Review Article

Hepatocellular Carcinoma: State of the Art Imaging and Recent Advances

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Abstract

The incidence of hepatocellular carcinoma (HCC) is increasing, with this trend expected to continue to the year 2030. Hepatocarcinogenesis follows a predictable course, which makes adequate identification and surveillance of at-risk individuals central to a successful outcome. Moreover, imaging is central to this surveillance, and ultimately to diagnosis and management. Many liver study groups throughout Asia, North America and Europe advocate a surveillance program for at-risk individuals to allow early identification of HCC. Ultrasound is the most commonly utilized imaging modality. Many societies offer guidelines on how to diagnose HCC. The Liver Image Reporting and Data System (LIRADS) was introduced to standardize the acquisition, interpretation, reporting and data collection of HCC cases. The LIRADS advocates diagnosis using multiphase computed tomography or magnetic resonance imaging (MRI) imaging. The 2017 version also introduces contrast-enhanced ultrasound as a novel approach to diagnosis. Indeed, imaging techniques have evolved to improve diagnostic accuracy and characterization of HCC lesions. Newer techniques, such as T1 mapping, intravoxel incoherent motion analysis and textural analysis, assess specific characteristics that may help grade the tumor and guide management, allowing for a more personalized approach to patient care. This review aims to analyze the utility of imaging in the surveillance and diagnosis of HCC and to assess novel techniques which may increase the accuracy of imaging and determine optimal treatment strategies.

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Introduction

Incidence rates of hepatocellular carcinoma (HCC) in the USA have tripled in the previous three decades, with future projections from the Surveillance, Epidemiology and End Results program indicating continued growth of HCC incidence to the year 2030.[1,2] HCC generally presents late in the disease process and as a result the associated mortality is relatively high, with sources estimating it to be the 3rd or 4th most common cause of death due to cancer worldwide.[1,3,4] Five-year survival is <16%, however when identified at an earlier stage the 5-year survival rates have been as high as 93%.[5,6] The aim of this review is to evaluate how imaging plays a part in the surveillance and diagnosis of HCC and to assess novel techniques which may increase the accuracy of imaging and determine optimal treatment strategies.

Carcinogenesis

HCCs typically arise in patients with chronic liver disease. Cirrhosis may or may not be present. The development of HCC is complex, with multiple steps known as 'hepatocarcinogenesis' and dictated by progressive genetic alterations.[7] Emerging research suggests intrahepatic stem cells as the likely cell of origin, as opposed to dedifferentiation of a hepatocyte.[8]

Regenerative nodules are the first step, consisting of rounded regions of hepatic parenchyma, surrounded by fibrosis.[9] Smaller regenerative nodules are generally not discernable on standard imaging and are benign entities. Dysplastic foci and ultimately dysplastic nodules then develop within these regenerative nodules or hepatic lobules in non-cirrhotic livers. Dysplastic nodules are composed of hepatocytes with precancerous changes, which ultimately develop to form HCC. Angiogenesis first occurs in dysplastic nodules, with the formation of unpaired arteries. This arterial supply increases from this stage through hepatocarcinogenesis and accounts for the arterial phase hyperenhancement associated with HCC on imaging.[10]

Stromal invasion is the predominant feature to differentiate HCC from dysplastic nodule, with tumor cells invading into the surrounding fibrous tissue.[11] The earliest form is analogous to a "carcinoma *in situ*" seen elsewhere in the body and is described as 'early HCC'. It replaces instead of displaces the hepatic parenchyma. Early HCCs are precursors to 'progressed HCC' but the rate at which this occurs is not clear.[12] Progressed HCCs demonstrate greater ability for vascular invasion and metastatic spread with displacement of the hepatic parenchyma. Increased size generally indicates higher grade, with larger masses (>2 cm) demonstrating heterogeneity with mosaic architecture and areas of necrosis or hemorrhage.[13] Higher grade lesions characteristically demonstrate vascular, biliary and tumor capsule invasion, increasing the risk for extrahepatic spread.[14,15] Most common

Keywords: Hepatocellular carcinoma; CT; MRI; Ultrasound; Advances.
Abbreviations: AASLD, American Association for the Study of Liver Diseases; CEUS, contrast-enhanced ultrasound; CT, computed tomography; FDG, fluorodeoxyglucose; HCC, hepatocellular carcinoma; IVIM, intravoxel incoherent motion imaging; LIRADS, Liver Imaging Reporting and Data System; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PET, positron emission tomography; TACE, transarterial chemoembolization.
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extrahepatic sites for metastases include the lung, abdominal lymph nodes and bone.[16]

Risk factors

Estimation of risk is required before patients can be stratified into specific surveillance programs. There are several factors associated with increasing risk of HCC, including geographical, ethnic, infectious and environmental considerations.

The incidence of HCC is highest in eastern and south-eastern Asia and northern and western Africa, with incidence rates >15/100,000.[17] The risk factors most commonly implicated include cirrhosis, hepatitis B and hepatitis C. The risk is independent of cause, with an incidence of 1–8% among individuals with compensated cirrhosis and 1% in individuals with chronic hepatitis.[18,19] For 20–56% of individuals, however, the diagnosis of HCC in cirrhotic livers is the first presentation of cirrhosis.[20,21]

Viral hepatitis, predominantly hepatitis B and C, are thought to account for >50% of cases of HCC.[4] The hepatitis B virus affects approximately 3.2% of people worldwide,[22] while hepatitis C virus accounts for approximately one-third of cases of HCC in the USA.[23] Environmental and ingested toxins demonstrate variable roles in increasing the incidence of HCC in various parts of the world. Alcohol has a demonstrated dose-effect relationship with the development of HCC.[24] Genetic and metabolic conditions, in the form of hereditary hemochromatosis, obesity, gallstone disease, type 2 diabetes mellitus, alpha-1 antitrypsin deficiency, acute intermittent porphyria and non-alcoholic fatty liver disease (NAFLD), also have demonstrated effect on increased risk of HCC.[25–31]

NAFLD is emerging as one of the most common causes of chronic liver disease and is thought to become one of the leading causes for liver transplant.[32,33] NAFLD occurs along a spectrum, ranging from steatosis to non-alcoholic steatohepatitis (commonly known as NASH) and finally cirrhosis. NASH is a known risk factor for HCC.[34,35] NASH may also progress to cirrhosis, with increased risk of HCC; however, HCC can occur in NAFLD patients in the absence of advanced fibrosis or cirrhosis.[36,37] It has been estimated that 4–22% of HCC occurs in the setting of NAFLD.

Surveillance

Multiple liver study groups have proposed surveillance programs for at-risk groups to detect HCC at an earlier stage.[38–44] Despite the worldwide utilization of surveillance programs, their validity, in survival terms, have yet to be conclusively verified. A recent meta-analysis assessed the effect of HCC surveillance on overall survival as well as other endpoints. The researchers found a prolonged survival with odds ratio of 1.9 (confidence interval: 1.67–2.17). Although they allow for lead-time bias, the method of surveillance varied within the meta-analysis.[45]

The major liver study groups advise use of ultrasound, with or without serum alpha-fetoprotein, for surveillance. The American Association for the Study of Liver Diseases (AASLD) advises ultrasound surveillance.[38] This is based on a previous Chinese study that demonstrated a reduction in mortality of 37% with this program and on a more recent Taiwanese study demonstrating a reduction in mortality of 31%.[46,47] The European societies utilize ultrasound surveillance only,[39,40] with other USA and Asian groups advising the use of ultrasound with alpha-fetoprotein as a biomarker.[41–44] When a lesion is identified on ultrasound, size dictates future management; however, there is no universally agreed-upon approach.

