· Review ·

Imaging advances in diagnosing and grading hepatitis B virus-related hepatocellular carcinoma

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Abstract

The development of most hepatocellular carcinomas (HCCs) follows a complex multistep process, progressing from chronic hepatitis to cirrhosis, regenerative nodule, low-grade dysplastic nodule, high-grade dysplastic nodule, small hepatocellular carcinoma, and progressed HCC. Throughout the process, different lesions have different pathological characteristics that are reflected in their unique imaging characteristics. Different imaging methods have their own advantages and disadvantages in the diagnosis and grading of HCC. Contrast-enhanced ultrasonography and gadolinium-enhanced magnetic resonance imaging are the most accurate for diagnosing precancerous lesions and small hepatocellular carcinoma. This article reviews the classification and pathological characteristics of liver nodules during the evolution of HCC, and the imaging diagnosis and grading of HCC.

Keywords: HBV, hepatocellular carcinoma, grading, diagnosis, dysplastic nodules, imaging

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors and one of the most lethal: its 5-year survival is only 18%. The primary cause of HCC in China is HBV infection and related cirrhosis [1]. The development of most HCCs follows a complex multistep process, progressing from chronic hepatitis to cirrhosis, regenerative nodule (RN), low-grade dysplastic nodule (LGDN), high-grade dysplastic nodule (HGDN), small hepatocellular carcinoma (SHCC), and progressed HCC [2-3]. LGDN appears to be the tipping point in liver carcinogenesis [4]. The annual incidence of LGDN conversion to cancer is approximately 10% [5]. HGDN is considered precancerous and 20% of these converts to cancer each year [5]. Therefore, there is a window of opportunity for clinical diagnosis of precancerous lesions and SHCC. Five-year overall survival is higher in patients cured in the precancerous or small liver cancer stages than in patients with large liver cancer [6-7]. However, the onset of HCC is insidious, and most patients are in the middle or late stage when symptoms appear, after the best time to treat has passed. Therefore, finding effective methods to detect precancerous lesions and SHCC earlier are of great significance to reduce HCC-related mortality. Owing to recent advances in imaging technology, imaging has become the main means of diagnosing HCC

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and its precursors. This article reviews the classification and pathological characteristics of liver nodules in the evolution of HCC, as well as the imaging diagnosis and grading of HCC.

Classification and pathological characteristics of liver nodules

During the evolution of HCC, nodular lesions are divided into RNs, dysplastic nodules, and SHCCs based on their pathological characteristics (Table 1) [2,8-9]. RNs are composed of normal proliferating hepatocytes surrounded by fibrous stroma. Because of the difficulty of histological identification, large RNs are usually classified as LGDNs [7]. Dysplastic nodules (DNs) are >1 cm in diameter and contain hepatocytes with atypical hyperplasia (cytoplasmic and nuclear abnormalities) and no evidence of histological malignant change They are divided according to the degree of cellular and structural atypia into LGDN and HGDN. SHCC is divided into early HCC (EHCC) and small and progressed HCC (SPHCC). EHCC refers to HCC with a diameter <2 cm, high degree of tissue differentiation, and no vascular invasion or distant metastasis; SPHCC has the same histological features as typical large HCC. The pathological differences between the different types of nodules provide a foundation for differentiating them using imaging.

Diagnosis and grading of HCC using imaging

The pathological characteristics of the different nodular lesions can be reflected on imaging. Each imaging modality has its own characteristics. In some cases, the application of only a single imaging technique may lead to a missed diagnosis or a misdiagnosis. For patients at high risk of HCC, routine ultrasonography (US) once every 3 to 6 months and enhanced computed tomography (CT) or magnetic resonance imaging (MRI) once every 6 to 12 months can significantly improve the rate of SHCC diagnosis [7,10-11].

Table 1. Pathological characteristics of the various nodular lesions in the evolution of hepatocellular carcinoma.

