Review Article
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Radiologic features of hepatocellular carcinoma related to prognosis

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The cross-sectional imaging findings play a crucial role in the diagnosis of hepatocellular carcinoma (HCC). Recent studies have shown that imaging findings of HCC are not only relevant for the diagnosis of HCC, but also for identifying genetic and pathologic characteristics and determining prognosis. Imaging findings such as rim arterial phase hyperenhancement, arterial phase peritumoral hyperenhancement, hepatobiliary phase peritumoral hypointensity, non-smooth tumor margin, low apparent diffusion coefficient, and the LR-M category of the Liver Imaging-Reporting and Data System have been reported to be associated with poor prognosis. In contrast, imaging findings such as enhancing capsule appearance, hepatobiliary phase hyperintensity, and fat in mass have been reported to be associated with a favorable prognosis. Most of these imaging findings were examined in retrospective, single-center studies that were not adequately validated. However, the imaging findings can be applied for deciding the treatment strategy for HCC, if their significance can be confirmed by a large multicenter study. In this literature, we would like to review imaging findings related to the prognosis of HCC as well as their associated clinicopathological characteristics. **(J Liver Cancer 2023;23:143-156)**

Keywords: Carcinoma, hepatocellular; Magnetic resonance imaging; Multidetector computed tomography; Prognosis

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, frequently occurring in patients with chronic liver disease or cirrhosis. HCC is characterized as a heterogeneous tumor considering its genetic and pathologic features and prognosis. The well-known prognostic factors of HCC include serum markers such as serum levels of α-fetoprotein (AFP) and protein induced by vitamin K absence or antagonists-II (PIVKA-II), pathologic features such as differentiation, microvascular invasion, satellitosis, subtype, immunohistochemical expression of keratin 19 (K19), and genetic features such as fibroblast growth factor 19 amplification and proliferative class.[1] Imaging findings representing the extent of tumor, including tumor size, number, gross vascular invasion, and extrahepatic metastasis, have also been recognized as prognostic factors and incorporated into current staging systems.[2-4]

Cross-sectional imaging findings play a crucial role in the diagnosis of HCC. Liver magnetic resonance imaging (MRI) protocols commonly consist of T2-weighted images, dual

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Table 1. Imaging findings of hepatocellular carcinoma and related histopathologic/molecular characteristics and prognosis

Imaging finding	Imaging sequence	Histopathologic finding	Immunohistochemistry and molecular finding	Clinical outcome
Fat in mass	In-phase and out-of-phase images of dual gradient-echo sequence	Common in early HCC <1.5 cm In case of steatohepatitic HCC, can be found at an advanced stage Less frequent MVI		Less early recurrence Longer progression-free survival Fewer distant metastasis
Rim APHE	Dynamic enhancement-arterial phase	Large necrotic area Abundant fibrous stroma Lower microvascular density Sinusoid-like microvascular pattern or VETC pattern Common in macrotrabecular-massive subtype Frequent MVI	Frequent expression of hypoxia-related marker (CAIX) and progenitor markers (K19 or EpCAM), *TP53* mutation	Rapid tumor growth Frequent early recurrence Poor overall survival Frequent extrahepatic metastasis Non-responder after TACE
Arterial phase peritumoral hyperenhancement	Dynamic enhancement-arterial phase	Frequent MVI		Frequent early recurrence
Enhancing capsule appearance	Dynamic enhancement-portal and delayed/transitional phase	Common in nodular types of HCCs Not common in early HCC showing vaguely nodular margin and advanced HCC showing infiltrative margin		Inconsistent
HBP hyperintensity	Hepatobiliary phase	Mostly observed in moderately differentiated HCC Less frequent MVI	Activation of Wnt/β-catenin pathway and/or hepatocyte nuclear factor 4-α pathway *CTNNB1* mutation Decreased expression of AFP, EpCAM, and glypican 3	Longer recurrence-free survival Longer overall survival
HBP peritumoral hypointensity	Hepatobiliary phase	Frequent MVI		Frequent early recurrence
Non-smooth tumor margin	Hepatobiliary phase	Single nodular with extranodular growth type or confluent multinodular type Frequent MVI Common in macrotrabecular-massive subtype	Frequent expression of progenitor markers (K19, EpCAM)	Frequent early recurrence
Low ADC	Diffusion-weighted image	Poor histologic grade Frequent MVI Common in macrotrabecular-massive subtype	Frequent expression of progenitor markers (K19)	Frequent early recurrence
LR-M category	Multiple sequences	Frequent MVI Poor histological differentiation	Frequent expression of progenitor markers (K19, EpCAM)	Frequent early recurrence Poor overall survival

HCC, hepatocellular carcinoma; MVI, microvascular invasion; APHE, arterial phase hyperenhancement; VETC, vessels that encapsulate tumor cluster; CAIX, carbonic anhydrase IX; K19, keratin 19; EpCAM, epithelial cell adhesion molecule; TACE, transarterial chemoembolization; HBP, hepatobiliary phase; AFP, α-fetoprotein; ADC, apparent diffusion coefficient.