In lesions <1 cm, the AASLD, Liver Imaging Reporting and Data System (LIRADS), National Comprehensive Cancer Network and European Association for the study of the Liver – European Organization for the Research and Treatment of Cancer recommend repeat ultrasound at 3- to 6-month intervals.[38,39,43,48] In lesions >1 cm, the AASLD recommends multiphase CT or magnetic resonance imaging (MRI) imaging. The Japanese Society of Hepatology recommends multiphase CT or MRI when a nodule of any size is detected.

Diagnosis

HCC is a unique malignancy in that it can be diagnosed based on imaging findings alone, as is the recommended approach by major societies on liver studies. Histological confirmation with biopsy is avoided due to inherent risks of invasive biopsy and a small but definite risk of needle track seeding. The imaging characteristics of arterial phase hyperenhancement with washout on portal venous and delayed sequence and enhancing capsule is the classic imaging appearance (Supplementary Fig. 1).

On imaging using dynamic contrast studies, the identification and discrimination of hepatocellular cancer from its precursors and other hepatic masses depend on multiple pathophysiological alterations which occur during hepatocarcinogenesis.[49] The generation of an altered arterial network and disappearance of portal venous flow to the nodule creates the typical arterial phase hyperenhancement and washout in portal venous and delayed phase appearance compared to background liver. The formation of a tumor capsule and fibrous septae are not seen in regenerative nodules, dysplastic nodules, or early HCCs but are seen in 70% of more progressed HCCs.[15]

Fat content varies throughout hepatocarcinogenesis. Hepatocytes tend to demonstrate higher fat content during early phases as dysplastic nodules or early HCCs.[50] The presence of diffuse fat in progressed HCCs is uncommon.[11,51] Iron deposition during this process also varies. Peak iron content occurs in dysplastic nodules and decreases as dedifferentiation progresses and is rarely seen in early and progressed HCCs.[52] Organic anionic transporting polypeptides (OATPs) are involved in the transport of bile salts and many other substrates into the hepatocytes, including the hepatocyte-specific agent gadoxetate disodium (Gd-EOB-DTPA).[10] Expression of these proteins decreases in high-grade dysplastic nodules and also in HCCs which result in decreased uptake of gadoxetate by the dedifferentiated lesions.[10,53]

Many societies offer guidelines on how to diagnose HCC. The American College of Radiology developed LIRADS[48] to standardize how data concerning HCC is acquired, interpreted and reported. This is supported by a specific lexicon, imaging algorithm, and illustrative atlas. Their guidance is intentionally designed to resemble that of the AASLD. The Organ Procurement and Transplant Network/United Network for Organ Sharing group have also published guidance to aid in interpretation and management (Supplementary Tables 2 & 3).

As outlined above, once a lesion is identified on non-contrast ultrasound measuring >1 cm, it is further evaluated with non-invasive diagnostic tests. For all guidelines, this involves multi-row detector CT or contrast-enhanced MRI using an extracellular contrast agent. The decision on whether to use

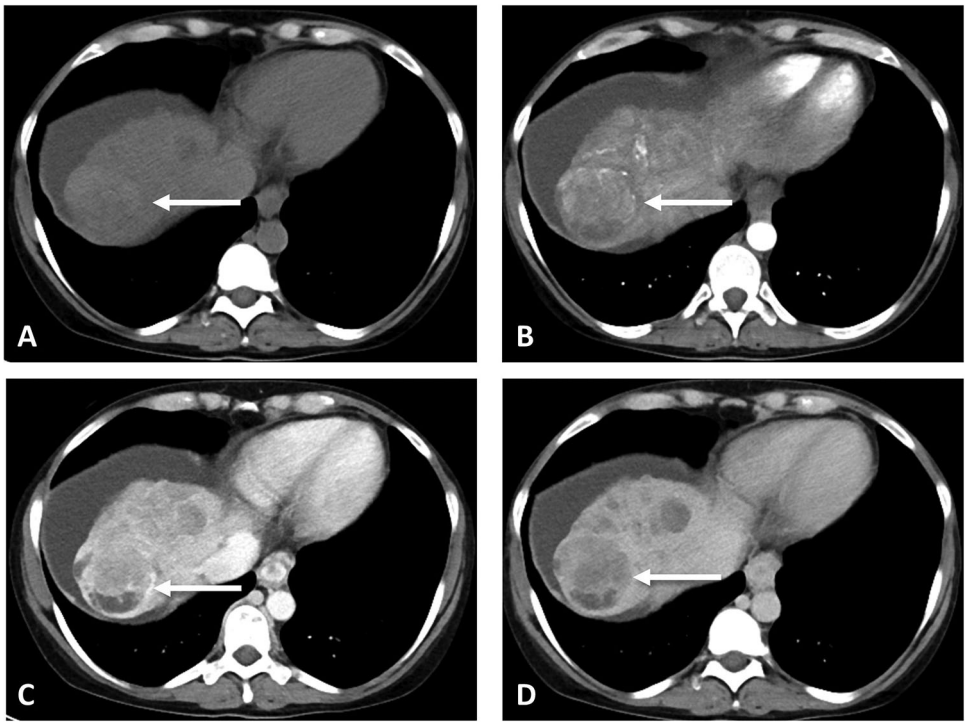

Fig. 1. Axial abdominal computed tomography in a 56-year-old male with alcoholic cirrhosis. Non-contrast enhanced (A), arterial phase (B), portal venous (C) and delayed phase (D) images illustrate multiple masses in the right liver with arterial phase hyperenhancement (arrow) that shows washout and pseudocapsule formation on portal venous phase and delayed imaging.

CT or MRI often depends on local protocol. Studies have demonstrated similar sensitivities between the two modalities, with MRI perhaps demonstrating a slightly higher diagnostic performance.[54–57] Contrast-enhanced ultrasound (CEUS) is advocated by some societies, namely the Japanese Society of Hepatology, Italian Association for the Study of Liver, the National Comprehensive Cancer Network, LIRADS, the Canadian Association for the Study of Liver and the Asian Pacific Association for the Study of Liver.[42,43,58–60]

The radiological hallmarks of HCC as visualized on CT or MRI are: a) arterial phase hyperenhancement with b) portal venous washout or delayed phase washout. This may be with or without c) enhancing capsule.[38,39] Pathological diagnosis is generally not recommended unless the lesion remains indeterminate on all available imaging. This is due to the high specificity of available imaging in diagnosing HCC based on typical appearance, which reaches 100% in some studies.[61] In contrast, the risk of major complications is 0.05% with biopsy and the risk of tumor seeding can be as high as 2.7%.[62]

Cross-sectional imaging

Multidetector CT is readily available and offers rapid acquisition of high spatial resolution images (Fig. 1). Typical protocols have three phases obtained after injection of intravenous iodinated contrast agent; late arterial phase (25–40 s post-injection), portal venous phase (65–80 s post-injection) and delayed phase (5–10 m post-injection). The late arterial phase allows for greatest appreciation of the arterial phase hyperenhancement associated with HCC. Subtraction images can also be reconstructed to aid in the detection of enhancement in the various phases. Contrast medium (extracellular contrast medium) is typically of low osmolarity with iodine concentration of 300–350 mg/mL. Injection rates vary from 4–8 mL/s. In our center, images of all enhancement phases are reconstructed in axial and coronal planes at 3 mm slice thickness.