Lesion Feature	Large RN	LGDN	HGDN	EHCC	SPHCC
Cell Atypia	None	Predominantly large cells	Predominantly small cells	Predominantly small cells	Predominantly small cells
Cell Density	Normal	≤ 1.3 times surrounding liver	1.3 - 2 times surrounding liver	Focally ≥ 2 times surrounding liver	Diffusely ≥ 2 times surrounding liver
Nucleocytoplasmic Ratio	Normal	Normal or slightly elevated	Elevated	Markedly elevated	Significantly elevated
Hepatic Plate Thickness	1 - 2 layers	1 - 2 layers	2 - 3 layers	Focally ≥ 3 layers	Mostly ≥ 3 layers
Hepatocellular Steatosis	Absent or rare	Absent or rare	Rare	Common	Rare
Portal Triad	Normal	Normal	Reduced	Markedly reduced/absent	Absent
Capsule	Absent	Absent	Absent	Absent/incomplete	Complete fibrous capsule
Lesion Boundary	Indistinct	Indistinct	Indistinct	Indistinct	Distinct
Non-paired Artery	Absent	Absent/rare	Rare	Common	Dense
Trabecular or Pseudoacinar Structure	Absent	Absent	Rare	Rare	Common
Stromal Infiltration	Absent	Absent	Absent	Rare	Common
Sinusoidal Capillarization	Absent	Rare	Common	Common	Common
Kupffer Cells	Normal	Mostly normal	Reduced	Markedly reduced	Markedly reduced/absent

Notes: Large RN, large regenerative nodule; LGDN, low-grade dysplastic nodule; HGDN, high-grade dysplastic nodule; EHCC, early hepatocellular carcinoma; SPHCC, small and progressed hepatocellular carcinoma.

Ultrasound

Ultrasound (US) is portable, economical, safe, and non-invasive and provides real-time imaging. It is a conventional method for clinical monitoring and follow-up of liver lesions. It can detect intrahepatic space occupying lesions with high sensitivity and accurately distinguish cystic lesions from solid. However, in the context of liver cirrhosis, US cannot accurately distinguish cirrhosis nodules, DN, and HCC. The sensitivity and specificity of US for detecting early liver cancer are only 65% and 97%, respectively. In addition, US imaging quality is easily affected by operator skill and experience and patient obesity [12].

Contrast-enhanced ultrasound (CEUS) is a conventional monitoring method for patients with nodular cirrhosis [13]. Because the metabolites of the contrast agent are excreted through the lung, CEUS can be used in patients with renal failure or iodine/gadolinium allergy. CEUS can continuously observe the entire arterial phase in real time, whereas contrast-enhanced CT or MRI can only acquire partial arterial phase information owing to the scanning time interval. On CEUS, LGDN mainly exhibits a “slow in and out” enhancement pattern, and most stages show equal enhancement; the appearance of HGDN is variable, including continuous low enhancement, early arterial low enhancement, and subsequent enhancement. HCC mainly shows high enhancement on CEUS in the arterial phase by “fast in and fast out” However, some HGDNs may also exhibit “fast in and fast out” enhancement, which is related to the increased blood supply to the hepatic artery, suggesting that cancer may have already developed [14]. CEUS has a high detection rate for SHCCs with a diameter of 1 to 2 cm. The 2024 National Health Commission Guidelines for the Diagnosis and Treatment of Primary Liver Cancer [10] suggests that CEUS is suitable for the detection and postoperative monitoring of multiple small lesions in the liver; it can also be used for preoperative tumor ablation evaluation and postablation follow-up.

CT

CT can be performed rapidly and has high spatial resolution; however, its soft tissue resolution and sensitivity are low. Although plain and contrast-enhanced CT are commonly used in the clinical diagnosis of HCC, their application in the diagnosis of DNs is limited. In one study of contrast-enhanced CT in the background of liver cirrhosis [15], the sensitivity of identifying LGDN, HGDN, EHCC, and SPCHCC was 20%–30%, 65%–71%, approximately 50%, and >90%, respectively. In a similar study of contrast-enhanced CT in SHCC in the background of liver cirrhosis [16], the overall detection rate was 81.25%; for lesions with a diameter ≤1 cm, the rate was 77.42%. On plain CT, most DNs are homogeneous and exhibit a density that is slightly lower or equal to that of the surrounding tissue, on contrast-enhanced CT, LGDNs and HGDNs show minimal enhancement in the arterial phase, no obvious enhancement in the portal venous phase, and mild enhancement in the delayed phase, which is similar to that in the liver parenchyma. As their abnormal arterial blood supply increases, some HGDNs will show significant enhancement in the arterial phase and low density in the portal venous phase, which is similar to the appearance of HCC [17]. Some EHCCs and SPHCCs have a capsule—these lesions typically show ring enhancement on enhanced CT, which can assist in making a diagnosis of HCC.

