**Meeting Summary** | Gastrointestinal Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2021.0593
Korean J Radiol 2022;23(7):697-719

Korean Journal of Radiology
KJR

# Gadoxetate-Enhanced MRI as a Diagnostic Tool in the Management of Hepatocellular Carcinoma: Report from a 2020 Asia-Pacific Multidisciplinary Expert Meeting

Cher Heng Tan[1, 2], Shu-cheng Chou[3], Nakarin Inmutto[4], Ke Ma[5], RuoFan Sheng[6], YingHong Shi[7], Zhongguo Zhou[8], Akira Yamada[9], Ryosuke Tateishi[10]

[1]Department of Diagnostic Radiology, Tan Tock Seng Hospital, Singapore; [2]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; [3]Division of General Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei City & Institute of Clinical Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; [4]Department of Radiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [5]Department of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [6]Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai Institute of Medical Imaging, Shanghai, China; [7]Department of Liver Surgery, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China; [8]Department of Hepatobiliary Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China; [9]Department of Radiology, Shinshu University School of Medicine, Matsumoto, Japan; [10]Department of Gastroenterology, The University of Tokyo Hospital, Tokyo, Japan

Gadoxetate magnetic resonance imaging (MRI) is widely used in clinical practice for liver imaging. For optimal use, we must understand both its advantages and limitations. This article is the outcome of an online advisory board meeting and subsequent discussions by a multidisciplinary group of experts on liver diseases across the Asia-Pacific region, first held on September 28, 2020. Here, we review the technical considerations for the use of gadoxetate, its current role in the management of patients with hepatocellular carcinoma (HCC), and its relevance in consensus guidelines for HCC imaging diagnosis. In the latter part of this review, we examine recent evidence evaluating the impact of gadoxetate on clinical outcomes on a continuum from diagnosis to treatment decision-making and follow-up. In conclusion, we outline the potential future roles of gadoxetate MRI based on an evolving understanding of the clinical utility of this contrast agent in the management of patients at risk of, or with, HCC.

**Keywords:** *Gadolinium-based contrast agent; Gadoxetate; Hepatocellular carcinoma; Magnetic resonance imaging*

## WHAT TECHNICAL CONSIDERATIONS EXIST FOR THE USE OF GADOXETATE IN MRI?

It is important for us to be familiar with the inherent technical limitations of gadoxetate in magnetic resonance imaging (MRI) of the liver and relevant mitigation techniques before we proceed to examine its current and future utility in clinical practice.

**Received:** July 22, 2021 **Revised:** February 21, 2022
**Accepted:** March 17, 2022
**Corresponding author:** Cher Heng Tan, MBBS, FRCR, MBA, Department of Diagnostic Radiology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore.
• E-mail: cherhengtan@ntu.edu.sg


### Reduced Arterial Phase Enhancement

Arterial phase images using gadoxetate MRI have been described as unsatisfactory because of weak arterial enhancement, attributed to the smaller administered volume and lower gadolinium content of gadoxetate compared with other gadolinium-based agents [1-3]. In a retrospective intra-individual study of 49 patients with 56 hepatocellular carcinomas (HCCs), comparing HCC imaging features using gadoxetate MRI, extracellular contrast media (ECCM) MRI with gadopentetate dimeglumine, and dynamic computed tomography (CT), arterial phase hyperenhancement (APHE) on gadoxetate MRI was superior to CT and not inferior

to gadopentetate dimeglumine [4]. More recently, a prospective study of dynamic contrast-enhanced (DCE) imaging in 66 patients with 83 HCCs showed similar perfusion parameters and lesion-to-liver contrast, even though liver parenchymal flow and enhancement occurred later with gadoxetate than with gadobenate dimeglumine [5]. However, in clinical practice, where visual evaluation of multiphasic contrast-enhanced MRI is the mainstay, Min et al. [6] showed that ECCM MRI identified APHE in a significantly higher proportion of patients (97.6%) than CT (81.5%; $p < 0.001$) or gadoxetate MRI (89.5%; $p = 0.002$). A broader consideration comparing the diagnostic performance of gadoxetate with ECCM and contrast-enhanced CT imaging, which reflects the discussions made by the advisory board, is covered in the ensuing sections of this review.

Several approaches have been proposed to increase arterial enhancement on gadoxetate MRI by achieving a favorable contrast bolus shape [3]. A slower injection rate of 1 mL/s stretches the bolus and increases the magnitude of the peak enhancement [3]. Gadoxetate doses above the approved 0.025 mmol/kg dose may prolong the peak arterial perfusion time and improve liver-to-lesion contrast [3]. Diluting gadoxetate with saline is not practical given the risk of non-sterility.

Subtraction imaging may further enhance the sensitivity of gadoxetate MRI for detecting APHE (Fig. 1). Subtraction images generated from unenhanced and arterial phases significantly increased sensitivity in diagnosing HCCs from 55.9% to 64.1%, with a non-significant decrease in specificity from 94.9% to 92.9%, in a retrospective analysis of 372 malignant nodules in 258 patients at risk of HCC [7].

