reduction assessed early (one week) after systemic therapy can be related to OS[44].

DCE-MRI semi-quantitative parameters (relative arterial, venous, and late enhancement; maximum enhancement; maximum relative enhancement, and time to peak) potentially can be used also to differentiate residual viable tumor tissue and effective treated lesions after TACE or RFA[41]; some of them, in a multivariate analysis, seemed also to predict the response to radiotherapy RT[42].

Some groups found that with DCE-MRI is possible to quantify the perfusion in the liver and HCC with an increased arterial flow and decreased portal venous flow in HCC compared with cirrhotic liver, with significant differences in the degree of arterial versus portal venous blood flow in treated and untreated HCCs[38].

Perfusion parameters could be correlate to the grading differentiation of HCC but in most of the cases, there are no significant differences in perfusions and grade of HCC differentiation, with the exception of the arterial fraction (ART)[40]. The ART parameter is a value estimated each time through perfusion equations obtained from the addition of the two input inflow (arterial and portal) into one[40]. Moreover, it has been suggested that ART can be used to assess response to local regional therapy in HCC[38,40,61].

In a recent study from Chen *et al*[39] the max-Ktrans seems to correlate with tumor grades (rho = - 0.382, *P* = 0.028). The Ktrans, Kep, and iAUC of high-grades HCC are significantly lower than that of low-grades HCC (*P* = 0.001, 0.031, 0.003, respectively), but there is no statistically significant differences for Ve between high grade and low grade HCC (*P* > 0.05)[39].

These results suggest that DCE-MRI ca be useful as a non-invasive marker of HCC angiogenesis, but new equipment and sequences and models are still under investigation and newer equipment are going to be applied in the next future to quantify the perfusion of HCC, as a biomarkers of degree of malignancy, prognosis and response to therapy[38-40].

**DIFFUSION WEIGHTED IMAGING**

DWI is a functional MRI sequence that allow the characterization of biological tissues based on the diffusion properties of water molecules, providing information about tissue cellularity and about the integrity of cellular membranes[2]. In fact, in high cellular tissue, the higher density of hydrophobic cellular membranes reduce the “apparent” diffusion of water protons[62], thus the water diffusion can be considered relatively “restricted”. More simply the “diffusion restriction” refers to a tumour signal intensity that is higher than the surrounding parenchyma (the liver for example) on high b-value DW MR images, and, to date, DW-imaging represents an integral part of the routine MR protocol for liver disease (Figure 4).

In 2010, Taouli *et al*[63] defined DW MR imaging, an attractive technique, that was reaching a potential for clinical use in the abdomen, particularly in the liver. Nowadays, in less than a decade, all the potential uses of DWI are greatly shown, and diffusion can be considered a useful tool for the diagnosis of focal liver lesions, with better results than T2-weighted images[64] especially in HCC[65]. The reasons are different: DWI add useful qualitative and quantitative information to standard sequences; it has short acquisition time and can be easily included to existing protocols, moreover, DWI do not need the use of contrast materials[66,67].