gradient-echo images to assess the presence of fat and iron, fat-suppressed T1-weighted dynamic enhancement images to characterize dynamic enhancement patterns, and diffusion-weighted images to assess the free diffusion of water molecules, which are known to be related to tumor cellularity or necrosis. Hepatobiliary phase images are added when gadoxetic acid (Gd-EOB-DTPA, Bayer HealthCare Pharmaceuticals, Berlin, Germany) is used as the contrast medium. Particularly, imaging findings in dynamic phases employing intravenous contrast agents are most important for HCC imaging diagnosis, since they reveal characteristic vascular changes during multistep hepatocarcinogenesis. In addition, the hepatobiliary phase is another key sequence that shows the difference between HCC and non-tumor livers. The uptake of gadoxetic acid by normal hepatocytes occurs via organic anion transporter polypeptide 8 (OATP8); the period when this uptake is most evident is called the hepatobiliary phase, which corresponds to approximately 15–20 minutes after intravenous injection of gadoxetic acid. Since the expression of OATP8 and the hepatobiliary uptake of gadoxetic acid decline progressively during multistep hepatocarcinogenesis, HCC exhibits a lower hepatobiliary uptake and signal intensity than non-tumor liver.[5]

The contemporary guidelines of HCC recommend imaging-only diagnosis of HCC without pathological confirmation when a hepatic lesion shows typical imaging findings of HCC in individuals at a high risk of HCC.[6-8] Since several HCC cases are diagnosed based on imaging findings, without obtaining tissue, it is difficult to apply genetic and pathologic prognostic factors in such cases. Recent studies have shown that imaging findings of HCC are not only relevant for the diagnosis of HCC, but also for identifying genetic and pathologic characteristics and determining the prognosis (Table 1).[9-12]

Here, we review the imaging features of HCC associated with the prognosis of HCC patients.

FAT IN MASS

Fat in mass is one of the Liver Imaging Reporting and Data System (LI-RADS) ancillary features favoring HCC in particular.[13] The loss of signal intensity on T1-weighted out-of-phase images compared with in-phase images of dual gradient-echo sequences suggests the presence of fat.[14] Because fat is rarely found in pure cholangiocarcinoma, the presence of intralesional fat is useful for the differential diagnosis between hepatocellular lesions and cholangiocarcinoma.[15] The mechanism by which fat develops inside HCC is presumed to be clonal expansion of hepatocytes with anomalous fat metabolism and cellular metabolic disturbances due to switching of the dominant blood supply from portal venous to hepatic arterial and the consequent ischemic/hypoxic con-

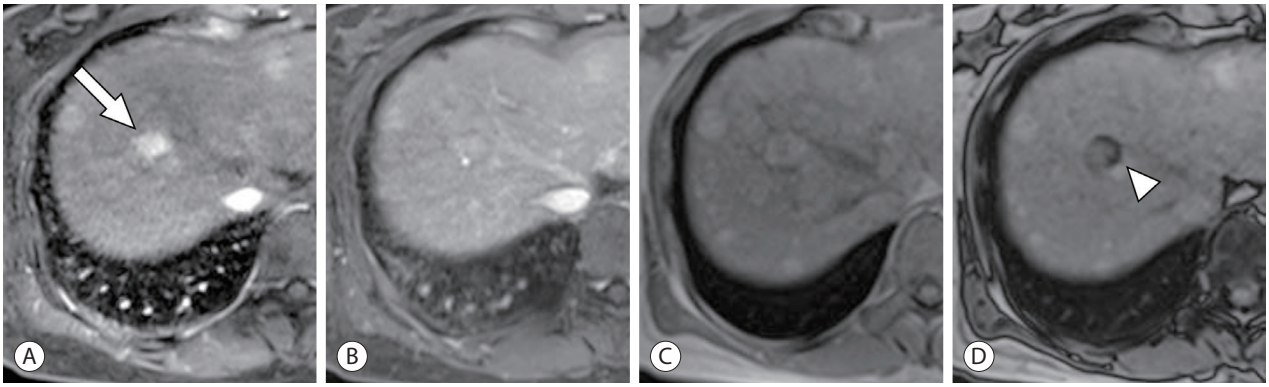

Figure 1. Hepatocellular carcinoma with fatty change in a 60-year-old woman. Approximately 1.8 cm non-rim arterial phase hyperenhancing hepatic nodule (arrow) (A) remains iso to slightly hyperintense in the hepatic parenchyma without washout appearance in the portal venous phase (B). In dual gradient-echo T1-weighted images (C, D), the signal intensity of the tumor decreased in the opposed-phase (arrowhead) (D) compared to the in-phase (C), suggesting the presence of intralesional fat. On pathologic examination, the lesion was Edmondson-Steiner grade I-II, which showed fatty changes in 60% of the tumor area.