MRI

MRI does not use ionizing radiation to acquire images and provides high resolution images from multiple directions. Moreover, MRI parameters can be varied

as needed based on clinical requirements. For liver lesions ≥2 cm, the diagnostic accuracy of MRI is equivalent to that of CT. For HCC <2 cm, the performance of MRI is better than that of CT, which is the most sensitive imaging method for detecting DNs [15,18]. Common MRI techniques include T1- and T2-weighted imaging, diffusion-weighted imaging (DWI), and susceptibility weighted imaging. On non-contrasted MRI, the combination of high signal intensity on T1-weighted imaging and low intensity on T2-weighted imaging strongly suggests DN [19]. Arterial phase enhancement and rapid elution are key features of HGDN and HCC in dynamic imaging [20]. On DWI, HCC nodules can be distinguished from DN by excessive proliferation of tumor cells, narrowing of tissue space, limited diffusion of water molecules, and low apparent diffusion coefficient (ADC) value. DWI can improve the detection rate and diagnostic accuracy of SHCCs ≤2 cm, particularly detection of hypovascular ones that do not show typical characteristics on dynamic enhanced MRI [21]. In the context of cirrhosis, the sensitivity, specificity, and accuracy of differentiating SHCC from DN using high intensity DWI signal were 94.6%, 68.2%, and 84.7%, respectively; the corresponding values for ADC ratio were 73.0%, 72.7%, and 72.9%, respectively [22]. The diagnostic efficiency of DWI texture analysis (area under the receiver operating characteristic curve [AUC], 0.94) is significantly higher than that of both high DWI signal intensity (AUC, 0.81) and ADC ratio (AUC, 0.72). High DWI signal intensity combined with high T2 signal intensity is the most specific feature to distinguish DN from atypical HCC [23].

The use of contrast significantly improves the sensitivity of MRI for early detection of liver nodules. The reported sensitivity and specificity of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (GD-EOBD-TPA)-enhanced MRI for liver cirrhosis nodules ≤2 cm is 96.0% and 96.6%, respectively. It also has high sensitivity (94.7%) and specificity (99.3%) for HGDN, and can accurately identify SHCC and HGDN [24]. The uptake of GD-EOBD-TPA by hepatocytes is mediated by organic anion transporter polypeptides 1B1 and 1B3. The expression of these transporters continues to decline during the occurrence of HCC. Therefore, in GD-EOBD-TPA-enhanced MRI, HCC exhibits high signal intensity in the arterial phase and low intensity in the late phase. Early HCC shows high signal intensity in the arterial phase and low intensity in the portal venous, delayed, and hepatobiliary phases. In contrast, HGDN shows iso- to low signal intensity and late low signal intensity in the arterial phase. LGDN shows isointensity or hyperintensity in both phases [5,25]. For HCC with a diameter ≤1 cm, GD-EOBD-TPA-enhanced MRI is superior to dynamic enhanced CT and CEUS in diagnostic efficiency. For eligible high-risk patients, GD-EOBD-TPA-enhanced MRI should be the first choice for diagnosis [26-27].

Molecular imaging

Molecular imaging can provide non-invasive visualization and quantitative description of genes, molecules, cells, and even tissues and organs in the body [28]. Its unique fusion image cannot only provide information regarding tumor stage, treatment response, and disease recurrence, but also information regarding tumor biology and molecular behavior. Such data assists with determining prognosis and evaluating results of treatment. However, molecular imaging is not recommended initially in patients with HCC, unless conventional imaging results are ambiguous [29]. Recent in-depth studies of the HCC tumor microenvironment have revealed new molecular targets which are being explored to prepare probes for molecular imaging [28,30]. Increasing evidence is showing that molecular imaging will play an increasingly important role in liver tumor imaging [31].

