International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Review Article

THE ROLE OF IMAGING IN DIAGNOSIS OF HEPATOCELLULAR CARCINOMA (HCC)

Dr. Deepika Dhakal[1*], Prof. Huang Jing Bai, Dr. Sunil Shrestha, Dr. Abhinandan Gupta, Dr. Sanjay Kumar Verma and Dr. Shashi Kumar Yadav

Clinical School Of Medicine,Yangtze University, Jingzhou, Hubei Province, P.R China

Department of Medical Imaging and Nuclear Medicine, The First Affiliated Peoples Hospital of Yangtze University, Jingzhou, Hubei, PR. China

ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and its incidence is expected to rise rapidly over the next decade due to the, association with chronic liver disease, particularly HBV and HCV. Imaging is important for establishing a diagnosis of hepatocellular carcinoma (HCC) and an understanding of the stepwise progression of hepatocarcinogenesis may aid in early diagnosis. Dynamic and multiphase contrast-enhanced computed tomography and magnetic resonance imaging still form the cornerstone in the diagnosis of HCC. In this article, we strive to review the imaging techniques and the characteristic features of hepatocellular carcinoma associated with cirrhotic liver, with emphasis on the diagnostic value of advanced magnetic resonance imaging (MRI) techniques.

Keywords: Ultrasonography, tomography, X-Ray computed, magnetic resonance imaging, cirrhosis, diagnostic imaging, contrast media

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. It ranks sixth in cancer incidence and third in cancer mortality worldwide[1]. It is the most prevalent liver cancer with up to three-quarter of cases in the world occurring in Asia due to the high prevalence of chronic viral hepatitis B[2].The common risk factors for hepatocellular carcinoma (HCC) are hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and alcoholic liver disease. Less common causes include nonalcoholic fatty liver, hereditary hemochromatosis, autoimmune hepatitis, alpha-1 antitrypsin deficiency and Wilson disease, some porphyria and schistosomiasis[3]. Due to the growing population of obesity and other metabolic syndromes, there is an increasing incidence of HCC due to non-alcoholic fatty infiltration liver disease; the incidence of HCC continues to grow in spite of the hepatitis B and C viruses' infection being prevented by the development of vaccines and anti-viral therapies[4, 5]. The fact that the classic imaging features could yield a definite diagnosis and the probability of needle track seeding are limiting the necessity of liver biopsy [6]. Therefore, HCC is the unique malignancy to be diagnosed by diagnostic imaging, exempting the necessity of a needle biopsy[7].

Patients diagnosed with HCC generally have a poor prognosis due to the aggressive nature of the disease[8]. Early diagnosis of HCC is imperative as several potentially curative treatments are available, especially when the lesion is small. Regular surveillance of patients is instituted for early detection of HCC in patients with chronic liver disease and particularly in those with advanced liver fibrosis.

Since imaging plays a decisive role in the diagnosis of HCC, it is critical that imaging examination might be performed according to generalized protocols (including the types of equipment, scanning parameters, administration of contrast agents and timing of acquisition) and the imaging findings might be interpreted and reported following a standardized terminology and categorization.

Imaging modalities of HCC:

Ultrasounography (US):

US is a non-invasive examination and has no ionic radiation on the human body. It remains inexpensive as well, which is recommended as the first choice for the screening and surveillance of HCC by the guidelines of almost all international societies [9]. Patients who have risk factors for developing HCC should undergo US surveillance every 3 to 6 months[10]. However, the sensitivity varies from 58% to 70% and is even poor for small HCC less than 1 cm [9-11]. Classic findings of HCC include hypoechoic nodules or mixed echogenic nodules due to tumor necrosis or fatty metamorphosis or a surrounding thin hypoechoic band indicating a capsule which is characteristic for HCC. Colored doppler flow imaging may show hypervascularity and tumor vascular shunting[12]. Contrast enhanced ultrasound (CEUS) with microbubble agents could reflect the real time dynamics of blood supply of the lesion, which is helpful in both detection and characterization of HCCs [13, 14].