ditions.[16,17] It is most often observed in early HCC <1.5 cm in diameter and tends to decrease with increasing tumor size and grade (Fig. 1).[17] However, in steatohepatitic HCC, which is most commonly found in background steatohepatitis or non-alcoholic fatty liver disease, intralesional fat can be observed not only in early HCC but also in advanced tumor grades.[18-20]

It has been reported that radiological or histological fat in mass is associated with infrequent microvascular invasion (MVI), suggesting that fat in mass may be associated with a better prognosis.[18,21,22] Indeed, several studies have reported an association between fat in mass and a favorable prognosis after curative treatment. Siripongsakun et al.[23] reported fewer distant metastases (4.3% vs. 21.7%) and longer time to progression in fat-containing HCCs than in non-fat-containing HCCs in a case-control study of patients who received local treatment or liver transplantation. A study conducted by Chen et al.[24] showed that fat in mass was a favorable prognostic factor for tumor recurrence in patients with LR-5 HCCs who underwent hepatic resection. Another study suggested that fat in mass was a favorable prognostic factor for patients undergoing radiofrequency ablation.[25]

IMAGING FINDINGS OF ARTERIAL PHASE

During multistep hepatocarcinogenesis, HCC becomes hypervascular with the development of unpaired arteries and sinusoidal capillarization.[26] Arterial phase hyperenhancement (APHE) is one of the most important imaging findings in HCC diagnosis. Typically, HCC shows APHE of non-rim pattern; LI-RADS defines it as "non-rim like enhancement in arterial phase unequivocally greater in whole or in part than liver."[13]

1. Rim arterial phase hyperenhancement

Rim-APHE is defined as a "spatially defined subtype of APHE in which arterial phase enhancement is most pronounced in the observation periphery" (Figs. 2-4).[13] Rim-APHE is more commonly seen in intrahepatic cholangiocarcinoma and combined hepatocellular and cholangiocarcinoma, and is uncommon (5.6–15.7%) in HCC.[27-30] It should be distinguished from the "enhancing capsule" and "arterial phase peritumoral enhancement," as described below.

HCCs with rim-APHE have more prominent hypoxic and fibrotic tumor microenvironments. HCC with rim-APHE in gadoxetic acid-enhanced MRI was associated with a larger proportion of necrotic area and fibrous stroma, frequent expression of hypoxia-related markers (carbonic anhydrase IX) and stem/progenitor markers (K19 or epithelial cell adhesion molecule [EpCAM]), and histopathologic macrotrabecular pattern.[11,30] HCC with rim-APHE shows a characteristic vascular phenotype, including lower microvascular density and

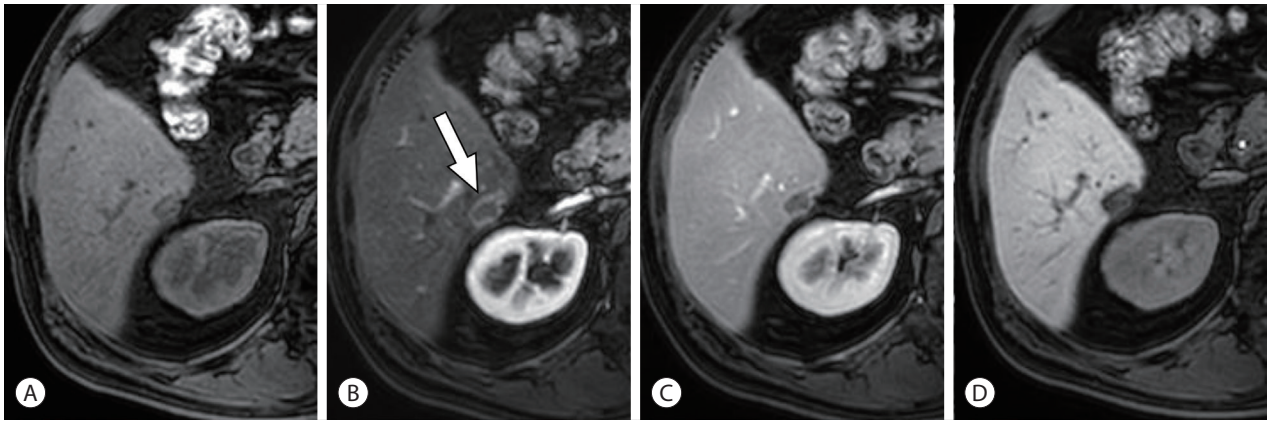

Figure 2. Hepatocellular carcinoma (HCC) with rim arterial phase hyperenhancement and non-smooth tumor margin in a 61-year-old man. In pre-contrast (A), arterial (B), portal venous (C), and hepatobiliary (D) phase images of gadoxetate-enhanced magnetic resonance imaging, a 1.8 cm hepatic nodule shows rim-like peripheral hyperenhancement in the arterial phase (arrow). Note the non-smooth margins of the tumor. On pathological examination, the lesion was a poorly differentiated HCC with microvascular invasion.