At present, positron emission tomography (PET)/CT and single photon emission CT/CT are the most widely used molecular imaging techniques for HCC detection. However, the sensitivity of using 18F-fluorodeoxyglucose PET alone to detect HCC is relatively low (between 50% and 65%). A study evaluating the ability of 18F fluorocholine and 18F-fluorodeoxyglucose PET in detecting and staging HCC in patients with chronic liver disease and suspected liver nodules [32] showed that 18F fluorocholine was significantly more sensitive (94% vs. 59%), especially in well differentiated tumors. Based on the high resolution of MRI, PET/MRI can be applied to the diagnosis of micromalignant liver nodules. A PET/MRI study of an alpha-fetoprotein/phosphatidylinositol glycan 3 double antibody-labeled probe showed that the probe not only improved the detection rate of HCC, it also improved the detection effect of heterogeneous micromalignant HCC [33]. The dual specificity T1-positive contrast-enhanced MRI probe for HCC also showed higher specificity and sensitivity in the diagnosis of early HCC, and was independent of tumor size and/or heterogeneity [34]. At present, the application of PET/MRI in HCC is mainly in the experimental stage. Its role needs to be further examined in large scale studies.

Artificial intelligence

To better stratify HCC patients before surgery, make more accurate treatment decisions, and improve patient outcomes, a non-invasive imaging method that can accurately predict histopathological characteristics and genes expressed is needed. Artificial intelligence has played an important role in personalized precision medicine.

Imageomics

Imageomics is a continuously developing technology that integrates imaging, computer science, mathematics, statistics and other disciplines. Imageomics can transform histopathological and physiological information in imaging into high-dimensional quantitative image features that can be mined. Furthermore, it can noninvasively and qualitatively/quantitatively analyze the spatial heterogeneity of tumors, reduce the subjectivity of human judgment, and contribute to the early diagnosis and treatment of HCC, and improve patient survival.

Most imaging studies of EHCC and its precancerous lesions have focused on the differentiation of HCC and non-HCC. Omics models based on CEUS, CT, or MRI can accurately distinguish HCC from other benign and malignant space occupying lesions [35-36]. One study constructed a multivariate regression model based on CEUS characteristics to identify RN, DN, and small HCC in the context of liver cirrhosis [37]. The model exhibited high sensitivity and can be used to actively monitor the progression of liver cirrhosis. A support vector machine (SVM) model based on CT images achieved good diagnostic efficiency in identifying HCC in patients with liver cirrhosis harboring indeterminate liver nodules [38]. Another model created to differentiate SHCC from DN based on contrast-enhanced CT also achieved good diagnostic efficiency [39]. Other researchers used SVM to establish an omics model based on non-contrast-enhanced MRI to diagnose liver nodules with diameter ≤2 cm; the specificity, accuracy, and sensitivity were 85.2%, 88.5%, and 100%, respectively, and the diagnostic efficiency of the model was significantly higher than that of radiologists [40]. An imaging omics model based on MRI classified liver nodules as hepatitis, cirrhosis, dysplasia. or and HCC with an accuracy rate of 81% [41]. This model in combination with the Liver Imaging Reporting & Data System (LIRADS) was able to identify SHCC and DNs in the context of liver cirrhosis with a sensitivity of 97.3%

and a specificity of 97.7% [42]. The DWI-SYM model, which compares the signal characteristics of MRI enhancement and DWI images, combined with imaging omics analysis improved the ability to detect DNs and had high specificity [43]. A model based on the whole domain histogram parameters of incoherent motion DWI in voxels to identify benign and malignant liver lesions also achieved high diagnostic performance [44]. Imageomics clearly has great application prospects in the early diagnosis of HCC.

Imaging genomics

Imaging genomics is a new technology that establishes a correlation between gene expression profile data and imaging features. Its ultimate goal is to develop specific imaging biomarkers [45]. Dynamic CT imaging features of liver cancer are closely related to the entire spectrum of HCC genes [46]. A combination of 28 imaging features can reconstruct 78% of the HCC gene expression spectrum, revealing cell proliferation, liver synthesis function, and patient prognosis. Ninety-one gene expression profiles related to microvascular invasion (MVI) in liver cancer have been isolated [47]. In addition, radiomics characteristics related to MVI gene expression profile have been isolated and used to establish a model for predicting MVI [48]. In terms of early diagnosis of HCC, a study of the relationship between LIRADS classification and characteristics and the fractional allele imbalance rate index showed that LIRADS category was positively correlated with the index: tumors with a high index were larger than those with a low index [49].