### Transient Severe Motion Artifact

Gadoxetate is associated with a very low risk of adverse events [8] and a lower frequency of allergic-like adverse events than macrocyclic ECCM [9,10].

Although usually a benign event, transient severe motion (TSM) adversely affects the image quality in the arterial phase, which is a critical part of HCC diagnostic assessment. TSM has been reported to be more common with gadoxetate than with other gadolinium-based agents and appears to be more prevalent in the West [11,12].

Factors that could influence the occurrence of TSM include previous episodes of TSM, a higher (off-label) gadoxetate volume of 20 mL at a fixed dose of 2 mL/s, a

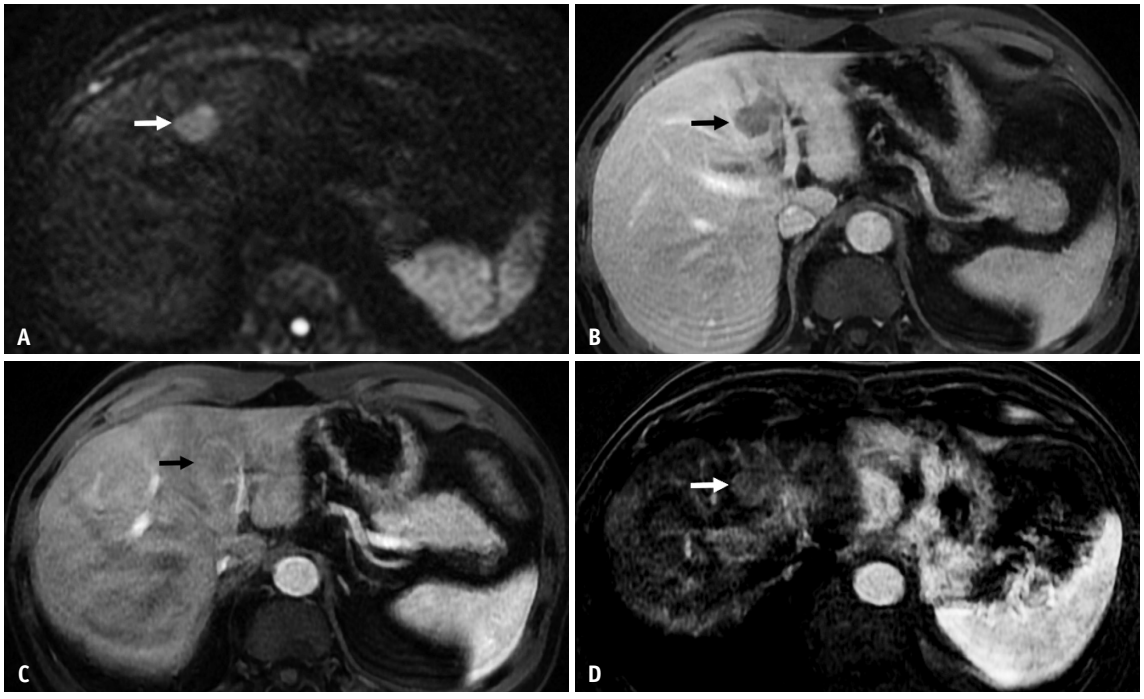


**Fig. 1. 58-year-old male chronic hepatitis B carrier with HCC nodule that had APHE better depicted with subtraction imaging.**
**A.** Diffusion-weighted imaging at 1000 s/mm$^2$ shows a nodule in segment 4 with moderate restricted diffusion (arrow) worrisome for malignancy. **B.** Axial fat-suppressed 3D gradient-recall echo image in the portal venous phase shows the nodule (arrow) demonstrating hypointensity consistent with washout. **C.** No corresponding APHE is demonstrated at the same region (arrow) where the nodule is expected to be. **D.** Subtraction imaging, however, reveals the nodule to possess mild non-rim APHE (arrow). Histology revealed poorly differentiated HCC. APHE = arterial phase hyperenhancement, HCC = hepatocellular carcinoma, 3D = three-dimensional


https://doi.org/10.3348/kjr.2021.0593

Korean Journal of Radiology
KJR

history of allergy to iodinated contrast media for CT, low body weight, chronic obstructive pulmonary disease, oxygen administration, and modified breath-holding [3,13-15].

Multiple arterial phase image acquisitions after a fixed delay can provide at least one set of well-timed arterial phase images and, in one study, were not compromised by TSM in 81% of patients [12,16]. Alternatively, shorter acquisition sequences can be used in single-phase examinations [3]. Motion-insensitive techniques, such as controlled aliasing in parallel imaging results in higher acceleration (dubbed as CAIPIRINHA), volume interpolated breath-hold examination (VIBE), and radial VIBE, are also promising [17].