A 1.5 or 3 Tesla field strength MR scanner can be utilized. Protocols vary per center; however, a 3D T1-weighted sequence with fat saturation and dynamic contrast enhancement is generally required (Fig. 2). Phases of enhancement are similar to those of CT described above. With the recent revision of LIRADS (LIRADs 2017), other features are recognized as secondary/ancillary for the diagnosis of HCC.[48] For example, abnormal restricted diffusion and hyperintensity on axial fat saturated T2-weighted sequence[48] (Fig. 2). The contrast media typically used are gadolinium-based extracellular agents. Hepatobiliary agents that are actively taken up by functioning hepatocytes are increasingly used in many European studies. HCCs are typically seen as hypointense lesions in the hepatobiliary phase, although a well-differentiated HCC can show uptake of hepatobiliary agent occasionally (Fig. 3).

Arterial phase hyperenhancement is deemed the most sensitive feature in the diagnosis of HCC, with figures as high as 96%.[61,63,64] It is defined in LIRADS as non-rim-like enhancement in all or part of an observation in the arterial phase that is unequivocally greater than that of the liver.[48] As this trait is present due to neovascularization, the sensitivity is decreased for early HCC where neovascularization is less well established.[65] There is also a wide differential associated with arterially enhancing lesions in the liver and therefore the specificity and positive predictive value of this feature is low.[64,66]

"Washout" refers to the progressive reduction in enhancement in later phases of the multiphase study, with a lesion

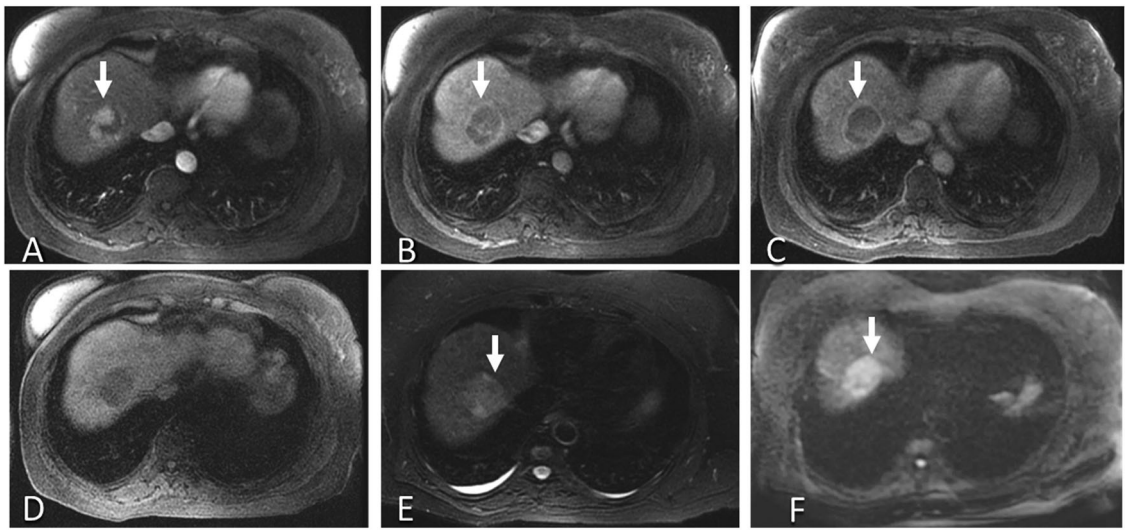

Fig. 2. Axial magnetic resonance imaging of the HCC in a 57-year-old patient with cirrhosis secondary to chronic hepatitis C infection. Arterial (A), portal venous (B), delayed (C) phase demonstrating arterial phase hyperenhancement in HCC (arrow) which washes out on portal venous and delayed phases. This mass demonstrates T1 hypointensity (D), and mild T2 hyperintensity (E) with mild restricted diffusion (F).

demonstrating decreased enhancement compared to neighboring liver in portal venous and delayed phases. The sensitivity of "washout" alone has been quoted as 53–79%, with a specificity of 62–100% in a per-nodule basis.[61,63,64] The assessment of "washout" however is quite subjective and difficult in cases of established cirrhosis. The use of hepatocyte-specific contrast agents may also add confusion. Hypoenhancement during the transitional phase (2–5 m) of hepatobiliary agent MRI should not be confused with "washout" associated with HCC. As a result, guidelines such as LIRADS advise for the assessment of "washout" in portal venous phase only when utilizing hepatocyte-specific contrast agents.

The appearance of an enhancing capsule around a lesion in at-risk patients demonstrates a sensitivity of 42–64% with a specificity of 86–96% for diagnosing HCC. It is visualized as a