a sinusoid-like microvascular pattern.[30] The sinusoid-like microvascular pattern, otherwise known as vessels that encapsulate the tumor cluster (VETC) pattern, is known to be associated with frequent microvascular invasion, metastasis, and poor prognosis.[31,32] HCC with rim-APHE is also associated with peculiar genetic characteristics, including TP53 mutations, cholangiocarcinoma-like, and proliferative gene expression.[9,11,33]

Rim-APHE of HCC is reported to be related to MVI,[34] rapid tumor growth,[35] frequent early recurrence, poor disease-free survival, poor overall survival, and an increased incidence of extrahepatic metastasis after curative resection or radiofrequency ablation.[11,28,29,36] It has also been reported that patients with HCCs showing rim-APHE have a high non-responder rate and low overall survival after chemoembolization.[37]

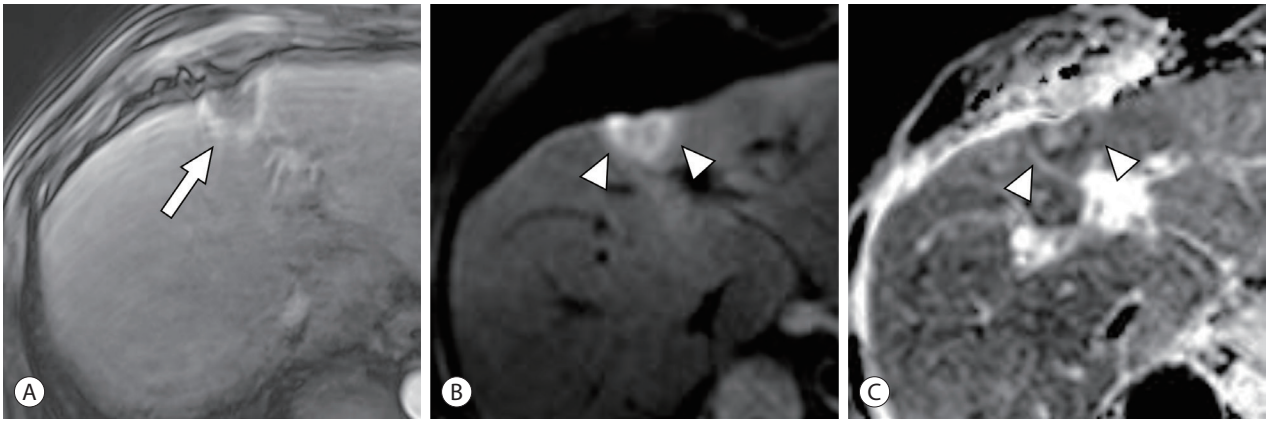

Figure 3. Hepatocellular carcinoma showing low apparent diffusion coefficient and LR-M features in a 68-year-old man. An approximately 3 cm hepatic mass showing irregular rim hyperenhancement (arrow) in the arterial phase (A). The lesion displays high signal intensity on diffusion-weighted imaging (b=800) (B) and low signal intensity in the apparent diffusion coefficient map (C), indicating diffusion restriction. Diffusion restriction is more pronounced in the periphery of the tumor, exhibiting a targetoid pattern (arrowheads in B, C). On pathological examination, the lesion showed positive expression of keratin 19 and microvascular invasion.

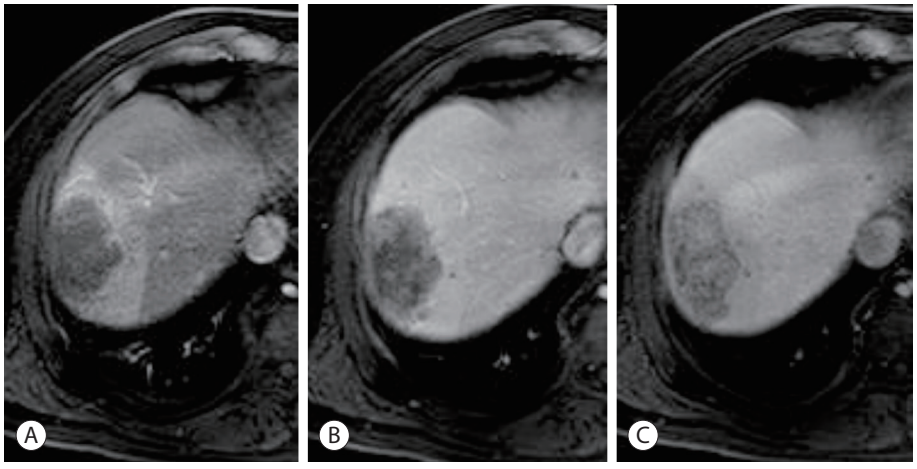

Figure 4. Hepatocellular carcinoma showing LR-M features and non-smooth tumor margin in a 57-year-old man. An approximately 6.5 cm hepatic mass shows rim hyperenhancement in the arterial phase (A), progressive enhancement in the transitional (B), and hepatobiliary phases (C). The mass had a targetoid appearance, as the signal intensities in the arterial and hepatobiliary phases exhibited a concentric layout. Note the arterial phase peritumoral hyperenhancement, hepatobiliary phase peritumoral hypointensity, and non-smooth tumor margins. On pathological examination of the percutaneous biopsy specimen, the lesion was poorly differentiated and positive for keratin 19.