### Reduced Sensitivity for HCC Detection in Hepatic Dysfunction

The major uptake transporter of gadoxetate in the hepatocyte cell membrane is organic anion-transporting polypeptide 1B3 (OATP1B3). For the majority (85%) of HCCs, the expression of OATP1B3 is reduced during progression, which explains the typical hypointensity of HCCs on gadoxetate MRI [18-20]. Reduced uptake of gadoxetate in poorly functioning livers can, therefore, reduce gadoxetate sensitivity for diagnosing HCCs [21]. Kim et al. [22] observed that in 189 patients with 240 HCCs, the diagnostic accuracy of gadoxetate MRI decreased with worsening severity of liver cirrhosis: from a mean accuracy of 0.974 in Child-Pugh class A to 0.904 in class B and 0.779 in class C. Concurrently, polymorphisms in *OATP* genes and concomitant medications that inhibit OATP1B3 may also reduce gadoxetate uptake [23,24] and limit diagnostic sensitivity.

## WHAT IS THE CURRENT ROLE FOR GADOXETATE MRI IN IMAGING DIAGNOSIS OF HCC?

To comprehend the current role of gadoxetate MRI for HCC diagnosis according to consensus guidelines, we will first need to compare its diagnostic performance against the established modalities of multidetector CT (MDCT) and ECCM MRI, followed by practical approaches to lesion assessment to maintain diagnostic performance.

### Comparison to MDCT

Clinical studies have affirmed the superiority of gadoxetate MRI over MDCT for the sensitivity of diagnosis, particularly for small HCCs. Tsurusaki et al. [25] assessed the performance of combined dynamic phase and hepatobiliary phase (HBP) images on gadoxetate MRI in a prospective intra-individual comparison versus MDCT in 54 patients with 83 histopathologically confirmed HCCs. The combined interpretation of the dynamic phase and HBP of gadoxetate MRI provided a significantly higher sensitivity for lesion detection (83%) than MDCT (70%). Gadoxetate MRI has also been reported to be superior to MDCT in detecting recurrence after radiofrequency ablation (RFA) [26] and hepatectomy [27].

A meta-analysis of 242 studies (15713 patients) published in 2016 reported that gadoxetate MRI provided a significantly higher per-lesion sensitivity and positive predictive value for HCC diagnosis (85.6% and 94.2%, respectively) than contrast-enhanced CT (73.6% and 85.8%) [28]. This conclusion has been corroborated by recent studies [29,30] and meta-analyses [31].

### Comparison to ECCM MRI

The diagnostic advantages of gadoxetate over other MRI contrast agents are less clear [17]. In a retrospective analysis by Semaan et al. [30], gadoxetate MRI was significantly superior to ECCM MRI in per-patient sensitivity (95.2% vs. 89.5%), but not in per-lesion sensitivity (76.8% vs. 78.5%). A meta-analysis by Feng et al. [32] on eight comparative studies on the diagnosis of HCC also reported similar per-lesion sensitivity rates between ECCM MRI and gadoxetate; however, it also reported that the sensitivity rate of ECCM MRI was significantly lower for HCCs smaller than 2 cm (< 2 cm, 66%; ≥ 2 cm, 87%). As these analyses pooled diagnostic performance, one may argue that there could be publication reporting bias in favor of gadoxetate.

Indeed, in the prospective intra-individual study by Min et al. [33], ECCM MRI showed better sensitivity and accuracy than gadoxetate MRI for the diagnosis of HCC in the Liver Imaging Reporting and Data System (LI-RADS) LR-5 category. Other head-to-head comparison studies seem to suggest that gadoxetate has a lower negative predictive value than ECCM for definite criteria of HCC according to LI-RADS [6,34]. However, it is interesting to note that the majority of head-to-head intra-individual comparison studies did not demonstrate significant reductions in specificity for diagnosis with the use of gadoxetate, [6,30,34,35] except for the study by Paisant et al. [36], where, in nodules 1–2 cm in size, specificity dropped to 66.1% for gadoxetate MRI versus 85.7% for ECCM MRI.

 https://doi.org/10.3348/kjr.2021.0593 

However, the sensitivity of gadoxetate has been found to be lower, perhaps attributable to lower per-lesion detection of APHE, as discussed earlier [6,35]. Depiction of the capsule appearance is poorer in the HBP of gadoxetate MRI [6,36], as is washout on the portal venous phase (PVP). Inclusion of transitional phase (TP) or delayed phase hypointensity, using gadoxetate as a criterion for washout, increases sensitivity comparable to [36], if not greater than [37-42], sensitivity of washout on PVP for ECCM.

Few studies have compared gadoxetate with other commercially available hepatocyte-specific agents [43,44]. The higher relative uptake of gadoxetate likely contributes to its superior diagnostic performance, particularly where a reduced signal is expected in the background liver tissues, such as in steatosis (Fig. 2) or reduced biliary excretory function. Overall, more head-to-head comparative studies are needed to recommend an MRI contrast agent over other agents.