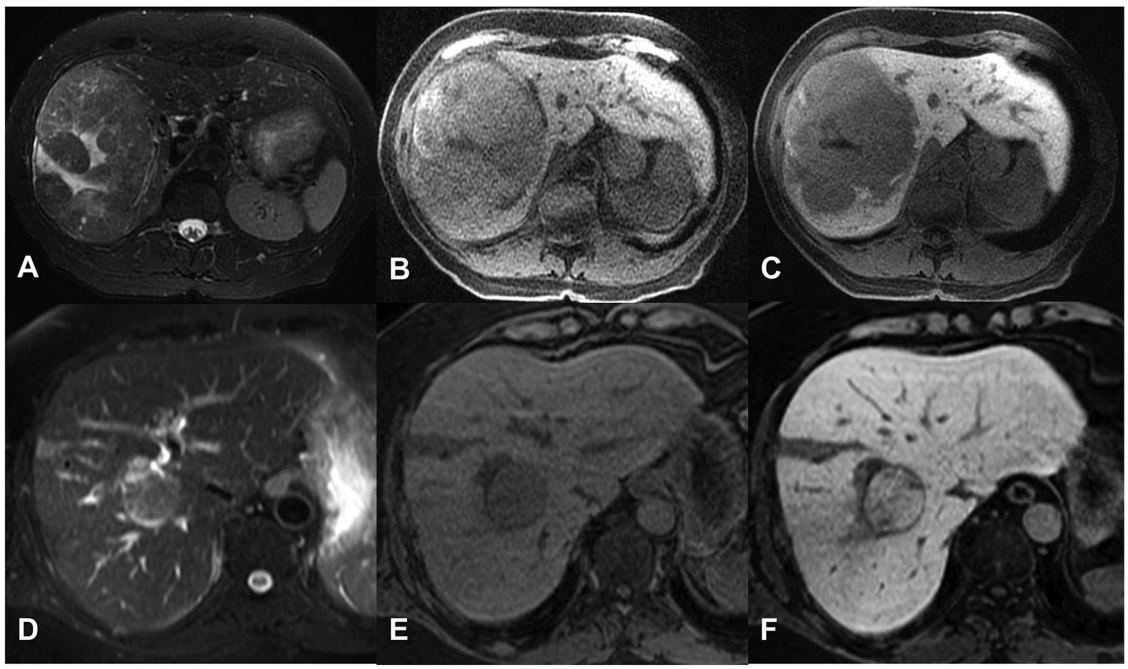

Fig. 3. Axial magnetic resonance imaging on a separate patient performed with hepatobiliary contrast agent (gadoxetate) in two separate patients. Axial T2-weighted (A) and pre-contrast T1-weighted (B) demonstrates a large hepatocellular carcinoma in the right liver with minimal uptake on hepatobiliary phase imaging (C). This contrasts to the second patient with HCC that also shows mild hyperintensity on T2-weighted (D) and hypointensity on T1-weighted (E) but demonstrates uptake of contrast in the hepatobiliary phase (arrow, F).

defined area of enhancement around a lesion in portal venous or delayed imaging. This may represent a true capsule but can also be secondary to fibrous tissue, compressed liver or prominent sinusoids.[67,68]

Lesion growth is also associated with risk of malignancy. HCCs have demonstrated variable tumor volume doubling times, from 9 days to years depending on tumor differentiation status.[69,70] Hepatocarcinogenesis progresses with lesion growth and therefore a larger lesion size is also associated with HCC.[71] Many guidelines use 1 and 2 cm as cut-offs for lesion size and associated risk of HCC.[72] Growth parameters as recommended by the Organ Procurement and Transplant Network/United Network for Organ Sharing define ≥50% growth in a <6 month period as associated with increased risk of HCC. LIRADS has added further parameters of ≥100% growth in a >6 month period or a new lesion >1 cm.[48]

LIRADS also defines ancillary features, which although not strongly sensitive or specific may aid with lesions where diagnosis is indeterminate based on the major features above. The presence of hyperintensity or diffusion restriction improves sensitivity, particularly for smaller lesions but is not specific for HCC.[73] HCCs are typically of mild to moderate T2 hyperintensity. High T2 intensity is associated with benign lesions, such as hemangiomas or cysts. Indeed, as dedifferentiation progresses, HCCs have demonstrated iso- to hypointensity on T2-weighted sequences. Mosaic pattern is associated with the variability of tissue components associated with HCC (Supplementary Fig. 2). Its utility is most useful in larger lesions, where regions of enhancement, necrosis, hemorrhage and fibrosis may be present in a tumor.[13] Finally, a nodule-in-nodule appearance is typically associated with dedifferentiation of (enhancing) HCC in a larger (isoenhancing) cirrhotic nodule.

Hepatobiliary contrast agents are contrast agents taken up by normally functioning hepatocytes *via* the OATP1 transporter. These agents behave like standard extracellular contrast, with distribution in vessel and extracellular spaces in the early phases. However, due to their uptake in hepatocytes, there is enhancement of normal hepatic parenchyma in the hepatocellular phase (15–20minutes) with little to no uptake in non-hepatocellular or non-functioning hepatocyte-containing lesions, such as HCC. The use of hepatocyte-specific contrast agents in assessing for HCC demonstrated sensitivity levels of 86% in a large meta-analysis.[74] A potential disadvantage is the reported breath hold artifacts during dynamic arterial phase witnessed in patients while using this contrast agent.[75]

CEUS

CEUS utilizes the generation of harmonic signals from resonating microbubbles to form a signal. These microbubbles consist of a lipid shell, measuring 3–5 μm in diameter, containing a perfluorocarbon gas. This is much larger than the molecules used in CT or MRI contrast agents and as a result remain completely intravascular, leading to differences in enhancement patterns between CEUS and conventional CT/MR imaging.

CEUS is utilized by many societies in their guidance on diagnosis of HCC, as it has been demonstrated as a valuable contributor in evaluating nodules in a cirrhotic liver.[76] Specific indications have been proposed and may include assessment of a nodule ≥1 cm in ultrasound, indeterminate nodules on CT/MR imaging, indeterminate nodules post-biopsy, and nodules in individuals where timing of the arterial phase may be difficult to ascertain, as well as visualization of lesions not seen on non-contrast ultrasound, selection of the most appropriate lesion for biopsy, assessment of tumor thrombus, and for post-treatment surveillance.[77]

The diagnosis of HCC with CEUS can be based on numerous imaging features (Supplementary Fig. 3). Arterial phase hyperenhancement is identified when enhancement is greater than the background liver within approximately the first 45 s. This may be present in the entire nodule or part of a nodule, when filling of the nodule occurs in a centripetal fashion. Progressive washout of the nodule is also typical of HCC. The onset of washout begins usually after 60 s but the nodule itself typically retains some internal enhancement, although less than surrounding hepatic parenchyma.[77] As with cross-sectional imaging, other features, such as increase in size over time, nodule-within-a-nodule appearance and mosaic appearance on grayscale imaging, are all factors making the diagnosis of HCC more likely. The validity of CEUS in lesion characterization and diagnostic performance has been proven in various studies.[74,78] A recent meta-analysis demonstrated similar diagnostic performance of CEUS versus gadolinium-enhanced MRI in detecting HCC, with a sensitivity/positive predictive value of 84.4%/89.3% for CEUS and 77.5%/83.6% for gadolinium-enhanced MRI.[74]

CEUS has its limitations. The most important limitation is that evaluation of the entire liver is not possible, potentially missing other nodules. Characterization of only one nodule is possible with one injection, however. The enhancement patterns overlap with several other benign lesions. Patient factors may limit visibility, with the technique being highly operator-dependent. Highly cirrhotic or fatty livers are challenging. Pseudoenhancement can also occur secondary to echogenic objects deep in the liver.[79]

Novel techniques

Techniques to improve the imaging of HCC are continuously evolving. In CT, perfusion analysis, dual-energy and textural analyses are being investigated to improve the sensitivity of this modality. With MRI, MR spectroscopy, MR elastography and T1 mapping are potential novel techniques.

CT perfusion

CT perfusion has the ability to assess hemodynamic changes in the liver or part of the liver. It is based on the increase and subsequent decrease in the concentration of iodinated contrast material in a region of liver as a function of time. It depends on factors such as blood volume, blood flow to an area, and permeability of capillaries to the contrast agent.[80] Parameters which may be assessed include blood flow in the artery, mean transit time between arterial inflow and venous outflow, and blood volume. The relationship of perfusion to pathological angiogenesis is not well understood.[81] It is believed to be associated with microvessel density within a tumor, which affects blood volume and flow. Mean transit time can be decreased due to increased vascular permeability in tumor vessels and the presence of arteriovenous shunts.