2. Arterial phase peritumoral hyperenhancement

Arterial phase peritumoral hyperenhancement refers to "early arterial phase wedge-shaped or irregular and circumferential enhancement in parenchyma adjacent to the tumor that fades during later phase" (Figs. 4-6).[13,38] It is thought to be compensatory arterial hyperperfusion due to decreased portal venous flow resulting from obstruction of minute portal vein branches around the tumor by microscopic tumor thrombi.[39] A few studies have reported it as a predictor of MVI [27,40-43] and early recurrence after curative resection.[28,44-46]

Arterial phase peritumoral hyperenhancement may resemble corona enhancement and it is therefore vital to differentiate between them.[13,38] Both imaging findings are observed in the peritumoral area during the late arterial phase. The arterial phase peritumoral hyperenhancement is caused by compensatory arterial blood flow; therefore, it appears in the early arterial phase and then fades out.[39] It often has a geographic or wedge-shaped boundary, with a straight border representing the vascular territory, and can be extensive. Corona enhancement is thought to be venous drainage of hypervascular

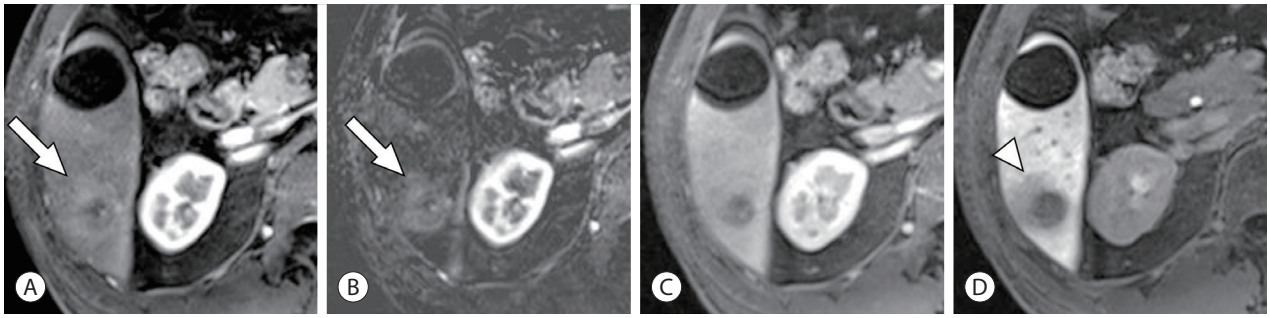

Figure 5. Hepatocellular carcinoma (HCC) with arterial phase peritumoral hyperenhancement and hepatobiliary phase peritumoral hypointensity in a 61-year-old man. In the arterial phase (A) and subtraction image from the pre-contrast scan (B) of gadoxetic acid-enhanced magnetic resonance imaging, arterial phase peritumoral hyperenhancement is seen (arrow) along with intratumoral hyperenhancement. In the portal venous phase (C), peritumoral hyperenhancement faded to nearly isointense to the hepatic parenchyma. In the hepatobiliary phase (D), an irregular area of peritumoral hypointensity (arrowhead) is observed. On pathological examination, the lesion was an Edmondson-Steiner grade III HCC with microvascular invasion.