## Incorporation into Consensus Guidelines for HCC Management

Both Asian and Western guidelines recommend surveillance for HCC in patients with liver cirrhosis or other risk factors [45-50]. Asian countries, including China, Japan, and Korea, engage in systematic nationwide surveillance, which is associated with earlier curative treatment and improved survival [51,52]. In Western countries, although surveillance is recommended by guidelines, its utilization in real-world practice is limited by physician and patient compliance [53].

Differences between Asian and Western guidelines reflect geographic variations in HCC epidemiology and treatment priorities [54,55]. All guidelines include APHE as a major criterion for HCC. In North America and Europe, diagnostic criteria are designed to achieve high specificity in HCC diagnosis to identify candidates for transplantation [46,48]. Assessment of washout is restricted to the PVP, which excludes the potential for false-positive results ("pseudo-washout") in the TP and HBP [55]. Asian guidelines additionally include washout in the TP or HBP of gadoxetate MRI because this criterion improves sensitivity for lesion detection [45,49,56-58] and thus provides opportunities for early interventional treatment [55,59], with certain caveats to maintain specificity.

## How to Overcome the Lower Specificity of Gadoxetate MRI for HCC Diagnosis

To address the decrease in specificity when incorporating TP/HBP washout into the diagnostic algorithm, findings from other MRI sequences that imply benignity or non-HCC malignancy could reduce the loss of specificity [60,61]. Combined APHE plus hypointensity on PVP and/or TP and/or HBP plus non-LR-1/2/M, which reflects the 2018 KLCA-HCC guidelines for HCC diagnosis, showed a sensitivity of 92.5% and specificity of 87.4% [60]. By excluding hemangiomas or cholangiocarcinomas and nodules with a targetoid appearance, the sensitivity of diagnosis using HBP washout was 95.2% and specificity was 82.0% versus 75.3% and 94.1% for washout confined to the PVP; the gain in sensitivity was arguably greater than the loss in

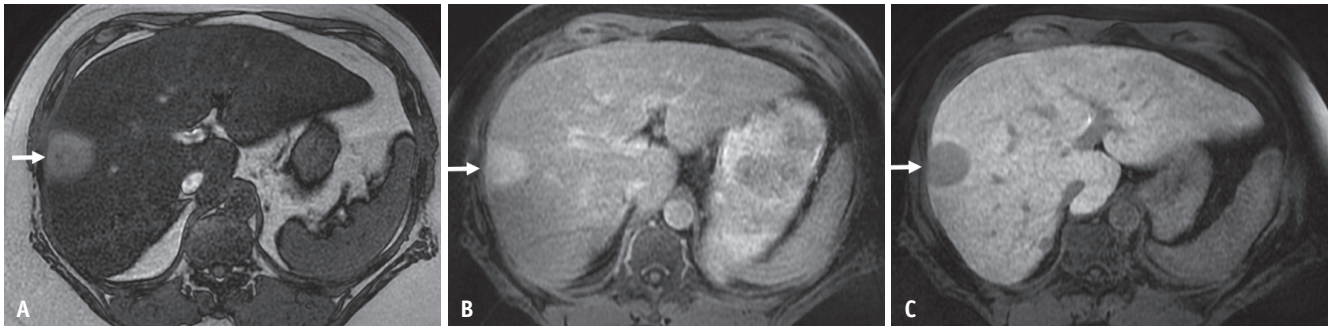


**Fig. 2. 56-year-old female with obesity and metabolic syndrome, in whom gadoxetate better depicted an HCC nodule due to higher concentration of physiological contrast uptake by the surrounding non-tumorous liver, in the hepatobiliary phase.**
**A.** Axial dual-gradient echo image in the opposed phase shows a circumscribed nodule (arrow) in subcapsular segment 5/8 of the liver surrounded by severe hepatic steatosis. **B.** Axial fat-suppressed 3D gradient-recall echo image in the hepatobiliary phase at 90 minutes post intravenous administration of gadobenate. The mass (arrow) appears hyperintense to the surrounding liver, which has a lower signal intensity than expected, due to the marked parenchymal steatosis. **C.** Axial fat-suppressed 3D gradient-recall echo image in the hepatobiliary phase at 20 minutes post intravenous administration of gadoxetate, performed 6 months following the prior scan **(B)**. The mass (arrow) appears clearly as a hepatobiliary defect, due to significantly larger quantity of gadolinium accumulated in the non-tumorous liver. An estimated 50% of dose of gadolinium is excreted via bile in the case of gadoxetate, as compared to 3%–5% in the case of gadobenate. Histology confirmed well-differentiated HCC.
HCC = hepatocellular carcinoma, 3D = three-dimensional


https://doi.org/10.3348/kjr.2021.0593

Korean Journal of Radiology
KJR

specificity [61]. Min et al. [62] found that the addition of at least two ancillary features, from among HBP-hypointense capsule, septum, and T2 spotty hyperintensity, significantly improved diagnostic accuracy (from 79.9% to 88.1%) and sensitivity (79.1% to 88.1%) without changing the specificity of HCC diagnosis (both 87.8%).