Deep learning

Applications of deep learning (DL) in the field of medical imaging include intelligent diagnosis, curative effect evaluation, and prediction of patient outcome. In HCC-related research, a convolutional neural network (CNN) model has been used to successfully predict the occurrence of HCC in patients with viral hepatitis, with an accuracy of 98.0% [50]. Multiphase contrast-enhanced MRI data has also been used to establish a CNN model to differentiate HCC and non-HCC lesions with an overall accuracy of 87.3% [51]. A CNN DL algorithm using the CT images from non-contrast-enhanced, arterial, and delayed phases to identify liver nodules had a diagnostic accuracy of 84.0%; the AUC value for distinguishing HCC and DN was 0.92 [52]. A SWWIN transformer DL model based on three-phase CT data distinguished HCC from non-HCC with an AUC of 0.887 [53]. At present, DL is mostly used in scientific research. Although its application in clinical practice has just begun, the future holds promise.

Outlook and summary

At present, the focus and challenge of HCC diagnosis and treatment have shifted to improving the detection of early HCC and precancerous lesions. However, the existing imaging technology still has some limitations in the context of liver cirrhosis. Existing imaging technologies must be used rationally, and we must continue to explore new ones. Furthermore, interdisciplinary cooperation is needed to establish low-cost imaging methods that are simple to use while providing reliable results.

In conclusion, different imaging methods have their own advantages and disadvantages in the diagnosis and grading of HCC. The introduction of artificial intelligence makes it possible to objectively analyze the characteristics of high-dimensional quantitative imaging and its relationship with clinical and genetic data, improve the rates of early tumor detection and cure, and ultimately improve survival in HCC patients.

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Jiachen Liu and Hongjun Li wrote the manuscript.

Conflicts of Interests

The author declares no conflict of interest.

References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024 (74):229-263.

[2] International Consensus Group for Hepatocellular Neoplasia. Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. Hepatology. 2009 (49):658-664.

[3] Chen QR. The pathological features of small and early hepatocellular carcinoma. Zhonghua Bing Li Xue Za Zhi. 2020 (49):1353-1357. In Chinese.

[4] Lu L, Jiang Z, Dai Y, Chen L. Low-grade dysplastic nodules revealed as the tipping point during multistep hepatocarcinogenesis by dynamic network biomarkers. Genes (Basel). 2017 (8):268.

[5] Liao Z, Tang C, Luo R, Gu X, Zhou J, Gao J. Current concepts of precancerous lesions of hepatocellular carcinoma: recent progress in diagnosis. Diagnostics (Basel). 2023 (13):1211.

[6] Nevola R, Ruocco R, Criscuolo L, Villani A, Alfano M, Beccia D, et al. Predictors of early and late hepatocellular carcinoma recurrence. World J Gastroenterol. 2023 (29):1243-1260.

[7] Expert Consensus Panel on Precancerous Lesions of Hepatocellular Carcinoma, Editorial Board of Chinese Journal of Hepatology. Expert consensus on the diagnosis and treatment of precancerous lesions of hepatocellular carcinoma (2023 edition). Chinese Journal of Hepatology. 2023 (31):1250-1261. In Chinese.

[8] Mao SY, Xie CM. Pathological basis and MRI diagnosis and differentiation of cirrhotic nodules and early liver cancer. Radiological Practice, 2019 (12):1285-1288. In Chinese.

[9] Evidence-based practice guidelines for standardized pathological diagnosis of primary liver cancer in China: 2015. Zhonghua Gan Zang Bing Za Zhi. 2015 (23):321-327. In Chinese.

[10] Department of Medical Administration, National Health Commission of the People's Republic of China. Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2024 edition). Chinese Journal of Hepatology. 2024 (32):581-630. In Chinese.

[11] Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clin Mol Hepatol. 2022 (28):583-705.

[12] Chartampilas E, Rafailidis V, Georgopoulou V, Kalarakis G, Hatzidakis A, Prassopoulos P. Current Imaging Diagnosis of Hepatocellular Carcinoma. Cancers (Basel). 2022 (14):3997.