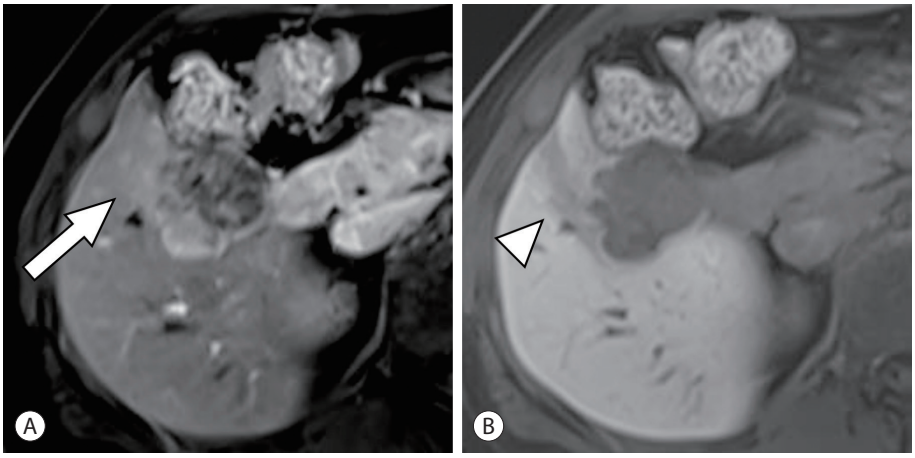

Figure 6. Hepatocellular carcinoma (HCC) with arterial phase peritumoral hyperenhancement, hepatobiliary phase peritumoral hypointensity, and non-smooth tumor margin in a 41-year-old woman. Arterial phase peritumoral hyperenhancement is seen (arrow) along with intratumoral hyperenhancement in the arterial phase (A) of the gadoxetic acid-enhanced magnetic resonance imaging. In the hepatobiliary phase (B), an irregular area of peritumoral hypointensity was observed (arrowhead). The margin of the tumor protrudes into the hepatic parenchyma and shows a non-smooth margin. On pathological examination, the lesion was multinodular confluent, macrotrabecular-massive HCC with microvascular invasion.

HCC; therefore, it is observed in the late arterial and early portal phases, then fades out, looks circumferential or eccentric, and is rarely extensive. Corona enhancement is an imaging finding of progressed HCC rather than early HCC, as it appears in the process of venous drainage change from intralesional hepatic vein to peritumoral sinusoid and portal vein at the later stage of hepatocarcinogenesis.[47] The area of corona enhancement might be the first site of micrometastasis,[39] and corona enhancement has been reported as a predictor of MVI[43] and early recurrence after surgery.[44-46]

However, as arterial peritumoral enhancement and corona enhancement often appear similar and multiple arterial phases with a high temporal resolution are required for accurate differentiation between them, studies have thus far not attempted to assess their prognostic value separately due to technical reasons. With recent advances in MRI technology, the impact of corona enhancement on prognosis may be re-evaluated in the future.

ENHANCING CAPSULE APPEARANCE ON PORTAL, DELAYED, OR TRANSITIONAL PHASES

The pathological fibrotic capsule is considered to be the result of compression of peritumoral fibrous tissue by the tumor and is closely related to the gross morphology of HCC.[48,49] HCCs showing a vaguely nodular type, mostly early HCCs, do not show a fibrotic capsule because of lepidic growth. Fibrotic capsules are mainly observed in nodular HCCs, including HCCs of the single nodular type, single nodular with extranodular growth type, and multinodular confluent type. The fibrotic capsule temporarily serves as a physical barrier to block tumor infiltration; however, capsular and extracapsular tumor infiltration emerge as HCC progresses, and eventually the capsule is seldom observed in the infiltrative type of HCC.[48,50] Collectively, the pathological fibrous capsule is not commonly observed; in early HCC it shows vaguely nodular margins and in advanced HCC it shows infiltrative margins.

"Enhancing capsule" is one of the major imaging features for diagnosis of HCC in LI-RADS. It refers to the observation of a smooth, uniform, sharp border around most or all of an observation in the portal venous phase, delayed phase, or transitional phase (Fig. 7).[13] The fibrous capsule is strongly associated with enhancing capsule appearance although this is not always the case. Approximately 14–17% of the enhancing capsules are not pathologically fibrous capsules, but pseudo-capsules consisting of prominent sinusoids and peritumoral fibrosis mimicking bridging fibrosis.[51,52]

Some studies have indicated that the presence of an enhancing capsule on imaging may be a good prognostic factor in patients undergoing hepatic resection or transarterial chemoembolization.[53-55] However, other studies have shown that the enhanced capsule is not significant for prognosis or relat-

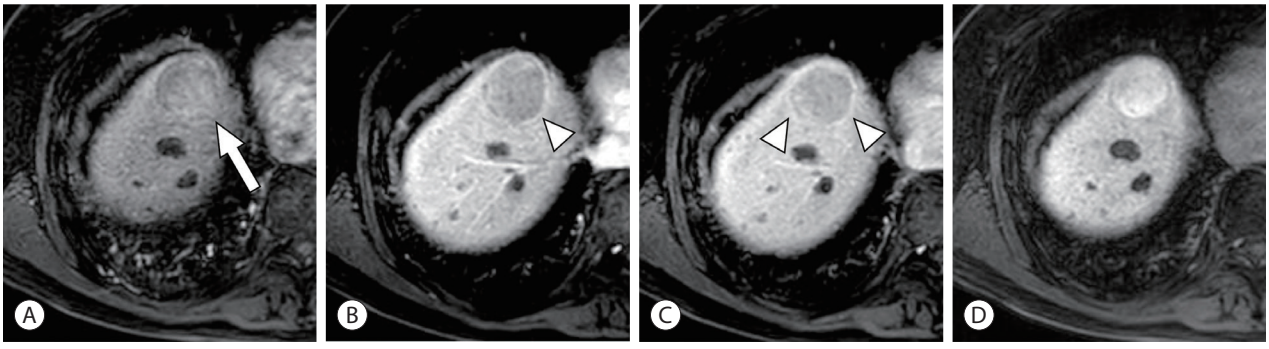

Figure 7. Hepatocellular carcinoma with enhancing capsular appearance and hepatobiliary phase hyperintensity in a 79-year-old man. An approximately 4 cm hepatic mass shows non-rim hyperenhancement (arrow) in the arterial phase (A) and washout appearance in the portal venous phase (B) of gadoxetic acid-enhanced magnetic resonance imaging. A smooth enhancing capsule (arrowheads) on the periphery of the lesion is seen in the portal venous (B) and transitional phases (C). The entire mass is hyperintense in the hepatobiliary phase (D). Pathological examination revealed complete capsule formation and nuclear expression of β-catenin, suggesting β-catenin pathway activation.