Combining imaging findings from different imaging modalities allows for the maximization of complementary strengths, such as real-time second-to-second assessment for the presence of APHE in contrast-enhanced ultrasound, as compared to the more conventional "static" evaluation of APHE on CT or MRI [63]. Further research on combined modality assessments, particularly with validation across different healthcare settings, is warranted.

## WHAT UNIQUE ENTITIES DOES GADOXETATE ALLOW DEPICTION OF?

The use of gadoxetate revealed entities that would not have been otherwise depicted on ECCM MRI without the TP or HBP phases. These entities are often present in cirrhotic livers and are increasingly recognized to have clinical implications, contributing to the value of gadoxetate MRI.

### Non-Hypervascular HBP-Hypointense Nodules

Non-hypervascular HBP-hypointense nodules (NHHNs) represent early HCCs, although approximately one-third are high-grade dysplastic nodules (HGDNs) [64]. Approximately one-third of NHHNs undergo hypervascular transformation to progress to HCC within 3 years [65]. Thus, NHHN may be associated with a higher grade of liver fibrosis. Progression to overt HCC is significantly higher in NHHNs than elsewhere in the hepatic parenchyma [66]. In the setting of hepatitis C virus infection, the risk of progression to HCC appears to be reduced when the viral load is eradicated with direct-acting antivirals (DAA) [67]; *de novo* HCC occurs more commonly than in patients without NHHN in the sustained viral response state [68].

Ancillary imaging features, such as T1 hyperintensity at baseline and a high growth rate, may be helpful in predicting HCC progression [69]. Concomitant T2-weighted (T2W) mild-to-moderate intensity and restricted diffusion-weighted images (DWIs) also increase the likelihood of malignancy [70]. Elevated serum alpha-fetoprotein (AFP) levels ≥ 100 ng/mL, well-defined margins, and hypointensity on pre-contrast T1W imaging suggest progressed HCC [71].

The significance of NHHNs is not completely understood, given that they can represent a range of lesions, from dysplastic nodules to progressed HCCs [72]. Therefore, the optimal management strategy for borderline lesions remains unclear. However, recent evidence points toward NHHNs as at-risk lesions in pretreatment as well as in post-treatment (RFA, resection, and transplant) settings (Table 1) [73-75], although one study did not find a significant difference in survival compared to patients without NHHN [76]. A meta-analysis of eight studies on 842 patients found that the overall pooled hazard ratio (HR) for intrahepatic distant recurrence (IDR) was lower following hepatectomy (2.14) than RFA (3.07), suggesting a role for NHHN in stratifying patients who would benefit from the former [77].

### Subcentimeter Arterially Enhancing and Hepatobiliary Hypointense Lesions

Subcentimeter arterially enhancing and hepatobiliary hypointense lesions (SAELs) are another type of intermediate-probability lesions that do not fit the guideline criteria for definite HCC. They may be at a higher risk than NHHN: the majority of SAELs (57.7%) progressed to overt HCC within 2 years [78]. Venous or late dynamic phase washout was more frequently observed in malignant than in benign SAELs (57.7% vs. 30.6%, respectively) [78]. Interestingly, combining hyperintensity on T2W images or DWI with APHE and washout did not increase the specificity for predicting SAEL progression to hypervascular HCC (both 90.6%) [79].

For SAELs that fulfill the washout criteria for HCC, recurrence-free survival did not differ between early treatment or watchful waiting, even though patients with more SAELs had higher rates of recurrence [80]. Percutaneous ultrasound (US)/MRI fusion-guided RFA is a viable treatment option for subcentimeter recurrent HCCs [81].

Overall, while optimal treatment strategies for NHHN and SAEL are still evolving, the current literature suggests that they warrant close monitoring as they would allude to a higher risk of *de novo* or metachronous HCC in high-risk patients (Fig. 3).

## WHAT IS THE IMPACT OF GADOXETATE MRI ON CLINICAL OUTCOMES?

Ultimately, the clinical utility of an imaging modality needs to be assessed beyond its diagnostic performance and measured by its impact on treatment outcomes and cost-effectiveness.