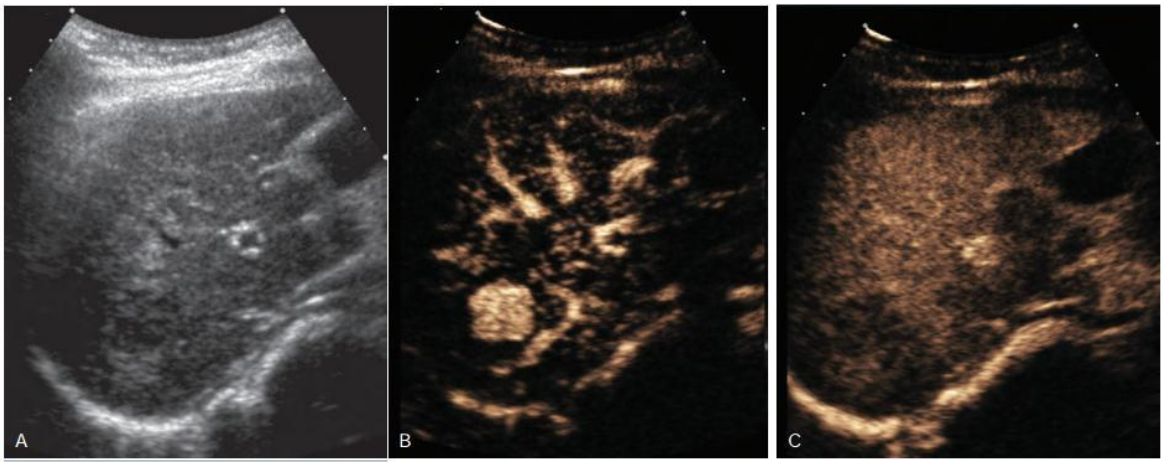

Figure 7: Classic hepatocellular carcinoma (HCC) detected on surveillance ultrasound.

A, Small hypoechoic mass in the right lobe of a small cirrhotic liver.**B**, Contrast-enhanced ultrasound (CEUS) image at the peak of arterial phase enhancement shows classic hypervascularity. **C**, CEUS image in the portal venous phase at 2 minutes. The lesion has washed out relative to the more enhanced liver.*(From Wilson SR, Burns PN.Microbubble enhanced ultrasound imaging: what role? Radiology 2010 [in press].)*

Multi-phasic enhanced computed tomography:

Multi-phasic enhanced computed tomography (CT) is the most common choice for the diagnosis of HCC. In the past decade, technical advances in CT scanners have yielded considerably faster acquisition time and a dramatically dropped radiation dose. There are technical requirements on the equipment and scanning parameters: at least 8 rows multi detector CT for fast acquisition, scanning with thin collimation not over 5mm, adequate amount of contrast medium used and a bolus injection rate over 3 mL/s [15]. Accurate timing is critical, at least three phases should be acquired after administration of iodinated contrast agents, namely hepatic arterial phase, portal venous phase and delayed phase [16]. Precontrast CT is suggested to provide a baseline to demonstrate the level of enhancement, and it may provide information on existence of fat content, iron, calcification, hemorrhage, and iodized oil after transarterial chemoembolization (TACE) treatment[17]. The arterial phase is a time range with the hepatic artery fully enhanced while hepatic veins are not enhanced yet, it could be divided into early and subsequently late hepatic arterial phase[18]. Late hepatic arterial phase is strongly recommended, because the hyperenhancement in HCC is more predominant in the late than the early arterial phase, and a majority of HCCs may show hyperenhancement only in the late hepatic arterial phase [19, 20]. Portal venous phase is acquired in which the images have the following characteristics: Portal veins and hepatic parenchyma are maximally enhanced, and hepatic veins are enhanced by antegrade flow as well [21]. Delayed phase should be acquired at least 3 minutes after the initial of injection when liver parenchyma is less enhanced than in portal venous phase[22]. The advantage of CT also affords the ability to perform three-dimensional reconstructions that may help with preoperative planning which is superior to MRI. Due to possible complications such as radiation, contrast media leaking, allergic reaction and contrast induced nephropathy, CT is not a choice of repeated surveillance [23].