This is also true in the assessment of HCC with blood volume, blood flow, hepatic perfusion index and arterial perfusion all being lower in normal hepatic parenchyma than in HCC.[82] Perfusion may aid in diagnosis and may also aid in grading tumors, with estimation of blood volume, mean blood flow and permeability surface area findings all being

significantly higher in well-differentiated HCC versus other grades.[83,84] CT perfusion may also assess tumor response and predict survival following particle embolization or treatment with sorafenib.[85,86] Factors such as blood flow and blood volume were found to significantly decrease after 1 day of treatment in an *in vitro* study.[87] Finally, CT perfusion may also aid in detecting recurrence, with the utility of the perfusion index and volumetric arterial enhancement fraction color mapping allowing earlier detection of recurrence following microwave ablation and transarterial chemoembolization (TACE).[88,89]

There are several challenges to the routine clinical use of CT perfusion in the assessment of HCC. For one, radiation dose reduction is required, as CT perfusion can result in higher radiation with doses ranging from 7.3 to 30.6 mSv.[90] In addition, lack of standardized protocol, reproducibility, motion artifacts and inability to sample the whole tumor are all further issues.[81,83]

Dual-energy CT

Dual-energy CT was first used clinically in 2006. It allows acquisition of information from two different x-ray spectra almost instantaneously, depending on the equipment used. Materials with different atomic numbers behave differently in these spectra, and this allows for improved analysis of this contrast in composition.[91]

This can be applied to the analysis of HCC in numerous ways. The improved contrast can allow greater differentiation of fat in liver lesions that can be associated with HCC.[92] The enhancement of small HCCs can also be amplified due to increased iodine concentration, without any increase in image noise (Fig. 4).[93] Various alterations in imaging techniques, such as utilizing monochromatic energy levels of 40–70 keV, may also demonstrate improved detection rates (Fig, 4).[94] Dual-energy CT may also have applications in assessing perfusional characterization of a lesion, which has been argued at potentially offering similar assessment capabilities as perfusion CT.[95]

Textural analysis

Textural analysis is an objective measure of tumor heterogeneity on CT and MRI. This is achieved by analyzing the distribution of pixels within the lesion (Fig. 5).[96] The most commonly used method is a statistical-based model. Tumors demonstrate heterogeneity on numerous levels; this is secondary to angiogenesis, variations in cellularity, areas of necrosis, and extravascular extracellular matrix.[97] Tumors with increased intratumoral heterogeneity are associated with poorer prognosis.[98]

With regards HCC, textural analysis has demonstrated potential in predicting survival and may be beneficial in identifying individuals suitable for TACE.[99] In the largest of these studies, CT textural analysis demonstrated an ability to differentiate patients who benefitted most in terms of survival when treated with TACE and sorafenib compared to TACE alone.[99] MR texture analysis is a more recent development assessing heterogeneity of pixels on T1 sequences post-contrast and this has demonstrated some potential in assessing tumor grade.[100]

A possible limitation of this technology is the lack of an agreed technique between studies, making comparison and ultimately validation difficult. The time needed to analyze these studies and create adequate 3D models is also not well understood, and whether this technique could be realistically introduced into the routine clinical schedule remains to be demonstrated due to the volume of data involved.

MR spectroscopy (MRS)

MRS assesses the concentrations of various metabolites within tissue. By doing this, it can assess the composition of a particular area of tissue but also indirectly assess the pathophysiology and metabolism.[101] The hydrogen (^{1}H) nucleus is most commonly utilized for MRS followed by phosphorus-31 (^{31}P), with carbon-13 (^{13}C) as another potential option.

In HCC, the presence of malignancy can be identified by assessing choline peaks and proton resonances of mobile lipids.[102] MRS has demonstrated efficacy in assessing response following TACE by determining levels of choline and its derivatives. Mean choline/lipid ratios are decreased following successful TACE treatment.[103] Tumor progression has been associated with an increase in phosphomonoesters.[104]

The major limitation of MRS is its low sensitivity in assessing smaller lesions, due excessive signal-to-noise ratio and effects of motion.[105] MRS can be technically demanding, with significant impact on scan time, and it needs a trained and expert physicist for input, and needs additional processing. All these features make MRS a research tool mainly and not easily applicable in routine clinical practice.

Elastography

The incidence of HCC increases with the progression of hepatic fibrosis and stiffness associated with chronic inflammation of the liver.[106] Assessment of hepatic stiffness was first utilized with ultrasonography, creating ultrasound elastography at the turn of the century. Ultrasound elastography has demonstrated high accuracy for staging liver fibrosis and ultimately allowing assessment of risk for HCC.[107,108] The development of point and 2D-shear wave may also allow increased characterization and differentiation of focal liver masses based on their stiffness.[109]

MR elastography (MRE) assesses the mechanical properties of tissues by analyzing the response of mechanical shear waves at a low frequency after they pass through the liver.[110] The utility of this technique, like ultrasound elastography, is predominantly to assess for hepatic fibrosis. However, recent evidence has demonstrated a link between tumor grade and tumor stiffness, with malignant tumors demonstrating greater stiffness on MRE (Fig. 6).[111] A threshold of 5.0 kPa is postulated as a threshold to allow differentiation between benign and malignant tumors.[111]

Stiffness may also indicate grade of malignancy, with a recent study indicating increased stiffness with increased tumor grade.[112] Data regarding utility of MRE in the diagnosis of HCC is lacking, but it still may be useful for characterizing a lesion by demonstrating increased liver stiffness that is suggestive of otherwise unsuspected liver fibrosis in the background parenchyma. A recent study has shown that stiffness of HCC measured with MRE may be useful to differentiate poorly differentiated HCC from moderately to well-differentiated HCC;[112] however, this needs to be confirmed in larger studies.

Intravoxel incoherent motion imaging (IVIM)

The diffusion motion of water in a region of tissue is assessed using diffusion-weighted imaging. Diffusion may be secondary