Although several DW imaging sequences can be applied to evaluate the liver, the single shot spin-echo (SE) echo-planar technique is the most frequently used in combination with fat suppression. Recent studies[68], compared free breathing (FB) vs respiratory triggered (RT) DWI for detecting HCC, using a 3 T scanner, a 32-channel torso-cardiac phased-array coil and dual-source parallel radiofrequency excitation and transmission technology. They concluded that FB-DWI provided better image quality and showed higher detectability of HCCs in patients with chronic liver disease compared to RT-DWI, without significantly reducing the SNR of the normal liver parenchyma or the lesion-to-non lesion CNR. DW imaging should not be considered a stand-alone sequence, but should be integrated in MR protocols: the combination of Gd-EOB-DTPA and DWI could allow the assessment of the three main processes in the hepatic multistep carcinogenesis (vascular changes, hepatocyte change and tissue diffusivity). A recent meta-analysis showed that the combination of gadoxetic acid-enhanced MRI and DWI significantly improves both diagnostic accuracy and specificity for HCCs associated with chronic liver disease[69]. Several studies underline the importance that DWI add to dynamic contrast-enhanced MRI, in characterization of small or atypically enhancing lesions[70,71]. In particular, Briani *et al*[71] demonstrated that the hypovascular lesions ≥ 10 mm that appeared hyperintense in DWI are associated with progression to hypervascular HCC. DWI can not only indicate the morphological characteristics of a lesion with a qualitative assessment, but with apparent diffusion coefficient (ADC) measurement can also provide a quantitative index of diffusion characteristics, analysing structure and tissue components. Some authors[70,72] suggested that a lesion-to-liver ADC ratio cut-off value of 0.92, may offer good sensitivity, specificity and accuracy in differentiating HCC vs dysplastic nodules (DN). Inchingolo *et al*[70], furthermore, obtained higher values (sensitivity 90.91%, specificity 80.95 % and accuracy of 83.55%), when the group of LGDNs was compared to the group that included both HGDNs and HCCs, with a cut-off of 0.95. Jiang *et al*[73] conducted a retrospective analysis of the correlation between qualitative and quantitative DWI and HCC tumour grade. They found that while SI values on DWI could distinguish only between well-differentiated HCC and moderately or poorly differentiated HCC, ADC values could distinguish between well, moderately, and poorly differentiated HCC, with the consequence of a better pre-operative and non-invasive histological characterization. Further applications of DW imaging are still ongoing, larger studies are need to validate these results. One example is the application of DWI concerning the prediction of microvascular invasion (MVI) in HCC. MVI still remains one of the important prognostic factors of HCC recurrence, especially after surgical resection or liver transplantation[74,75]. In the past other imaging characteristics have previously been suggested as predictors of MVI, such as tumour size, shape and margin, capsule, peritumoral enhancement, and dynamic enhancement pattern; but recently Yang *et al*[76] proposed a new integrated evaluation of T2 and DWI images by defining the concept of “diffusion- and T2-weighted imaging mismatch”. They demonstrated that this new “DWI/T2 mismatch” was an independent predictor of MVI (odds ratio 4.521, *P* = 0.035), with a high specificity (95.65%). Another potential application of DWI is the assessment of liver tumour response to novel therapy. In fact, while a change in tumour size is the common effect of conventional chemotherapy, loco-regional therapies may lead to stability of tumour size or even an increase in hepatic tumour; moreover novel molecular-targeted therapies may alter the morphology of the tumour by affecting its angiogenesis, with unchanged tumour size[77]. Recent studies have shown the possibility to differentiate viable tissue from necrosis on the basis of ADC cut-off values, because necrosis has higher ADC values[78,79]. For patients with hepatocellular carcinoma treated with Sorafenib, a transient decrease in tumour ADC value approximately 1 month after treatment has been reported to be suggestive of haemorrhagic necrosis; however, a sustained decrease in ADC at 3-mo follow-up may indicate viable tumour or its progression[80]. ADC values in patients with hepatocellular carcinoma treated with transarterial radioembolization (TARE) have been shown to increase, a finding suggestive of cellular necrosis, and increased ADC values in such cases may be an early marker of treatment response before changes in tumour size are observed[81]. Despite the several attempts to use of ADC values in clinical practice, reproducibility of volumetric quantification with diffusion-weighted imaging is not well established. Moreover, there are some technical aspects that need to be considered, like the differences in scanner equipments, the lack of a standardized DWI protocol, the low reproducibility and comparability of ADC measurements among different studies and finally the susceptibility of ADC maps to noise and artefacts[64].

**MR ELASTOGRAPHY**

MR elastography (MRE) is an MRI-based method for the quantitative assessment of liver fibrosis and increased stiffness. This technique is based on the application of mechanical waves (generate through the machine), to the region of interest (the liver). These waves and their wave-length are located in the liver through different elastographic sequences (the most used are gradient-echo sequences with motion-encoding gradients) to obtain different set of images and maps. With two different reconstruction algorithm applied to this set of images is possible to obtain a final colored image, called “confidence map”, with different stiffness areas of the liver expressed with different colours which correspond to different in kilo-pascal values (kPa).

Different studies have demonstrated the possibility to use MRE for assessment of mild degree of liver fibrosis[82-84] and to differentiate malignant and benign nodules in the liver[85]. A recent study tried to understand if there was a correlation between HCC stiffness detected with MRE and HCC pathologic features[84]. Tumour stiffness (TS) seemed to be higher in moderate/well differentiate HCC in comparison to poor differentiate HCC (6.5 ± 1.2 kPa *vs* 4.9 ± 1.2 kPa, *p* < 0.01); but at moment, no correlation is found to liver parenchyma stiffness, vascular invasion and tumour encapsulation[84].