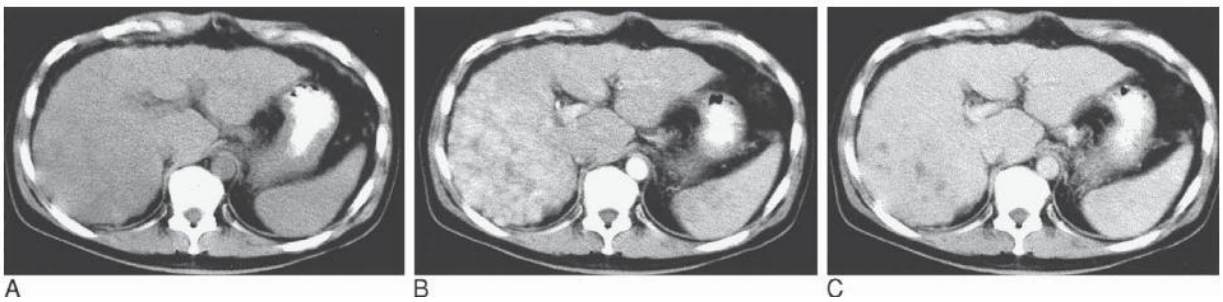

Figure 10: Multi-focal HCC

A biphasic CT (unenhanced (A), arterial phase (B) portal phase (C)) examination demonstrates the multifocal and extensive nature of the tumour, which is only fully apparent during the transient enhancement of the arterial phase.

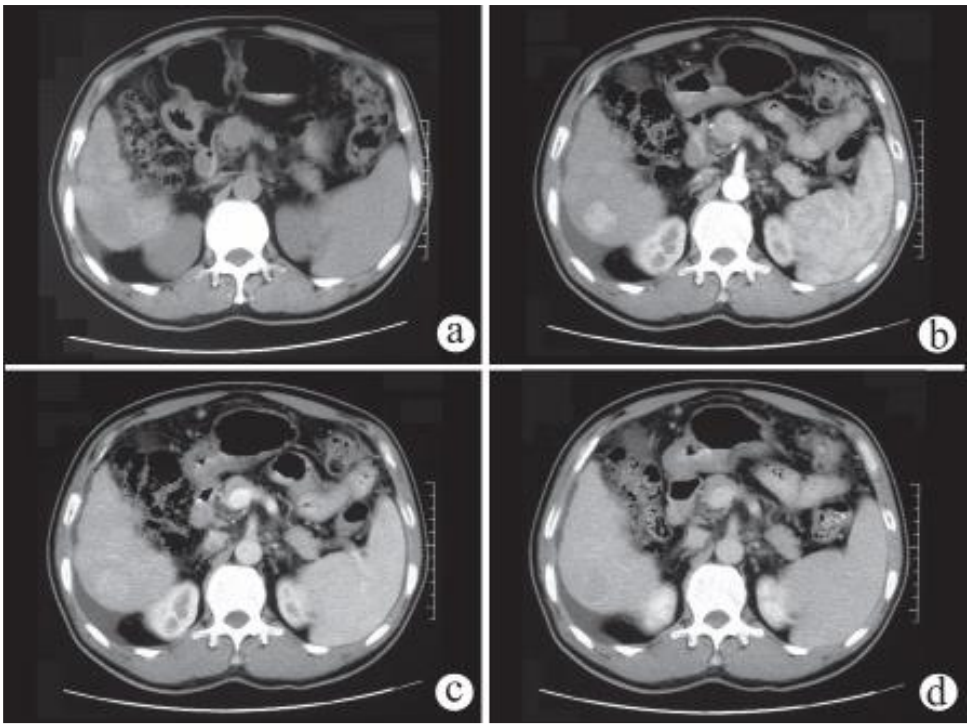

Figure 3: Multiphasic enhanced CT of a HCC associated

with cirrhosis: (a) Precontrast CT showed a hypoattenuationnodule; while the nodular contour, parenchymal heterogeneityin attenuation, ascites and splenomegaly were indicative of cirrhosis. **(b)** In arterial phase, the nodule showed unequivocal hyperenhancement which had much higher enhancement than the adjacent background and precontrast baseline. **(c)** In portal venous phase, the nodule showed less enhancement but still higher than the background liver. **(d)** In delayed phase, the nodule demonstrated unequivocal washout which showed lower attenuation than the adjacent parenchyma.