https://doi.org/10.3348/kjr.2021.0593

**Table 1. NHHN as a Clinical Prognostic Marker**

| Authors | Patients | Assessments | Key Results | Conclusion(s) |
|---|---|---|---|---|
| Increased Progression to HCC | | | | |
| Kim et al. 2016 [69] | 60 patients with CLD, with 114 NHHNs | Gadoxetate MRI | • 27 NHHNs in 21 patients transformed to HCC<br>• Hypervascularization associated with T1 hyperintensity (HR 2.69; $p$ = 0.021), history of HCC (HR 2.64; $p$ = 0.021), and initial lesion size (HR 1.09; $p$ = 0.046)<br>• Growth rate of nodules more powerful determinant than baseline clinical and MR features | Careful follow-up should be considered after detection of NHHNs or a higher growth rate |
| Hwang et al. 2017 [66] | 714 patients with CLD, 120 with NHHNs | Gadoxetate MRI<br>Transient elastography for LS assessment | • NHHNs significantly associated with log LS (OR 1.48; $p$ = 0.002) and hepatitis B infection (OR 3.14; $p$ = 0.017)<br>• 2-year cumulative progression rate of overt HCC: 34.1% from corresponding nodules, 18.3% in other parts of liver ($p$ = 0.071) | NHHNs on gadoxetate MRI frequently progressed to HCC |
| Suh et al. 2017 [65] | 944 patients with CLD, 1819 NHHNs (16 studies, meta-analysis) | Gadoxetate MRI | • Overall rate of hypervascular transformation: 28.2%<br>• Cumulative incidence of progression: 1 year, 18.3%; 2 years, 25.2%; 3 years, 30.3%<br>• Nodule size (cutoff ≥ 9 mm) was significant predictor for progression | NHHNs detected on gadoxetate MRI carry significant risk of transforming into hypervascular HCCs |
| Joo et al. 2020 [71] | 298 patients with CLD or cirrhosis, with 334 NHHNs | Gadoxetate MRI<br>Pathologic analysis | • Progressed HCCs diagnosed in 44.0%, early HCCs in 20.4%, high-grade DNs in 27.5%, and low-grade DNs or regenerative nodules in 8.1% of NHHNs<br>• Independent predictors for progressed HCC: serum AFP level ≥ 100 ng/mL (OR 2.7; $p$ = 0.01) and MRI features including well-defined margin (OR 5.5; $p$ = 0.003), hypointensity at precontrast T1-weighted imaging (OR 3.2; $p$ < 0.001), intermediate hyperintensity at T2-weighted imaging (OR 3.4; $p$ < 0.001), and restricted diffusion (OR 1.9; $p$ = 0.04) | NHHNs corresponded mainly to progressed HCCs, early HCCs, and high-grade DNs |
| Shimizu et al. 2020 [67] | 221 patients with HCV infection, 30 with NHHNs | Gadoxetate MRI before and after DAA therapy | • Progression of NHHN to HCC at 2 years significantly reduced after eradication of HCV ($p$ = 0.022)<br>• Hyperintensity on T2-weighted images (RR 14.70; $p$ < 0.001) and achieving SVR (RR 0.29; $p$ = 0.043) were independent factors associated with risk of HCC<br>• During follow-up, 6 (9.2%) NHHNs in the SVR cohort became undetectable on HBP images | Eradication of HCV by DAAs could reduce the hypervascularization rate of NHHNs |
| Toyoda et al. 2021 [68] | 383 patients with HCV infection, 32 with NHHNs | Gadoxetate MRI before and after DAA therapy | • Incidence of *de novo* HCC after SVR higher in patients with NHHNs than without (1-, 3-, 5-year incidence: 9.8%, 24.2%, and 41.6% vs. 0%, 1.2%, and 4.4%; $p$ < 0.0001)<br>• Presence of NHHNs before DAA therapy (adjusted HR 10.86; 95% CI 4.03–31.64) and cirrhosis (adjusted HR 7.23; 95% CI 1.88–35.85) independently associated with higher incidence of HCC after SVR | Presence of NHHNs before DAA therapy is a strong risk factor for the development of *de novo* HCC after SVR |
| Predicting post-treatment recurrence | | | | |
| Lee et al. 2015 [73] | 139 patients with early-stage HCC, 110 with NHHNs | Gadoxetate MRI pre-RFA | Estimated 5-year RFS rate: 27.9% in patients with NHHNs vs. 71.3% in patients without NHHNs (HR 2.84; $p$ = 0.006)<br>IDR rate at 5 years: 67.5% in patients with NHHNs vs. 17.9% in patients without NHHNs ($p$ < 0.001) | Presence of NHHNs on gadoxetate MRI is a predictive factor of recurrence after RFA of early-stage HCC, particularly IDR |