[13] Chartampilas E, Rafailidis V, Georgopoulou V,

Kalarakis G, Hatzidakis A, Prassopoulos P, et al. Guidelines and good clinical practice recommendations for contrast-enhanced ultrasound (CEUS) in the liver—update 2020 WFUMB in cooperation with EFSUMB, AFSUMB, AIUM, and FLAUS. Ultrasound Med Biol. 2020 (46):2579-2604.

[14] Ren J, Lu Q, Fei X, Dong Y, D Onofrio M, Sidhu PS, et al. Assessment of arterial-phase hyperenhancement and late-phase washout of hepatocellular carcinoma—a meta-analysis of contrast-enhanced ultrasound (CEUS) with SonoVue® and Sonazoid®. Eur Radiol. 2024 (34):3795-3812.

[15] Kim BR, Lee JM, Lee DH, Yoon JH, Hur BY, Suh KS, et al. Diagnostic performance of Gadoxetic acid-enhanced liver MR imaging versus multidetector CT in the detection of dysplastic nodules and early hepatocellular carcinoma. Radiology. 2017 (285):134-146.

[16] Xia ZY, Yan LF, Liang CH. Comparison of diagnostic value of enhanced CT and MRI multi-phase enhancement scanning for small liver cancer. Journal of Integrated Traditional Chinese and Western Medicine on Liver Diseases. 2024 (34):624-626. In Chinese.

[17] Wang XY, Wang Z. Advances in imaging of dysplastic nodules of the liver. Imaging Research and Medical Application. 2020 (4):2-4. In Chinese.

[18] Inchingolo R, Faletti R, Grazioli L, Tricarico E, Gatti M, Pecorelli A, et al. MR with Gd-EOB-DTPA in assessment of liver nodules in cirrhotic patients. World J Hepatol. 2018 (10):462-473.

[19] Gao F, Cai P, Liu C, Xia F, Wang J. Research progress on imaging features of precancerous nodules of hepatocellular carcinoma. Chinese Journal of Hepatology. 2020 (28):9-13. In Chinese.

[20] Zhong X, Tang H, Lu B, You J, Piao J, Yang P, et al. Differentiation of small hepatocellular carcinoma from dysplastic nodules in cirrhotic liver: texture analysis based on MRI improved performance in comparison over gadoxetic acid-enhanced MR and diffusion-weighted imaging. Front Oncol. 2020 (9):1382.

[21] Liu M, Li H, Zhang Y, Zhang Q, Wang S. Research progress on magnetic resonance imaging of small hepatocellular carcinoma in the context of cirrhosis. Beijing Medical Journal. 2017 (39):950-952. In Chinese.

[22] Zhong X, Li JS, Chen ZJ, Yin JX, Gui S, Sun ZQ, et al. MR diffusion-weighted imaging texture analysis for differentiating small hepatocellular carcinoma with atypical enhancement from hyperplastic nodules in cirrhosis. Chinese Journal of Hepatology. 2020 (28):37-42. In Chinese.

[23] Shin SK, Kim YS, Choi SJ, Shim YS, Jung DH, Kwon OS, et al. Characterization of small (≤3 cm) hepatic lesions with atypical enhancement feature and hypointensity in hepatobiliary phase of gadoxetic acid-enhanced MRI in cirrhosis. Medicine (Baltimore). 2017 (96):e7278.

[24] Renzulli M, Biselli M, Brocchi S, Granito A, Vasuri F, Tovoli F, et al. New hallmark of hepatocellular carcinoma, early hepatocellular carcinoma and high-grade dysplastic nodules on Gd-EOB-DTPA MRI in patients with cirrhosis: a new diagnostic algorithm. Gut. 2018 (67):1674-1682.

[25] Bartolozzi C, Battaglia V, Bargellini I, Bozzi E, Campani D, Pollina LE, et al. Contrast-enhanced magnetic resonance imaging of 102 nodules in cirrhosis: correlation with histological findings on explanted livers. Abdom Imaging. 2013 (38):290-296.

[26] Department of Medical Administration, National Health Commission of the People's Republic of China. Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2024 edition). Chinese Journal of Hepatology. 2024 (32):581-630. In Chinese.

[27] Hasegawa K, Takemura N, Yamashita T, Wata-

dani T, Kaibori M, Kubo S, et al. Clinical practice guidelines for hepatocellular carcinoma: the Japan Society of Hepatology 2021 version (5th JSH-HCC Guidelines). Hepatol Res. 2023 (53):383-390.