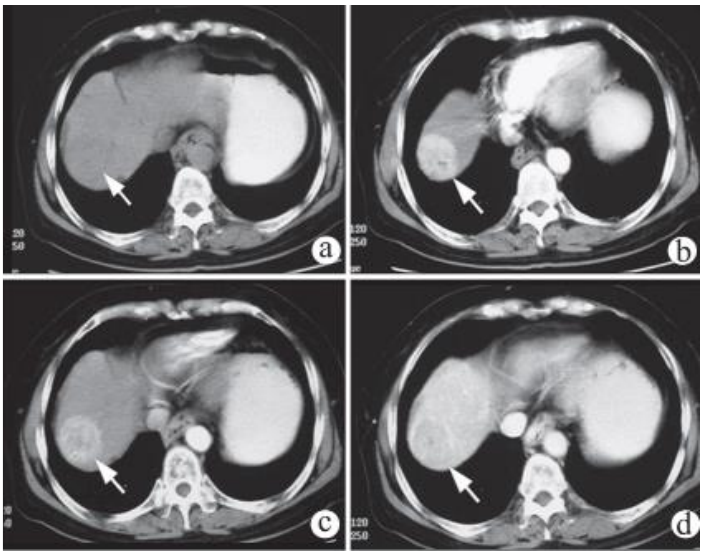

Figure 4: Capsule appearance of HCC (Arrow). (a)

Precontrast CT showed an equivocal hypoattenuation nodule. **(b)** In early arterial phase, the nodule showed remarkable and heterogeneous hyperenhancement. **(c)** In late arterial phase,the nodule showed less enhancement but still higher than the background liver. **(d)** In portal venous phase, the nodule demonstrated unequivocal washout and a hyperattenuationringwas seen along margin of HCC namely capsule appearance.

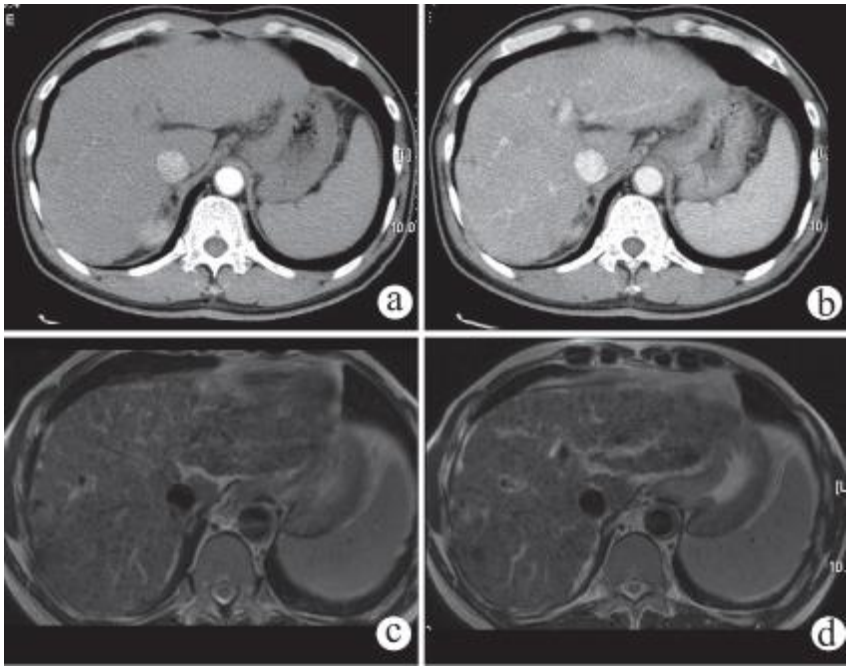

Figure 6: Nodule in nodule appearance in a cirrhotic liver.

A heterogeneous enhanced nodule in arterial phase **(a)** andportal venous phase **(b).** CT could be seen adjacent to the right margin of the liver. **(c**and **d)** On T2WI sequence, the majority of nodules showed iso- and hypo-

intense, there was a smaller nodule with moderately high T2 intense in the center of bigger nodule, histopathological findings had provedit was a small HCC in a high grade dysplastic nodule (HGDN).