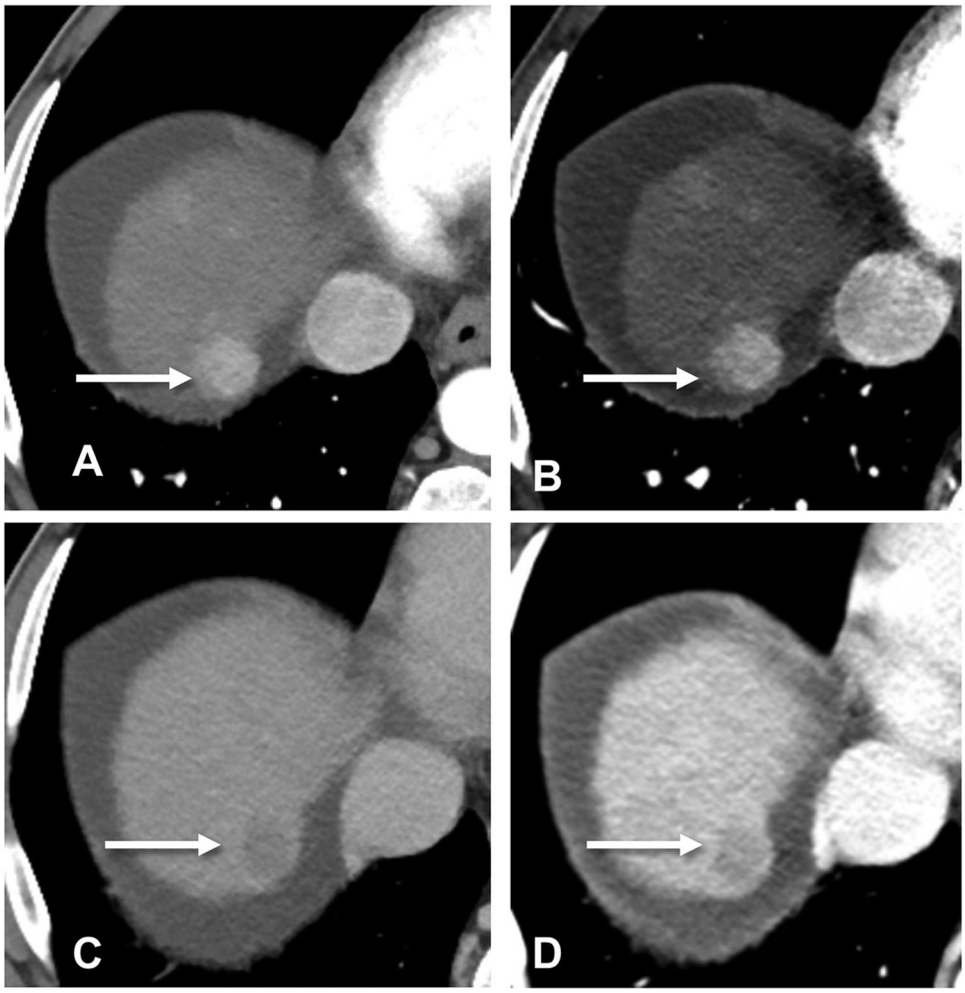

Fig. 4. Dual-energy computed tomography demonstrating a hepatocellular carcinoma with arterial phase hyperenhancement on 0.6 linear blend (A) and 50 keV (B) imaging. The hepatocellular carcinoma also demonstrates washout on delayed linear blend (C) and 50 keV (D) images. (Images courtesy of Dr. Joel G. Fletcher, Radiology, Mayo Clinic, Rochester, MN, USA.)

to molecular diffusion or secondary to microcirculation in vessels.[113] The sensitivity of this imaging technique is based on the b-value. Low b-values offer a high signal-to-noise ratio but decreased sensitivity in discerning molecular diffusion to diffusion secondary to microcirculation. High b-values allow almost complete elimination of diffusion secondary to

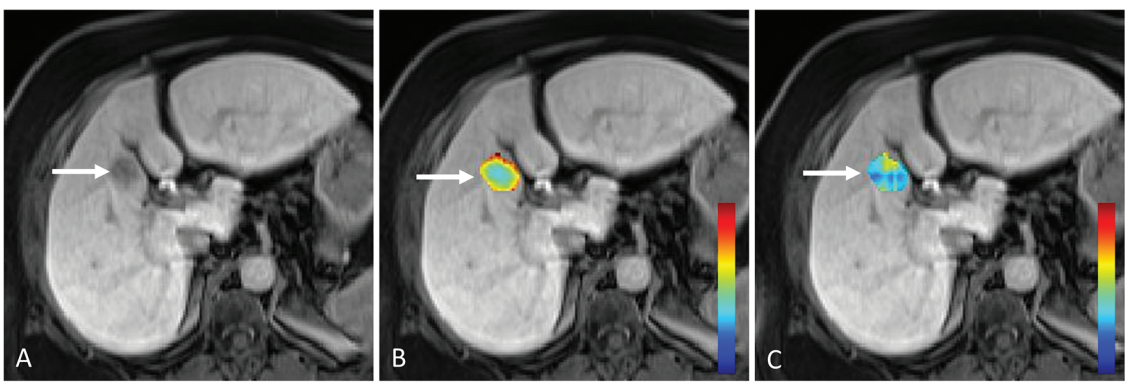

Fig. 5. Hepatobiliary phase image (A) showing a 2 cm hepatocellular carcinoma lesion in the right liver lobe of a 63-year-old female patient with cirrhosis and hepatitis C. Texture maps of Haralick featuring Energy (B, average value 0.005; range 0 – 0.03) and Contrast (C, range 0–70; average value 20.6) are overlaid on the lesion. (Images courtesy of Dr. Bachir Taouli and Dr. Stefanie Hectors, Mount Sinai Medical Center, New York, NY, USA.)

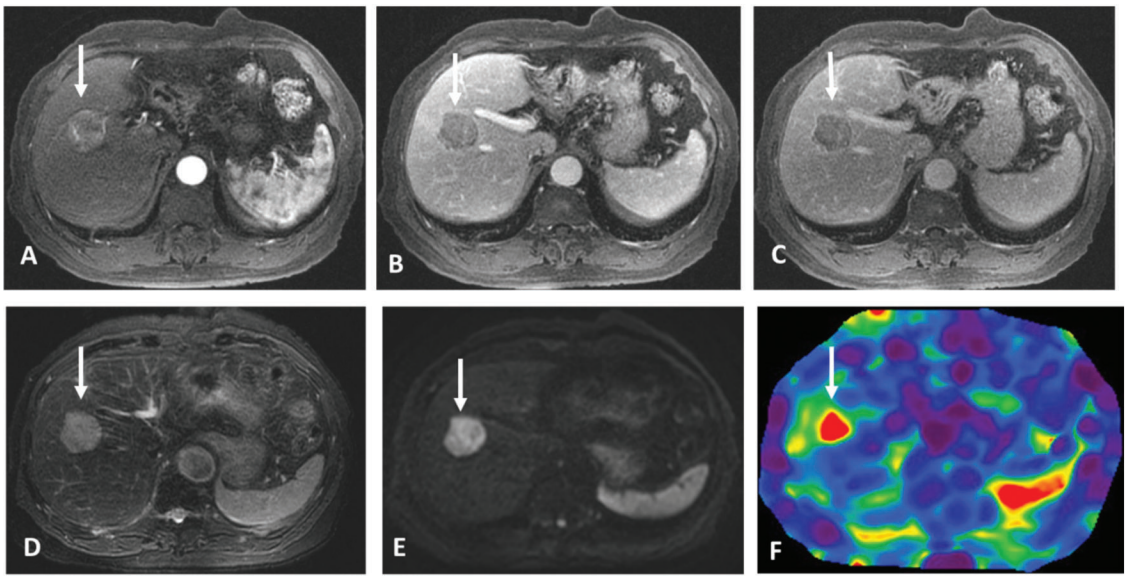

Fig. 6. Axial magnetic resonance imaging of the abdomen of a 63-year-old patient with chronic hepatitis. (A) Demonstrates mosaic arterial phase hyperenhancement with washout and pseudocapsule formation on portal venous phase (B) and delayed phase imaging (C). The mass demonstrates moderate signal intensity on T2-weighted image (D), moderate restricted diffusion (E) and increased stiffness on magnetic resonance elastography (F). The mean stiffness of the hepatocellular carcinoma was 8.2 kPa and the background hepatic stiffness of only 2.9 kPa suggestive of a non-cirrhotic liver parenchyma.

microcirculation but provide poor image quality due to low signal.[114,115] IVIM imaging utilizes a range of b-values to offer information on both molecular diffusion and the microcirculation within the lesion. Parameters which are frequently utilized are the true molecular-diffusion coefficient (D), perfusion related diffusion coefficient (D*) and the perfusion fraction (f) (Fig. 7).