Another important application of MRE regards the assessment to treatment response and in particular loco-regional treatment [90Yttrium radio-embolization (RE), trans-arterial chemoembolization (TACE), and radiofrequency ablation (RFA)][86].

In two animal studies[87,88] reduction in TS was associated with histologically proven central necrosis[89] and decreased cellular proliferation and moderate induction of apoptosis[88]. In a preliminary study on humans, MRE seems to provide early evidence of therapeutic response demonstrating that treated tumours have significantly lower TS compared to untreated tumours (3.9 ± 1.8 kPa *vs* 6.9 ± 3.4 kPa, *p* = 0.006) and cirrhotic liver, while intra-tumoral haemorrhage is associated with higher TS. TS seems to relate with visually assessed percentage of necrosis and ER, more in patients treated with RE[86].

MRE still has the limitation of hepatic iron overload, which can decrease hepatic signal intensity in gradient echo based MRE sequences to unacceptably low levels[83]. On the other hand, MRE enables qualitative and quantitative assessment of TF without the use of gadolinium chelates[86].

Despite some of the limitations of MRE, it remains a promising technique not only for the evaluation of liver fibrosis but also in the spectrum of diagnosis and prognosis of HCC[83,84,86].

**RADIOMICS**

Radiomics represents the possibility to convert digital medical images (CT, MR, or positron emission tomography images) into high-dimensional data[89]; the hypothesis is that biomedical images contain information that reflects underlying pathophysiology and that these relationships can be revealed *via* quantitative image analyses. MRI based radiomics signature are currently investigated in glioblastoma, breast and faringeal cancer. Nowadays there are not studies about the possibility to use radiomics in the assessment of HCC. The main works are still focus on some complex texture analysis, taking in account just few features, which represent a small and impaired part of radiomics data analysis.

Controversial results are obtained from different studies concerning the use of texture analysis in the assessment of HCC[90-93]. The main problems are generate from the difference in equipment, contrast phase chosen for the analysis, type of segmentation (circular ROI *vs* tumor shape ROI, slice analysis vs volumetric ROI analysis). Recently two studies have been published on the possibility to use complex texture analysis in MRI to assess the malignancy of HCC (Zhou *et al*[94]) or to predict the progression of hypovascular nodules (detected with gadoxetate disodium acid during hepatobiliary phase) into a hypervascular HCC lesions[90]. In both studies volumetric region of interest (VOI) were evaluated.

All these preliminary studies demonstrated that, among different features assessed with texture analysis some of them seem to have a better performance on specific dynamic phase (arterial or hepatobiliary) and can give useful information. In order to differentiate low grade and high grade HCC[94], “mean intensity value” (a histogram feature) presented significantly larger values in low-grade HCCs than in the high-grade HCCs and the values of gray-level run-length nonuniformity (GLN) were significantly smaller in low-grade HCC than in high-grade HCCs.

Moreover, in another study, different histogram metrics showed the possibility to predict the progression of hypovascular nodule into an HCC[90], using different flip angles and volumetric region of interest.

Radiomics appears to offer a nearly limitless supply of imaging biomarkers, that could potentially aid cancer detection, diagnosis, assessment of prognosis, prediction of response to treatment, and monitoring of disease status[89]. Further studies and validations are required among the performance of the features by themselves, their application according to the different contrast phases available during MRI sequences, and the different MRI equipment.

**CONCLUSION**

MRI of the liver represents an important tool for the detection and characterization of focal liver lesions and for the evaluation of diffuse liver disease. The main advantages of MRI relies on superior soft tissue contrast, absence of ionizing radiation and possibility of performing functional and advanced imaging techniques. Unlike conventional MR imaging sequences, which are usually reported qualitatively based on the varying brightness of tissue, functional MR-imaging techniques offers quantitative data. Among the different functional MR imaging techniques, DWI, MR elastography, and T1-weighted DCE sequences are the most likely to find clinical use at present or in the near future in liver imaging.

The attractions of MR functional imaging include the addition of qualitative and quantitative functional information to conventional anatomic sequences, into routine clinical protocols, in order to offer to the clinicians further comprehensive information about the biology, behaviour and prognosis about HCC lesions.