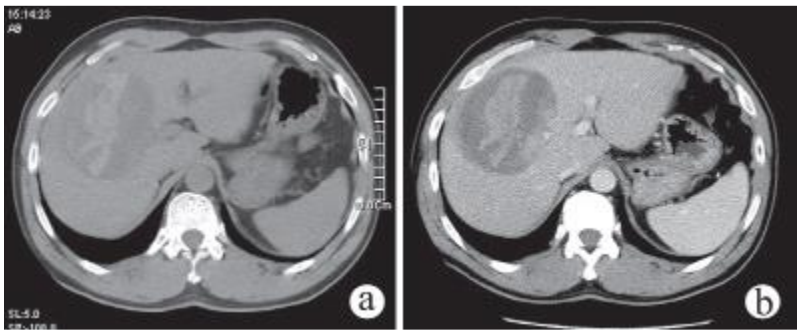

Figure 7: Intratumoral hemorrhage in a poorly **differentiated HCC.** 48-year-old man with sudden abdominal pain and history of hepatitis B virus infection. US revealed a mixedhyperechogenity mass in right lobe. **(a)** Precontrast CT showed a heterogeneous mass with irregular hyperattenuation in the central area. **(b)** Contrast CT demonstrated no enhancement in either hyperattenuation area or the majority of hypoattenueation area which were proved to be blood products in different stages, a small portion of soft tissue with moderate enhancement could be seen in the left margin on portal venous phase, which proved to be poorly differentiated HCC with intratumoral hemorrhage.

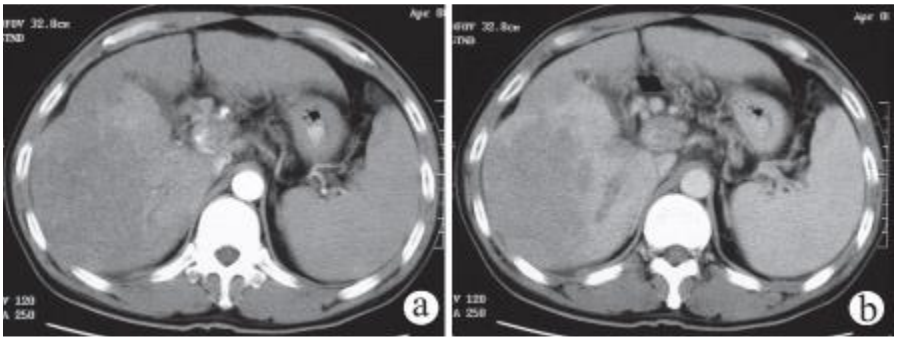

Figure 8: Tumoral thrombus in portal vein from a masslike **HCC. (a)** Hyperenhancement and arterials could be seen in the expanded but occluded portal vein lumen in arterial phase. **(b)** Rapid washout in vein could be seen in portal venous phase, no antegrade blood flow could be found in branches of the portal vein. A definite diagnosis of HCC with portal vein invasion could be made for the irregular mass in right lobe.

Magnetic resonance imaging (MRI):

MRI is superior in both detection and characterization of HCC and is continuing to improve its performance and capability. The sensitivity and the specificity of MRI are reported at 91% and 95% as compared to 81% and 93% with MDCT [24]. The standardized imaging protocol includes T2-weighted sequences to reveal the lesion in high resolution anatomic details, pre-contrast and multi-phasic enhanced 3D T1-weighted gradient echo sequences, and chemical shift in/opposed phase imaging which is sensitive to lipid content [24, 25]. The protocol of contrast examination is similar to contrast CT, and both early and late hepatic

arterial phase might be acquired without fear of ionic radiation [26]. The functional imaging is an added advantage of MRI. Among functional imaging techniques, diffusion weighted imaging (DWI) is the most promising method, it is based on differences of Brownian motion (diffusion) of water molecules within tissues in vivo. For tissues with increased cellularity and destroyed cell integrity such as malignancy, the diffusion of water molecules is restricted, which shows altered signal intensity and parametric changes on DWI [27]. DWI is useful for detecting small HCC and differentiating compared to benign entities, however, it is not as robust and stable in image quality as T1WI and T2WI sequences and the positive predicting value and negative predicting value are controversial (Figure 1) [28, 29]. Currently, DWI is suggested but not required in most of the institutes. The contrast medium commonly used for MRI is non-specific gadolinium-based contrast agents, however, hepatocyte specific contrast agents are promising in both detection and characterization of HCC[30]. Among of several commercially available contrast agents, gadoxetatedimeglumine is a newer agent which enables both dynamic contrast and hepatocyte specific imaging with one administration[31]. Approximately half of the agent is taken up by hepatocytes and excreted into the bile in about 20 min after routine contrast imaging, which is called hepatobiliary phase[31]. Typically, HCCs appear hypointense in hepatobiliary phase because of lack of normal hepatocytes, which is a main feature for differentiating HCC from both regenerative nodules and dysplastic nodules which appear isointense (Figure 2)[32, 33]. However, about 10% of HCCs appear hyperintense compared to background parenchyma in hepatobiliary phase, because of overexpression of organic anion transporter peptide (OATP) proteins that are responsible for the transportation and uptake of the agent [34]. Gadoxetatedimeglumine has proved its value in distinguishing small HCCs. The major limitation of the agent is lack of pure delayed phase, because the early uptake of the agent in delayed phase might superimpose true delayed enhancement, as a consequence, it might obscure the capsule which is diagnostic for HCC, the accumulation of the agent in the delayed phase might likewise mimic a tumor which is characteristic of delayed enhancement such as cholangiocarcinoma[35]. Until now, in North America and European countries, gadoxetatedimeglumine is not widely used as compared to its use in East Asia[36, 37]