ed to a worse prognosis.[27,56] The inconsistent results regarding the prognostic significance of the pathologic or radiologic capsule in literature may be attributed to the heterogeneity of the lesions included in each study.

IMAGING FINDINGS OF HEPATOBILIARY PHASE

In multistep hepatocarcinogenesis, OATP8 expression gradually decreases, resulting in a decrease in hepatobiliary phase signal intensity on MRI, and these changes are known to precede the formation of unpaired arteries.[57] Therefore, hepatobiliary phase hypointensity is a useful imaging finding for malignant transformation of hepatic nodules. In contrast, hepatobiliary phase isointensity represents the normal functioning of hepatocytes and biliary drainage inside the lesion, which generally suggests benignity.[13]

1. Hepatobiliary phase hyperintensity

Approximately 9–15% of HCC show hyperintensity in the hepatobiliary phase due to OATP8 overexpression,[58,59] which is related to the activation of the Wnt/β-catenin pathway and/or hepatocyte nuclear factor 4-α pathway (Fig. 7).[60] They should be differentiated from focal nodular hyperplasia and hepatocellular adenomas with β-catenin mutation.[61,62]

Most (approximately 80%) hepatobiliary phase hyperintense HCCs were moderately differentiated, while some were well differentiated and were not observed in poorly differentiated HCCs.[63] In addition, these HCCs have less frequent MVI, lower serum levels of AFP and PIVKA-II, and decreased immunohistochemical expression of AFP, EpCAM, and glypican 3.[58,63,64] Hepatobiliary hyperintense HCC tends to be associated with favorable prognosis after hepatic resection.[59,65]

2. Hepatobiliary phase peritumoral hypointensity

Peritumoral hypointensity in the hepatobiliary phase refers to a "wedge-shaped or flame-like hypointense area of hepatic parenchyma located outside of the tumor margin" (Figs. 4-6).[66] It is not currently included in the LI-RADS lexicon, but several studies have demonstrated its importance as a predictor of MVI.[27,66-68] It is hypothesized that this feature reflects peritumoral perfusion alteration caused by microscopic tumor thrombi in peritumoral portal venules, resulting in decreased OATP8 function in hepatocytes around the tumor.[66]

Although the sensitivity of peritumoral hypointensity in the hepatobiliary phase of MVI is low (31.7–38.0%), its specificity is reported to be high (92.5–93.2%).[27,66] A few recent studies also reported it as a significant predictor of early tumor recurrence or shorter disease-free survival after curative resection, radiofrequency ablation, or liver transplantation, when applied in combination with other imaging findings (such as arterial phase peritumoral enhancement, satellite nodule, ill-defined tumor margin) and clinical findings (such as elevated serum AFP or PIVKA-II).[27,67-70]

3. Non–smooth tumor margin

Non-smooth tumor margin indicates that the tumor has a minute budding portion at its periphery protruding into the liver parenchyma in the hepatobiliary phase (Figs. 2, 4, 6).[71] This is thought to reflect histopathologic single nodular with extranodular growth type or confluent multinodular type, which are known to have a higher risk of MVI than the single nodular type.[27,72,73]

It has been reported as an independent predictor of MVI,[27,34,40,74,75] progenitor subtype,[76] macrotrabecular-massive subtype,[10] and early recurrence after curative resection.[24,27,46,71]

LOW APPARENT DIFFUSION COEFFICIENT ON DIFFUSION–WEIGHTED IMAGE

A low apparent diffusion coefficient (ADC) is a common radiological finding observed in various malignant tumors. Theoretically, as cell density increases and the nucleus/cytoplasm ratio increases in neoplastic tissue, it results in decreased free diffusion of water molecules, which can lead to increased signal intensity in diffusion-weighted imaging (DWI) and a decrease in the ADC value (Fig. 3).[77] Both the increased DWI signal and decreased ADC value suggest restricted diffusion of water molecules, but the DWI signal intensity also reflects the T2 signal. In contrast, as ADC ex-

cludes the effect of the T2 signal from DWI, it is regarded as a reliable index that more accurately depicts diffusion restriction. Contrarily, intratumoral necrosis can decrease signal intensity in DWI and increase ADC values.[78]

Low ADC values have been reported to be related to poorer histological grade,[79-81] presence of MVI,[82-84] expression of progenitor cell markers,[85,86] and proliferative signatures of HCC.[87-89] A few studies have reported that a low ADC value is a significant predictor of early recurrence after curative resection of HCC.[79,90]

ADC values are quantitative, but ADC values and diffusion-weighted signal intensities vary substantially depending on the imaging technique and MRI scanner; therefore, it is difficult to suggest a generalizable cutoff value that can be used clinically.[91] Additionally, HCC is frequently accompanied by necrosis, and the ADC value may vary significantly depending on the location of the measurement within the lesion.