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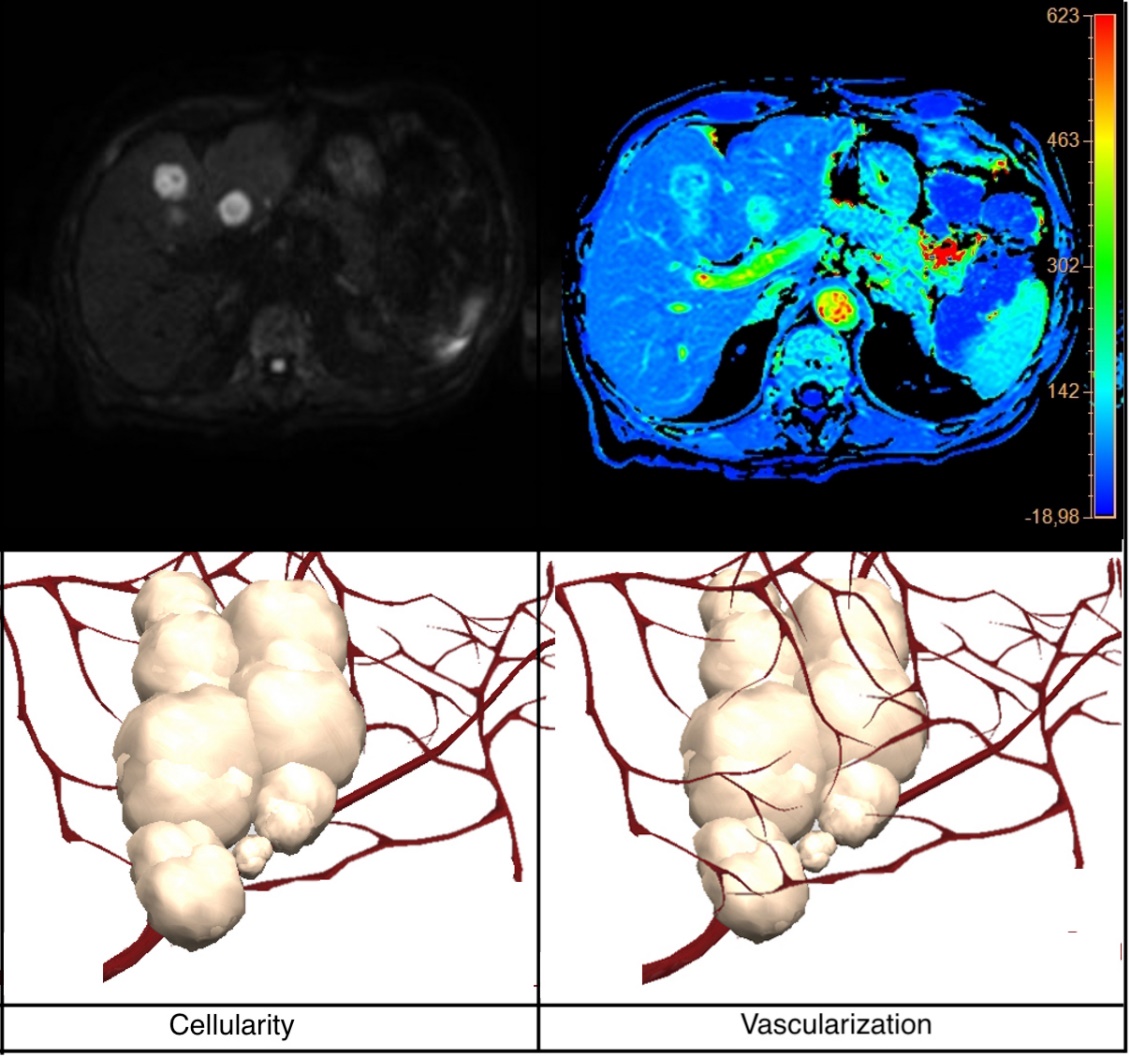
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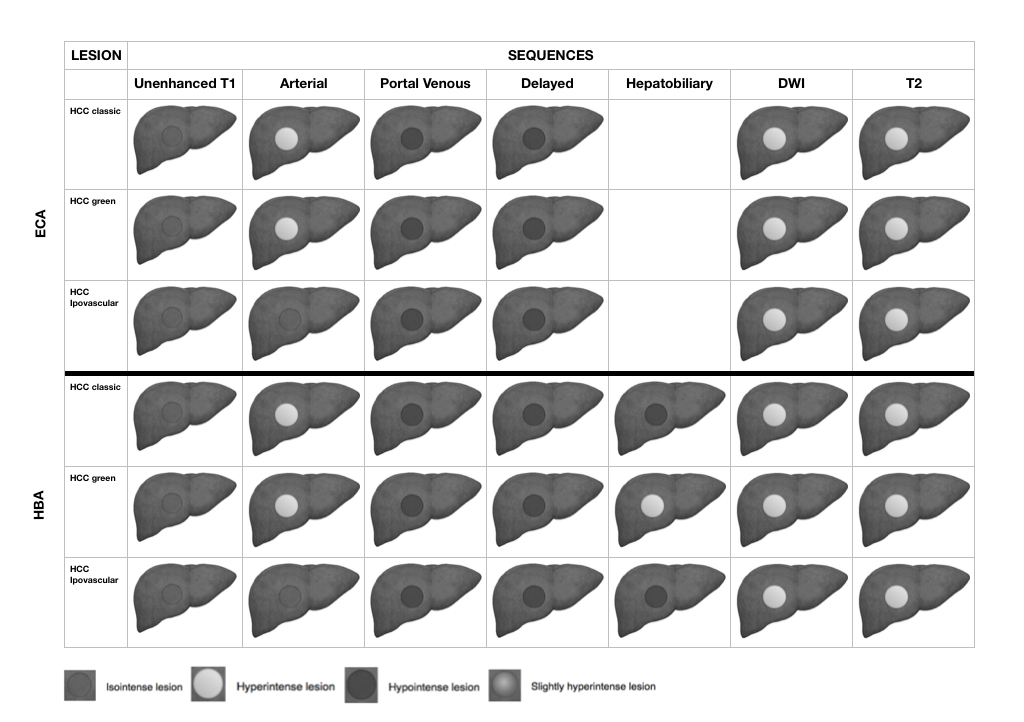
Grade C (Good): 0