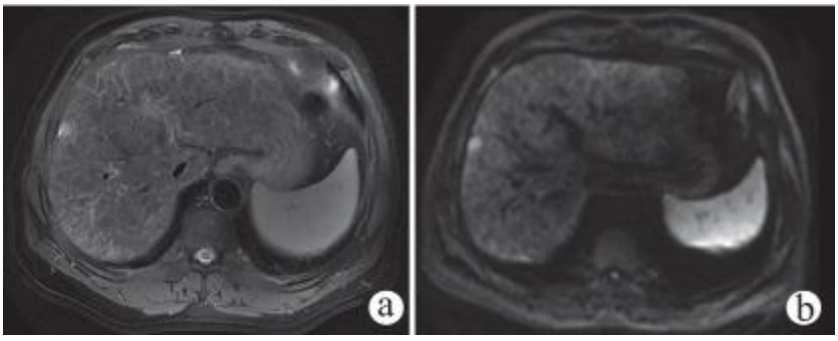

Figure 1: MRI feature of a small HCC associated with liver **cirrhosis. (a)** A moderate hyperintense nodule was revealed on fast suppressed T2WI sequence in the right margin, many smallhypointense nodules could be seen in the background parenchyma suggesting the existence of cirrhosis. **(b)** The small HCC demonstrate remarkably hyperintense on diffusion weighted images, suggesting restriction of water molecule movement in the tumor.

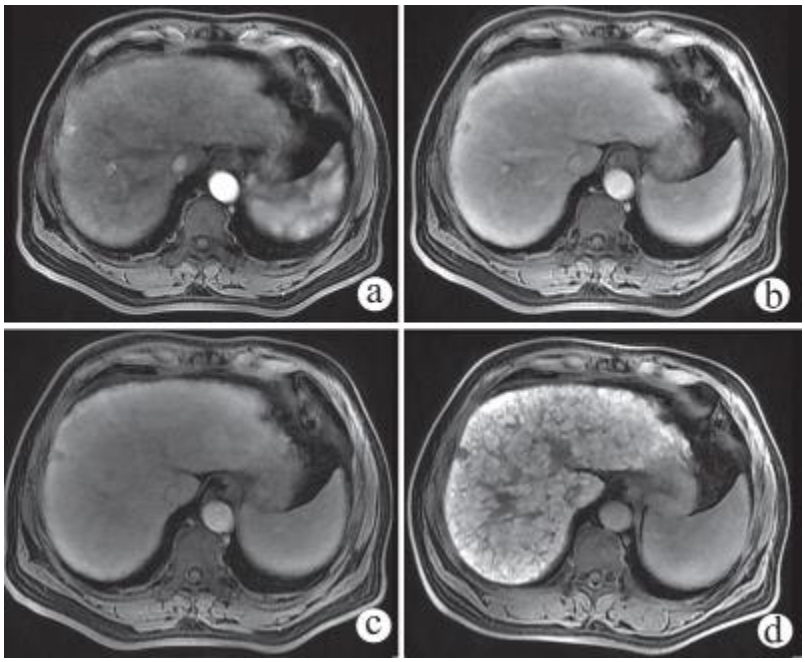

Figure 2: Gadoxetatedimeglumine enhanced T1 weighted MR imaging of a small HCC (the same case as in Figure 1). **(a)** The nodule shows remarkable hyperenhancement in arterial phase. **(b)** Rapid washout was observed in portal venous phase. **(c)** The nodule showed low intensity in delayed phase. **(d)** There was no uptake in the nodule in hepatobiliary phase.