There is limited data available on the use of IVIM in HCC. Apparent diffusion coefficient values are lower in malignant lesions compared to benign lesions.[116] D and D* values, however, were found to be more reliable with increased accuracy in diagnosing and grading malignant liver lesions compared to apparent diffusion coefficient values.[117] In a small study, IVIM was successful in differentiating HCC from focal nodular hyperplasia.[118] Additionally, the utility of IVIM in assessing response to therapy has also been assessed *in vitro*, yielding positive results.[119]

T1 mapping

T1 mapping is a method utilized to assess T1 relaxation time within tissue. It has been employed in cardiac MRI with or without IV contrast to asses for fibrotic changes within the myocardium, presence of myocardial infarction, presence of a cardiomyopathy or myocarditis, and presence of amyloid or excessive iron deposition.[120]

Functioning hepatocytes take up hepatocyte-specific contrast agents. This allows assessment of hepatic vascularity, as with extracellular contrast media, but also allows assessment of specific hepatocellular properties. Measuring T1 relaxation time within tumors before and also after the administration of gadoxetic acid therefore allows quantitative evaluation of properties and uptake within these tumors.[121] With this combined use of T1 mapping and Gd-EOB-DTPA, it may be possible to differentiate normal liver, fatty liver only and non-alcoholic steatohepatitis,[122] and assess for the presence of fibrosis[123] or focal lesions, such as hemangiomas from hepatic metastases.[124] There is also evidence that it may allow adequate grading of HCC (Fig. 8).[125]

Radiogenomics

Human disease is now assessed on a genomic level. With the completion of the Human Genome Project, molecular biomarkers have been utilized to guide individualized treatment of the patient's particular pathology. Early research into this area has demonstrated potential, but these are often based on isolated case reports.[126] As radiology plays an integral part in disease diagnosis and management, attempts have been made to correlate imaging features to the genetic data associated with a condition. Radiogenomics is a term coined to describe the process of correlating the imaging phenotype to the disease genotype and associated characteristics.

The field of Radiogenomics is only beginning to flourish. In the assessment of HCC, the expression of 74% of the 6,732 genes associated with HCC could be predicted based on 28 imaging features.[127] This was achieved by assessing for the presence of 138 separate imaging traits in 28 HCCs. For instance, a channel of radio-dense signal during arterial phase CT was taken to represent internal arteries. By creating and "association map" between this imaging feature and gene expression, certain relationships were uncovered. Using this method, 91 genes were shown to be associated with the presence of microscopic venous invasion. The presence of these genes could be predicted based on the presence of internal arteries and absence of hypodense halos.[127] In a separate study, doxorubicin resistance could be predicted based on the presence of 61 genes. Following analysis of imaging features, the presence of a poorly defined tumor margin was associated with this genetic signature and, ergo, doxorubicin resistance.[128]

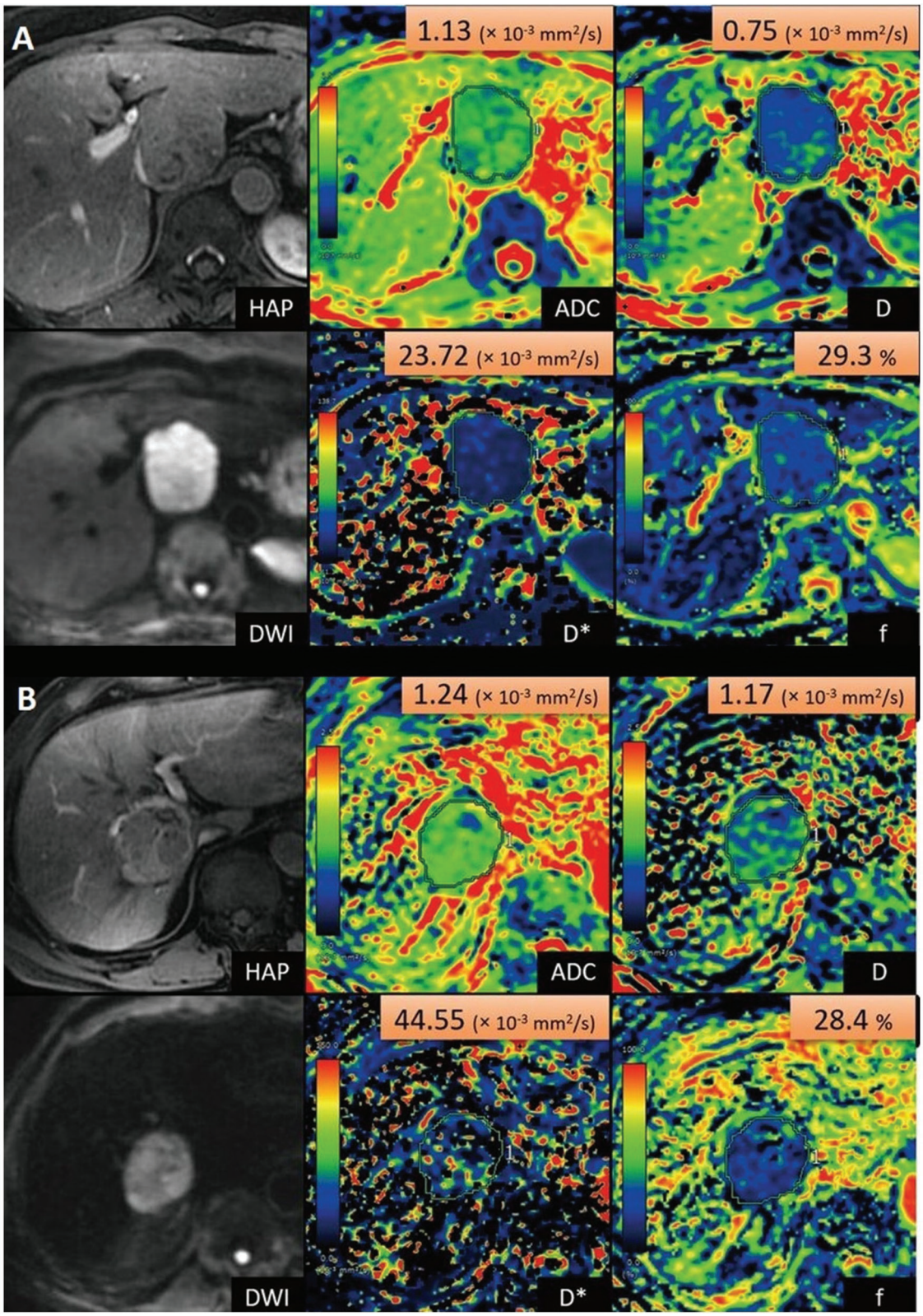

Fig. 7. Intravoxel incoherent motion imaging of hepatocellular carcinoma. Hepatic arterial phase (HAP), diffusion weighted imaging (DWI), apparent diffusion coefficient map (ADC), true molecular-diffusion coefficient map (D), perfusion related diffusion coefficient map (D*) and the perfusion fraction map (f) in a high grade (A, top panel) and a low-grade hepatocellular carcinoma (B, bottom panel). Both hepatocellular carcinomas show hyperenhancement and restricted diffusion with lower ADC in high grade hepatocellular carcinoma. Cut-off values of 1.14×10^{-3} mm^2/sec for ADC and 1.07×10^{-3} mm^2/sec for D have been postulated to differentiate high (A) from low grade lesions (B). (Images courtesy of Dr. Utaroh Motosugi and Dr. Shintaro Ichikawa, Yamanashi University, Japan.)