[28] Zhao D, Cao J, Zhang L, Zhang S, Wu S. Targeted molecular imaging probes based on magnetic resonance imaging for hepatocellular carcinoma diagnosis and treatment. Biosensors (Basel). 2022 (12):342.

[29] Llovet JM, De Baere T, Kulik L, Haber PK, Greten TF, Meyer T, et al. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2021 (18):293-313.

[30] Zong J, Fan Z, Zhang Y. Serum tumor markers for early diagnosis of primary hepatocellular carcinoma. Hepatocell Carcinoma. 2020 (7):413-422.

[31] Tong AK, Tham WY, Too CW, Tai DW, Chow PK, Ng DC. Molecular imaging and therapy of liver tumors. Semin Nucl Med. 2020 (50):419-433.

[32] Wang T, Zhang KH. New blood biomarkers for the diagnosis of AFP-negative hepatocellular carcinoma. Front Oncol. 2020 (10):1316.

[33] Ma XH, Wang S, Liu SY, Chen K, Wu ZY, Li DF, et al. Development and in vitro study of a bi-specific magnetic resonance imaging molecular probe for hepatocellular carcinoma. World J Gastroenterol. 2019 (25):3030-3043.

[34] Ma XH, Wang S, Liu SY, Chen K, Wu ZY, Li DF, et al. Bi-specific T1 positive-contrast-enhanced magnetic resonance imaging molecular probe for hepatocellular carcinoma in an orthotopic mouse model. World J Gastrointest Oncol. 2022 (14):858-871.

[35] Masokano IB, Liu W, Xie S, Marcellin DFH, Pei Y, Li W. The application of texture quantification in hepatocellular carcinoma using CT and MRI: a review of perspectives and challenges. Cancer Imaging. 2020 (20):67.

[36] Zhao X, Liang P, Yong L, Jia Y, Gao J. Radiomics study for differentiating focal hepatic lesions based on unenhanced CT images. Front Oncol. 2022 (12):650797.

[37] Duan Y, Xie X, Li Q, Mercaldo N, Samir AE, Kuang M, et al. Differentiation of regenerative nodule, dysplastic nodule, and small hepatocellular carcinoma in cirrhotic patients: a contrast-enhanced ultrasound-based multivariable model analysis. Eur Radiol. 2020 (30):4741-4751.

[38] Mokrane FZ, Lu L, Vavasseur A, Otal P, Peron JM, Luk L, et al. Radiomics machine-learning signature for diagnosis of hepatocellular carcinoma in cirrhotic patients with indeterminate liver nodules. Eur Radiol. 2020 (30):558-570.

[39] Xing YH, Huang ZJ, Hou YH. Application of radiomics based on enhanced CT in differentiating small hepatocellular carcinoma from atypical dysplastic nodules. Chinese Journal of CT and MRI. 2023 (21):107-109. In Chinese.

[40] Gao X, Bian J, Luo J, Guo K, Xiang Y, Liu H, et al. Radiomics-based distinction of small (≤2 cm) hepatocellular carcinoma and precancerous lesions based on unenhanced MRI. Clin Radiol. 2024 (79):e659-e664.

[41] Li D, Huo L, Wan MY, Jia NY, Wang JL. Application of radiomics based on a novel support vector machine in the classification of liver nodules. Journal of Chinese Electronic Microscopy Society. 2022 (39):278-290. In Chinese.

[42] Zhong X, Guan T, Tang D, Li J, Lu B, Cui S, et al. Differentiation of small (≤3 cm) hepatocellular carcinomas from benign nodules in cirrhotic liver: the added value of MRI-based radiomics analysis to LI-RADS version 2018 algorithm. BMC Gastroenterol. 2021 (21):155.

[43] Li YQ, Zhang J, Jia NY. Differentiation of small hepatocellular carcinoma from dysplastic nod-

ules using a radiomics model based on diffusion-weighted imaging. Journal of Practical Radiology. 2024 (40):60-63, 91. In Chinese.

[44] Ai Z, Han Q, Huang Z, Wu J, Xiang Z. The value of multiparametric histogram features based on intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI) for the differential diagnosis of liver lesions. Ann Transl Med. 2020 (8):1128.