LR-M CATEGORY OF LI-RADS

LR-M is a diagnostic category of LI-RADS for malignant tumors, not definitely HCC. Tumors of LR-M include targetoid masses or non-targetoid masses with the following appearances: infiltrative appearance, marked diffusion restriction, necrosis or severe ischemia, and other features suggestive of non-HCC malignancy.[13] A targetoid appearance (concentric arrangement of internal components), reflects peripheral hypercellularity, central stromal fibrosis, or ischemia, which are observed in various phases or sequences. This includes peripheral washout, delayed central enhancement (Fig. 4), targetoid diffusion restriction (Fig. 3), and targetoid appearance in the transitional or hepatobiliary phase, in addition to the rim-APHE described above. Although it is frequently reported in non-HCC malignancies, such as intrahepatic cholangiocarcinoma, combined hepatocellular cholangiocarcinoma, or metastasis, 22–36% of LR-M lesions were found to be HCC, because of the high prevalence of HCC in patients with underlying chronic liver disease.[92-95]

HCCs showing LR-M features have been reported to be associated with MVI,[67] poor histological differentiation,[96] and stem/progenitor marker expression, including K19 and EpCAM.[76,97] LR-M HCCs are likely to have a higher risk of early recurrence and poor overall survival after resection and a higher risk of tumor recurrence five years after liver transplantation.[36,67,96,98] A study by Choi et al.[98] demonstrated such trends in all primary liver cancers, as well as HCCs with LR-M features. Recently, Moon et al.[99] reported that the presence of rim-APHE was an independent prognostic factor for postoperative survival, while the 5-year overall survival and recurrence-free survival of LR-M HCCs without rim-APHE were not different from those of LR-4/5 HCCs. However, whether rim-APHE is a more important prognostic factor than the other LR-M features needs to be validated in other studies.

CURRENT LIMITATIONS AND THE NEED FOR FUTURE RESEARCH

Several imaging findings that indicate a poor prognosis, such as rim-APHE and non-smooth tumor margins, arterial phase peritumoral enhancement, and peritumoral hypointensity in the hepatobiliary phase, usually appear in combination. Currently, there is no consensus regarding which of these imaging findings is the most significant prognostic factor. One of the reasons for this variability may be that different studies use different definitions for imaging findings, and a more standardized definition of each imaging finding is needed to ensure consistent evaluation and validation of their prognostic significance. Moreover, the substantial interobserver variability of these imaging results has been identified as a drawback. Min et al.[100] reported that there was considerable interobserver variability in each radiologic finding or combination (κ=0.38–0.47) and predicted the probability of MVI based on imaging findings (κ=0.41) evaluated on gadoxetate-enhanced MRI. For HCCs <3 cm, there was no difference in interobserver agreement for MVI according to the reviewers' experience (κ=0.43 vs. 0.47, P>0.999), while for HCCs >3 cm, more experienced reviewers showed higher agreement than the less experienced reviewers (κ=0.65 vs. 0.21, P<0.001). Quantitative imaging analysis such as radiomics, can be utilized to reduce interobserver variability;

however, the results of quantitative analysis vary significantly with imaging instruments and protocols of imaging studies.

The majority of research has been conducted in Northeast Asia, where hepatitis B is the most prevalent cause of liver disease, and the prognosis of patients with favorable liver function who underwent hepatic resection has been investigated. In addition, most studies to date have been conducted retrospectively at a single institution with relatively small sample sizes. Therefore, it is not clear whether it can be generalized and applied to Western patients or to advanced HCCs not undergoing hepatic resection. Currently, these predictive imaging results are not incorporated into major HCC treatment guidelines because there are no well-validated imaging findings. A large-scale, multicenter study is needed in the future.

CONCLUSION

Recent studies have demonstrated the possibility that imaging features can predict not only pathological findings, such as histologic grade, presence of MVI, and pathological subtypes of HCC, but also the risk of tumor recurrence and survival. The imaging phenotype consisting of each radiological feature and/or its combination has the potential to be used for individualized treatment decisions in the future.

Conflict of Interest

Hyungjin Rhee is an editorial board member of Journal of Liver Cancer, and was not involved in the review process of this article. Shin Hye Hwang declares that she has no potential conflicts of interest to disclose.

Ethics Statement

This review article is fully based on the articles which was already published and did not involve additional patient participants. Therefore, IRB approval is not necessary.

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Data Availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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Writing-review & editing: HSH, HR
Approval of final manuscript: HSH, HR

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