https://doi.org/10.3348/kjr.2021.0593

Korean Journal of Radiology
KJR

**Table 1. NHHN as a Clinical Prognostic Marker (Continued)**

| Authors | Patients | Assessments | Key Results | Conclusion(s) |
|---|---|---|---|---|
| Song et al. 2017 [74] | 141 patients with IDR after RFA for HCC | Gadoxetate MRI pre-RFA | • Precursor nodules (majority NHHNs) present in 46 (32.7%) patients<br>• Time to recurrence was 16.6 months in patients with precursor nodules vs. 24.0 months for patients without precursor nodules ($p$ = 0.011) | Patients with NHHNs had a shorter time to recurrence |
| Lee et al. 2019 [75] | 345 patients with single nodular HCC ≤ 3 cm, 81 with NHHNs | Gadoxetate MRI prehepatectomy or pre-RFA | • Presence of NHHNs was a significant factor affecting RFS after both hepatic resection (HR 2.75; $p$ = 0.004) and RFA (HR 1.78; $p$ = 0.004)<br>• 5-year RFS after resection: 34.0% with NHHN vs. 65.0% with non-NHHN<br>• 5-year RFS after RFA: 28.0% with NHHN vs. 51.0% with non-NHHN | In non-NHHN, resection offers higher RFS than RFA |
| Kim et al. 2020 [77] | 842 patients with HCC, 321 with NHHNs (8 studies, meta-analysis) | Gadoxetate MRI prehepatectomy or RFA | • Pooled HR for IDR in NHHN vs. non-NHHN groups = 2.44 (2.14 post-hepatectomy, 3.07 post-RFA) | The presence of NHHN increases risk of IDR and could stratify patients for hepatectomy |
| Takeishi et al. 2020 [76] | 290 HCC patients, 66 with NHHNs | Gadoxetate MRI prehepatectomy | • Untreated NHHN vs. no NHHN: no significant difference in RFS or OS up to 8 years post resection ($p$ = 0.103 and $p$ = 0.103, respectively)<br>• Treated NHHN and untreated NHHN: no significant difference in RFS or OS ($p$ = 0.158 and $p$ = 0.109, respectively) | NHHN detected on gadoxetate MRI did not reflect prognosis of HCC after hepatectomy |

AFP = alfa-fetoprotein, CI = confidence interval, CLD = chronic liver disease, DAA = direct-acting antiviral, DN = dysplastic nodule, HBP = hepatobiliary phase, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hazard ratio, IDR = intrahepatic distant recurrence, LS = liver stiffness, MRI = magnetic resonance imaging, NHHN = non-hypervascular HBP-hypointense nodule, OR = odds ratio, OS = overall survival, RFA = radiofrequency ablation, RFS = recurrence-free survival, RR = relative risk, SVR = sustained virologic response

## Treatment Decision-Making

Multidisciplinary team (MDT) care, with contributions from oncologists, hepatologists, gastroenterologists, surgeons, and radiologists, is widely regarded as the standard of care in HCC [46,82,83], irrespective of the choice of MRI contrast agent. In several retrospective studies, MDT care was associated with improved survival [84,85] and reduced mortality [86], particularly in patients with poor liver function [87].

The diagnostic arm of the Sorafenib and Microtherapy Guided by Primovist Enhanced MRI in Patients with Inoperable Liver Cancer trial (dubbed as SORAMIC trial) was the first prospective study to investigate the impact of greater diagnostic accuracy on treatment decisions [88]. Gadoxetate MRI using extended criteria for typical, atypical, and early HCC and HGDN [89] identified significantly more patients with more than four lesions than CT and consequent treatment decisions more closely matched definitive treatment decisions: 81.2%–83.3% for gadoxetate MRI versus 70.8%–73.4% for CT. A small retrospective study addressing early HCC reported that the addition of gadoxetate MRI to MDCT detected 18 more (of 82) HCCs and changed therapeutic decisions in 11 more (of 33) patients [90]. Kim et al. [91] found that gadoxetate MRI identified 74 additional nodules in 53 of 323 (16.4%) patients initially investigated by CT, leading to a change in the Barcelona Clinic Liver Cancer stage and treatment plan in 43 (13.3%) patients.

In liver transplantation (LT), accurate lesion detection is critical for allocating recipient candidates according to the Milan criteria. The diagnostic performance of gadoxetate MRI either equals [92] or is superior to MDCT in LT cohorts. The additional use of HBP images significantly improved sensitivity for the detection of small (1–2 cm) HCCs and accuracy of patient allocation (from 88.9% to 92.1%) [73].

## Survival and Recurrence Prediction

The higher lesion detection rates and positive impact on treatment decision-making provided by gadoxetate MRI compared to MDCT may translate to higher rates of overall and recurrence-free survival. In a large retrospective study (n = 30023 patients) by Kang et al. [93], all-cause mortality rates per 100 person-years were 36.3 in the CT alone, 15.2 in the CT + gadoxetate MRI (HR 0.64), and 21.7 in the CT + ECCM MRI groups (HR 0.71). For patients with localized disease, mortality was significantly lower in the CT + gadoxetate MRI group than in the CT + ECCM MRI