Grade D (Fair): D

Grade E (Poor): 0

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**Figure 1 Schematic comparison between diffusion weighted images (on the left) and perfusion maps (on the right) showing the meaning from pathophysiological point of view of the two different functional magnetic resonance techniques.** The diffusion offers qualitative information strictly related to tissue cellularity, while perfusion sequences offers qualitative information about tissue vascularization.

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**Figure 2 Schematic representation showing dynamic contrast enhanced sequences, diffusion weighted images and T2-weighted features in typical, green, and hypovascular hepatocellular carcinoma, comparing information from extra cellular contrast agent and hepatoBiliary contrast agent.** ECA: Extra cellular contrast agent; HBA: Hepatobiliary contrast agent; DWI: diffusion weighted images.

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**Figure 3 Gd-EOB-DTPA enhanced magnetic resonance images of a 67-year-old male patient with large hepatocellular carcinoma lesion in the right liver lobe.** Panels a-b: T1-weighted sequences “in and out of phase” demonstrate a heterogeneous mass slightly hypointense without signal drop in “out of phase” sequence. Panels c-d: T2-weighted image without and with fat saturation demonstrate a slightly hyperintense mass with a central, homogeneous hyperintense area, as per necrosis. Panels e-h: dynamic contrast-enhanced images delineate the typical contrast behavior of hepatocellular carcinoma (HCC): hyperenhancement during the arterial phase (f) followed by wash-out in portal and delayed phase (g-h). In the hepatobiliary phase image 20 min after Gd-EOB-DTPA injection the nodule appears highly hypointense compared with the surrounding enhanced liver (panel i). Panel l: on the diffusion weighted image HCC lesion is hyperintense due to the restriction of water diffusion. Panel m-n: perfusion images derived from semiquantitative analysis (Relative Arterial Enhancement and maximum enhancement) the HCC is characterized by high vascularity intensity signals, showed as hot-spots signals.