[45] Pinker K, Shitano F, Sala E, Do RK, Young RJ, Wibmer AG, et al. Background, current role, and potential applications of radiogenomics. Magn Reson Imaging. 2018 (47):604-620.

[46] Segal E, Sirlin CB, Ooi C, Adler AS, Gollub J, Chen X, et al. Decoding global gene expression programs in liver cancer by noninvasive imaging. Nat Biotechnol. 2007 (25):675-680.

[47] Chen X, Cheung ST, So S, Fan ST, Barry C, Higgins J, et al. Gene expression patterns in human liver cancers. Mol Biol Cell. 2002 (13):1929-1939.

[48] Banerjee S, Wang DS, Kim HJ, Sirlin CB, Chan MG, Korn RL, et al. A computed tomography radiogenomic biomarker predicts microvascular invasion and clinical outcomes in hepatocellular carcinoma. Hepatology. 2015 (62):792-800.

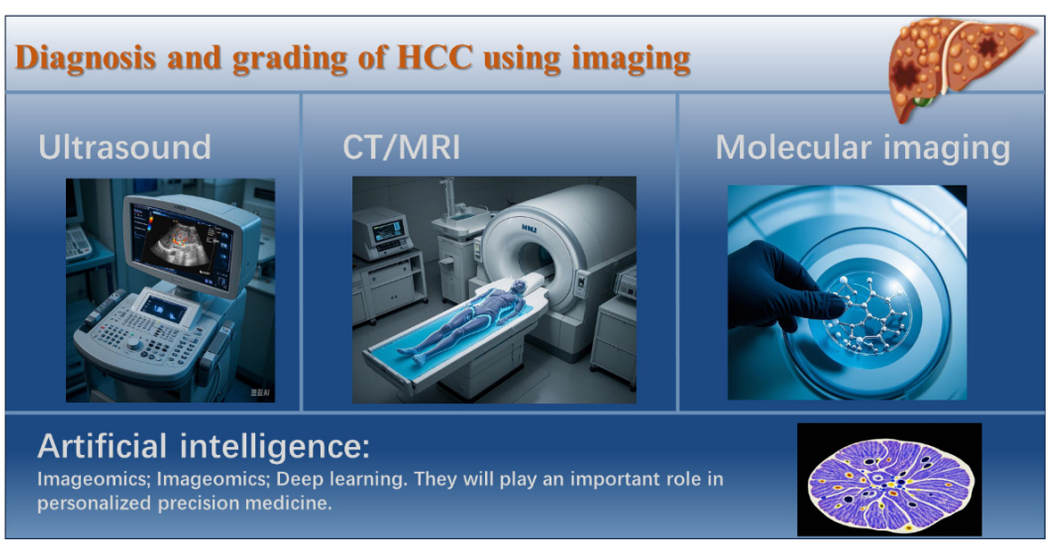
[49] Furlan A, Almusa O, Yu RK, Sagreiya H, Borhani AA, Bae KT, et al. A radiogenomic analysis of hepatocellular carcinoma: association between fractional allelic imbalance rate index and the liver imaging reporting and data system (LI-RADS) categories and features. Br J Radiol. 2018 (91):20170962.

[50] Phan DV, Chan CL, Li AA, Chien TY, Nguyen VC. Liver cancer prediction in a viral hepatitis cohort: A deep learning approach. Int J Cancer. 2020 (47): 2871-2878.

[51] Oestmann PM, Wang CJ, Savic LJ, Hamm CA, Stark S, Schobert I, et al. Deep learning-assisted differentiation of pathologically proven atypical and typical hepatocellular carcinoma (HCC) versus non-HCC on contrast-enhanced MRI of the liver. Eur Radiol. 2021 (31): 4981-4990.

[52] Yasaka K, Akai H, Abe O, Kiryu S. Deep learning with convolutional neural network for differentiation of liver masses at dynamic contrast-enhanced CT: A preliminary study. Radiology. 2018 (286):887-896.

[53] Xu Y, Zhou C, He X, Song R, Liu Y, Zhang H, et al. Deep learning-assisted LI-RADS grading and distinguishing hepatocellular carcinoma (HCC) from non-HCC based on multiphase CT: a two-center study. Eur Radiol. 2023 (33):8879-8888.



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