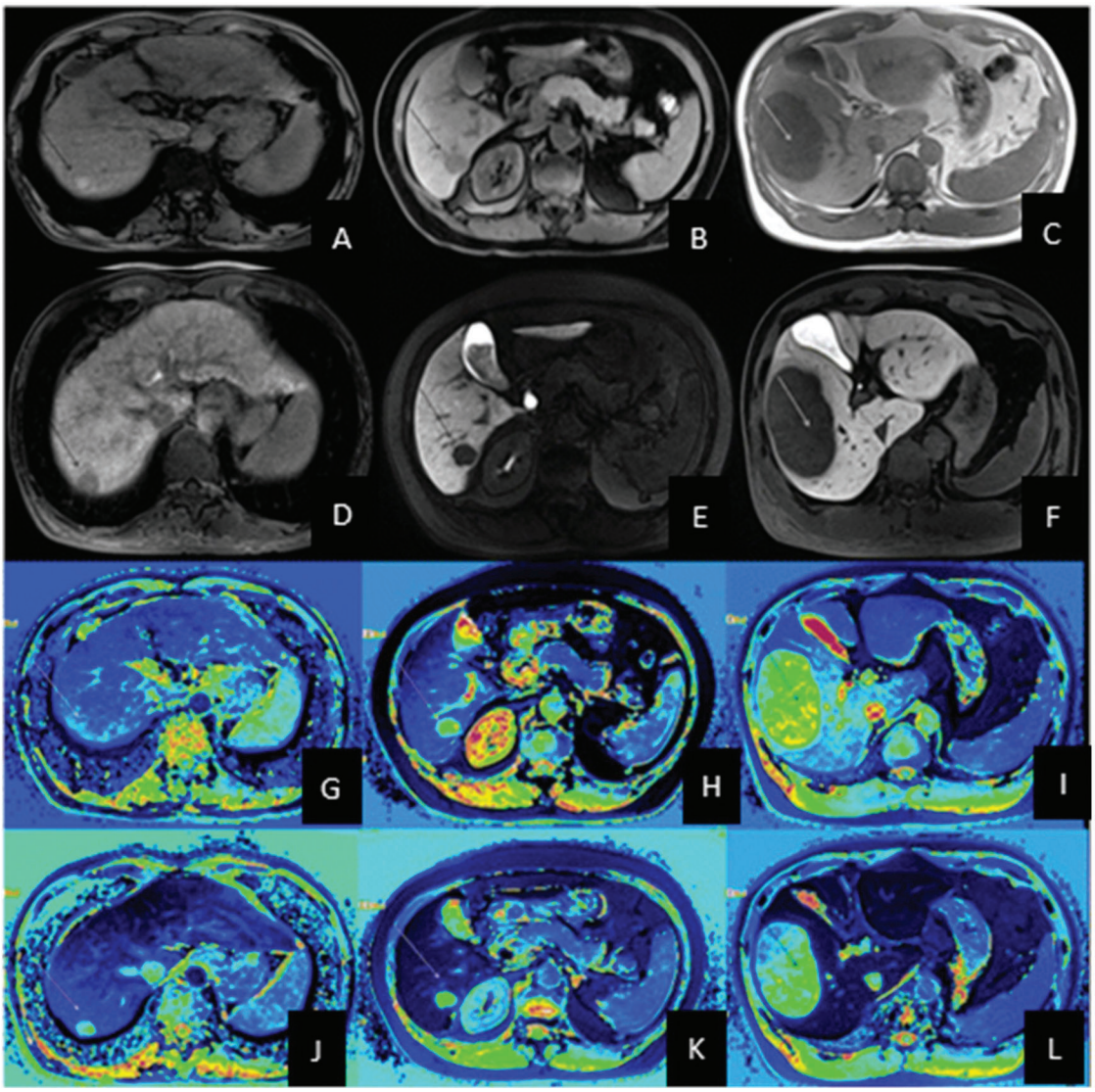

Fig. 8. Magnetic resonance imaging of the abdomen of separate patients with low grade (column 1), intermediate grade (column 2) and high grade (column 3) hepatocellular carcinoma. Top row (A to C) showing T1-weighted images, second row (D to F) showing hepatobiliary phase images, third row (G to I) showing T1 mapping of T1-weighted images, and bottom row (J to L) illustrating the T1 mapping of hepatobiliary phase images. Column 1: T1p 892 ms, T1e 388 ms, T1d = 504 ms, T1d % = 56.50 %; Column 2: T1p 1696 ms, T1e 1444 ms, T1d = 252 ms, T1d % = 14.90 %; Column 3: T1p 2134 ms, T1e 1494 ms, T1d = 640 ms, T1d % = 30.00 %. In general, T1d and T1d% decrease with increasing tumor grade. T1p (pre-contrast), T1e (enhanced), T1d (difference) between T1p and T1e and T1d% percentage difference between T1p and T1e. (Images modified and reproduced with permission from Peng *et al.*, 2016 (reference.126).)

Positron emission tomography (PET)

PET CT with fluorodeoxyglucose (FDG) has limited use in HCC despite its popularity in the assessment of other malignancies. Although increased uptake of FDG has been shown to correlate with increased tumor grade, there is no current role within any diagnostic algorithm due to the low sensitivity of FDG PET in assessing tumors. However, FDG PET is useful for detection of metastatic HCCs elsewhere (Supplementary Fig. 4). The metastatic lesions take up FDG well, suggesting a more aggressive phenotype of HCC.

Flurodeoxygalactose is considered as a possible alternative to FDG. As the name suggests, it utilizes galactose metabolism instead of glucose metabolism as a tracer for intrahepatic and extrahepatic HCC. In a retrospective study, sensitivity of flurodeoxygalactose PET/CT was comparable to multiphase CT, with high specificity.[129]

Conclusions

HCC is a malignancy associated with a high mortality. Early identification with a robust screening program is essential and must adapt into a wider management algorithm. Professional study groups have advocated guidelines to aid clinicians and radiologists in the management of HCC. LIRADS attempts to standardize the lexicon associated with HCC and to create an imaging algorithm to improve the homogeneity of data acquisition and image reporting.

In contrast, radiogenomics and other advances in imaging are designed to appreciate the heterogeneity of HCC with

imaging and promote treatment individualized towards each tumor-specific signature. Advances such as T1 mapping, textural analysis and perfusion imaging have the potential to allow greater accuracy in diagnosis and staging, combined with potential direction on personalized treatment.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Contributed to literature review and manuscript preparation (PN), manuscript revision and preparation (SKV).

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