**Figure 4 Gd-EOB-DTPA enhanced magnetic resonance images of a 61-year-old patient with hepatocellular carcinoma nodule in theVII segment of the liver.** Panels a-b: a single nodule slightly hypointense on the T1-weighted ”in phase” sequence (a) with a signal drop in the “out of phase” sequence, as per fat deposition. Panels c-d: on T2-weighted image without and with fat saturation the nodule appears slightly hyperintense. Paneles e-h: dynamic contrast-enhanced images demonstrate the typical contrast behavior of hepatocellular carcinoma: which appear hypervascular during the arterial phase (f) with wash-out in portal and delayed phase (g-h). Panel i-l: diffusion weighted image (DWI) shows the hyperintense pattern of the lesion which appear hypointense on the relative apparent diffusion coefficient map (arrowhead). Previously treated lesion with transarterial chemoembolization is recognizable, in panel a-e-f-g-h, at V segment of the liver (arrow). No any restriction of signal intensity is evident on DWI (panel i-l).

**Table 1 Gadolinium-based magnetic resonance imaging contrast agent**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Contrast agent** | **Category** | **Relaxivity** | **Structure** | **Concentration (mmol/mL)** | **Reccomended dosage (mmol/kg)** |
| Gadoterate-meglumine | ECFAs | Standard | macrocyclic | 0.5 | 0.1 |
| Gadobutrol | ECFAs | Standard | macrocyclic | 1.0 | 0.1 |
| Gadoteridol | ECFAs | Standard | macrocyclic | 0.5 | 0.1 |
| Gadopentetate- dimeglumine | ECFAs | Standard | Linear | 0.5 | 0.1 |
| Gadoversetamide | ECFAs | Standard | Linear | 0.5 | 0.1 |
| Gadodiamide | ECFAs | Standard | Linear | 0.5 | 0.1 |
| Gadofosfaset-trisodium | BPCAs | High | Linear | 0.25 | 0.03 |
| Gadobenate- dimeglumine | HCAs | High | Linear | 0.5 | 0.1 |
| Gadoxetate-disodium | HCAs | High | Linear | 0.25 | 0.025 |

ECFAs: Extracellular fluid agents; BPCAs: Blood pool agents; HCAs: Hepatocyte-specific contrast agents.

**Table 2 magnetic resonance imaging perfusion with dynamic contrast-enhanced magnetic resonance imaging in the assessment of hepatocellular carcinoma focus on diagnosis and characterization, response to therapy and prognosis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Magnet (Tesla)** | **Contrast agent** | **Parameters** | |
| Diagnosis and characterization |
| Taouli *et al*[38] | 2013 | 1.5 T | Gadobenate-dimeglumine and gadopentetate-dimeglumine | AF, VF, ART, DV, MTT | |
| Chen *et al*[39] | 2017 | 3 T | GD-EOB-DTPA | Ktrans, Kep, iAUC, max-Ktrans | |
| Jajamovich *et al*[40] | 2016 | 3 T | Gadobenate-dimeglumine | ART, K trans, ve, kep, τ | |
| Abdullah *et al*[61] | 2008 | 1.5 T | Gadoterate-dimeglumine | HPI, MTT, DV, TF, AF, PF | |
| Response to therapy |
| Ippolito *et al*[41] | 2016 | 1.5 T | GD-EOB-DTPA | | ME, MRE, RAE, RE, RLE, RVE, TTP |
| Taouli *et al*[38] | 2013 | 1.5 T | Gadobenate-dimeglumine and Gadopentetate-dimeglumine | | AF, VF, ART, DV, MTT |
| Chen *et al*[45] | 2016 | 1.5 T | Gadodiamide | | Peak, Slope, AUC, Ktrans, Kep, Ve |
| Prognosis |
| Chen *et al*[45] | 2016 | 1.5 T | Gadodiamide | | Peak, Slope, AUC, Ktrans, Kep, Ve |
| Chen *et al*[45] | 2016 | 1.5 T | Gadodiamide | | ART, AF, PF, TF, MTT, DV, PEAK, SLOPE, AUC |

ART: arterial fraction; K trans: contrast agent transfer rate constant from plasma to extravascular extracellular space; VE: extravascular extracellular volume fraction; Kep: contrast agent intravasation rate constant; τ: mean intracellular water molecule lifetime; ME: maximum enhancement; MRE: maximum relative enhancement; RAE: relative arterial enhancement; RE: relative enhancement; RLE: relative late enhancement; RVE: relative venous enhancement; TTP: time to peak; HPI: hepatic perfusion index; MTT: mean transit time; DV: distribution volume; TF: total blood flow; AF: arterial blood flow; PF: portal blood flow; AUC: area under the gadolinium distribution-time curve.