SUMMARY

Thanks to the growing knowledge on biological behaviors of hepatocellular carcinomas (HCC), as well as continuous improvement in imaging techniques and experienced interpretation of imaging features of the nodules in cirrhotic liver, the detection and characterization of HCC has improved in the past decade. A number of practice guidelines for imaging diagnosis have been developed to reduce interpretation variability and standardize management of HCC, and they are constantly updated with advances in imaging techniques and evidence based data from clinical series. In this article, we strive to review the imaging techniques and the characteristic features of hepatocellular carcinoma associated with cirrhotic liver, with emphasis on the diagnostic value of advanced magnetic resonance imaging (MRI) techniques and utilization of hepatocyte-specific MRI contrast agents. We also briefly describe the concept of liver imaging reporting and data systems and discuss the consensus and controversy of major practice guidelines.

Conflict of interest: None

REFERENCES

1. Ferlay, J., et al., *Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008.* Int J Cancer, 2010. **127**(12): p. 2893-917.
2. Omata, M., et al., *Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma.* Hepatol Int, 2010. **4**(2): p. 439-74.

3. Llovet, J.M., A. Burroughs, and J. Bruix, *Hepatocellular carcinoma.* Lancet, 2003. **362**(9399): p. 1907-17.
4. Di Martino, M., et al., *Hepatocellular carcinoma (HCC) in non-cirrhotic liver: clinical, radiological and pathological findings.* European radiology, 2014. **24**(7): p. 1446-1454.
5. Szklaruk, J., P.M. Silverman, and C. Charnsangavej, *Imaging in the diagnosis, staging, treatment, and surveillance of hepatocellular carcinoma.* American Journal of Roentgenology, 2003. **180**(2): p. 441-454.
6. Silva, M.A., et al., *Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis.* Gut, 2008. **57**(11): p. 1592-6.
7. Sherman, M., *The radiological diagnosis of hepatocellular carcinoma*. 2010, Nature Publishing Group.
8. El-Serag, H.B. and K.L. Rudolph, *Hepatocellular carcinoma: epidemiology and molecular carcinogenesis.* Gastroenterology, 2007. **132**(7): p. 2557-76.
9. Maida, M., et al., *Staging systems of hepatocellular carcinoma: a review of literature.* World Journal of Gastroenterology: WJG, 2014. **20**(15): p. 4141.
10. Bruix, J. and M. Sherman, *Management of hepatocellular carcinoma: an update.* Hepatology, 2011. **53**(3): p. 1020-1022.
11. Nam, C.Y., et al., *CT and MRI improve detection of hepatocellular carcinoma, compared with ultrasound alone, in patients with cirrhosis.* Clinical Gastroenterology and Hepatology, 2011. **9**(2): p. 161-167.
12. Lencioni, R., et al., *Small hepatocellular carcinoma: differentiation from adenomatous hyperplasia with color Doppler US and dynamic Gd-DTPA-enhanced MR imaging.* Abdominal imaging, 1996. **21**(1): p. 41-48.
13. Sugimoto, K., et al., *Correlation between parametric imaging using contrast ultrasound and the histological differentiation of hepatocellular carcinoma.* Hepatology Research, 2008. **38**(3): p. 273-280.
14. Liu, G., et al., *Correlation between enhancement pattern of hepatocellular carcinoma on real-time contrast-enhanced ultrasound and tumour cellular differentiation on histopathology.* The British journal of radiology, 2007. **80**(953): p. 321-330.
15. Luca, A., et al., *Multidetector-row computed tomography (MDCT) for the diagnosis of hepatocellular carcinoma in cirrhotic candidates for liver transplantation: prevalence of radiological vascular patterns and histological correlation with liver explants.* European radiology, 2010. **20**(4): p. 898-907.
16. Honda, H., et al., *Vascular changes in hepatocellular carcinoma: correlation of radiologic and pathologic findings.* AJR. American journal of roentgenology, 1999. **173**(5): p. 1213-1217.
17. Doyle, D.J., et al., *Value of the unenhanced phase for detection of hepatocellular carcinomas 3 cm or less when performing multiphase computed tomography in patients with cirrhosis.* Journal of computer assisted tomography, 2007. **31**(1): p. 86-92.
18. Asayama, Y., et al., *Arterial blood supply of hepatocellular carcinoma and histologic grading: radiologic-pathologic correlation.* American Journal of Roentgenology, 2008. **190**(1): p. W28-W34.
19. Marrero, J.A., et al., *Improving the prediction of hepatocellular carcinoma in cirrhotic patients with an arterially-enhancing liver mass.* Liver Transplantation, 2005. **11**(3): p. 281-289.

20. Yoon, S.H., et al., *Multiphasic MDCT enhancement pattern of hepatocellular carcinoma smaller than 3 cm in diameter: tumor size and cellular differentiation.* American Journal of Roentgenology, 2009. **193**(6): p. W482-W489.
21. Furlan, A., et al., *Hepatocellular carcinoma in cirrhotic patients at multidetector CT: hepatic venous phase versus delayed phase for the detection of tumour washout.* The British journal of radiology, 2011. **84**(1001): p. 403-412.
22. Iannaccone, R., et al., *Hepatocellular carcinoma: role of unenhanced and delayed phase multi–detector row helical CT in patients with cirrhosis.* Radiology, 2005. **234**(2): p. 460-467.
23. Barrett, B.J. and P.S. Parfrey, *Preventing nephropathy induced by contrast medium.* New England Journal of Medicine, 2006. **354**(4): p. 379-386.
24. Chou, R., et al., *Imaging techniques for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis.* Annals of internal medicine, 2015. **162**(10): p. 697-711.
25. Willatt, J.M., et al., *MR Imaging of hepatocellular carcinoma in the cirrhotic liver: challenges and controversies.* Radiology, 2008. **247**(2): p. 311-330.
26. Yu, J.S., et al., *Contrast enhancement of small hepatocellular carcinoma: usefulness of three successive early image acquisitions during multiphase dynamic MR imaging.* AJR. American journal of roentgenology, 1999. **173**(3): p. 597-604.
27. Nasu, K., et al., *Diffusion-weighted imaging of surgically resected hepatocellular carcinoma: imaging characteristics and relationship among signal intensity, apparent diffusion coefficient, and histopathologic grade.* American Journal of Roentgenology, 2009. **193**(2): p. 438-444.
28. Nishie, A., et al., *Diagnostic performance of apparent diffusion coefficient for predicting histological grade of hepatocellular carcinoma.* European journal of radiology, 2011. **80**(2): p. e29-e33.
29. Davenport, M.S., et al., *Repeatability of diagnostic features and scoring systems for hepatocellular carcinoma by using MR imaging.* Radiology, 2014. **272**(1): p. 132-142.
30. Park, H.S., et al., *Differentiation of well-differentiated hepatocellular carcinomas from other hepatocellular nodules in cirrhotic liver: Value of SPIO-enhanced MR imaging at 3.0 Tesla.* Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine, 2009. **29**(2): p. 328-335.
31. Kitao, A., et al., *The uptake transporter OATP8 expression decreases during multistep hepatocarcinogenesis: correlation with gadoxetic acid enhanced MR imaging.* European radiology, 2011. **21**(10): p. 2056-2066.
32. Ichikawa, T., et al., *Detection and characterization of focal liver lesions: a Japanese phase III, multicenter comparison between gadoxetic acid disodium-enhanced magnetic resonance imaging and contrast-enhanced computed tomography predominantly in patients with hepatocellular carcinoma and chronic liver disease.* Investigative radiology, 2010. **45**(3): p. 133-141.
33. Park, M.J., et al., *Small hepatocellular carcinomas: improved sensitivity by combining gadoxetic acid–enhanced and diffusion-weighted MR imaging patterns.* Radiology, 2012. **264**(3): p. 761-770.

34. Kim, J.Y., et al., *Hyperintense HCC on hepatobiliary phase images of gadoxetic acid-enhanced MRI: correlation with clinical and pathological features.* European journal of radiology, 2012. **81**(12): p. 3877-3882.
35. Rimola, J., et al., *Cholangiocarcinoma in cirrhosis: absence of contrast washout in delayed phases by magnetic resonance imaging avoids misdiagnosis of hepatocellular carcinoma.* Hepatology, 2009. **50**(3): p. 791-798.
36. Kim, T.K., et al., *Analysis of gadobenate dimeglumine–enhanced MR findings for characterizing small (1–2-cm) hepatic nodules in patients at high risk for hepatocellular carcinoma.* Radiology, 2011. **259**(3): p. 730-738.
37. Granito, A., et al., *Impact of gadoxetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance on the non-invasive diagnosis of small hepatocellular carcinoma: a prospective study.* Alimentary pharmacology & therapeutics, 2013. **37**(3): p. 355-363.