https://doi.org/10.3348/kjr.2021.0593

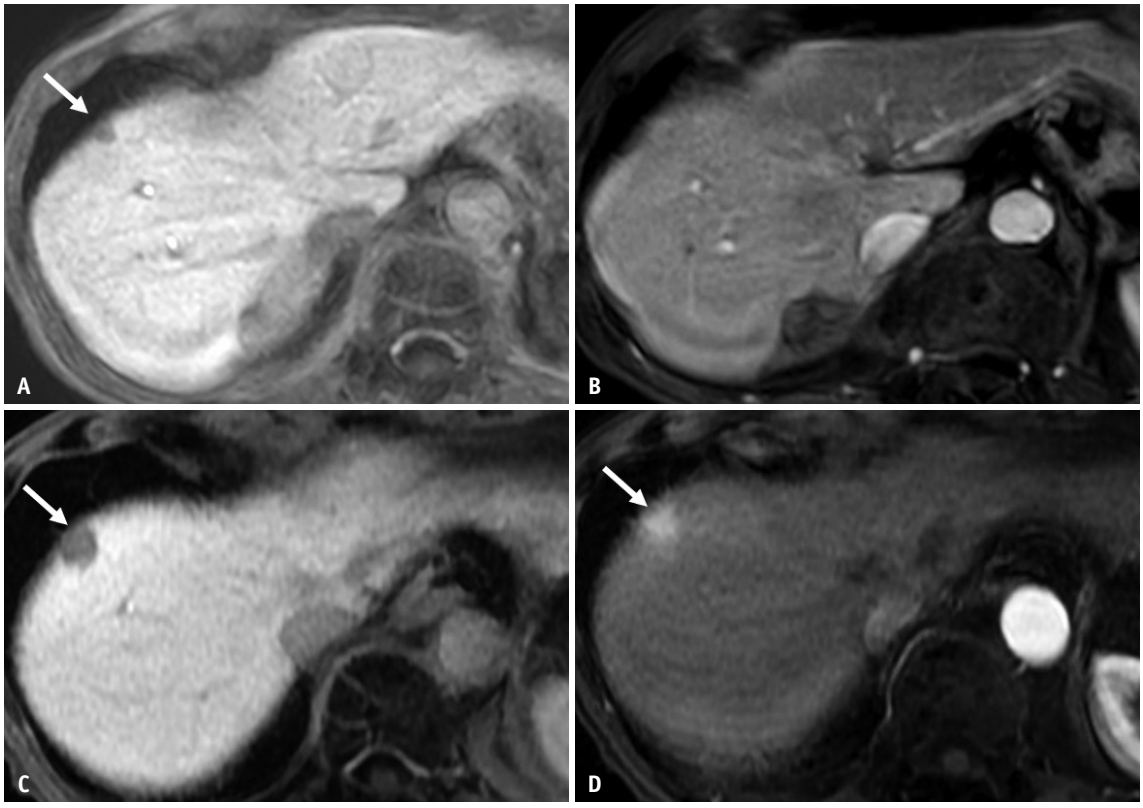


**Fig. 3. 80-year-old male with chronic hepatitis B viral infection and known history of HCC, presenting with NHHN that developed definite HCC features within 6 months.**
**A.** Axial fat-suppressed 3D gradient-recall echo image in the HBP (gadoxetate at 20 minutes) shows a subcentimeter hypointense nodule (arrow) in the subcapsular segment 8 near the hepatic dome. **B.** Corresponding late arterial phase image does not reveal enhancement—this would be in keeping with a NHHN. **C.** Axial fat-suppressed 3D gradient-recall echo image in the HBP (gadoxetate at 20 minutes) performed 6 months later shows increase in the size of the nodule (arrow). **D.** Corresponding arterial phase shows non-rim arterial phase hyperenhancement (arrow), in keeping with definite HCC. HBP = hepatobiliary phase, HCC = hepatocellular carcinoma, NHHN = non-hypervascular HBP-hypointense nodule, 3D = three-dimensional

group (HR, 0.89; $p$ = 0.008). A primary limitation of this study is the potential selection bias, even after adjusting for confounders, including centers administering treatment. However, similar findings were reported in a smaller study, where direct comparisons between gadoxetate MRI and CT (thereby reducing confounding factors) were made [91].

The HBP features depicted by gadoxetate may be contributory. In a study by Kim et al. [94], the median disease-free survival (DFS) in the ECCM MRI group (35.8 months) was longer than that in the gadoxetate MRI group with NHHN (25.8 months) but shorter than that in the gadoxetate MRI group without NHHN (48.6 months). Another study reported that the presence of satellite nodules and peritumoral hypointensity in HBP were independent factors associated with tumor recurrence, regardless of the Milan criteria [95]. In patients who underwent LT, the presence of NHHN predicted DFS within and outside the Milan criteria [96].

A large retrospective study of 549 patients with HCC within the Milan criteria showed that a predictive model built on preoperative imaging and laboratory factors (aspartate aminotransferase:platelet ratio index, tumor size, arterial rim enhancement, and presence of NHHNs) was non-inferior to combined preoperative and postoperative histopathologic factors in predicting early recurrence after curative resection [97]. A local tumor progression prediction model following RFA for HCC has also been reported [98]. These multimodal prediction models require testing and validation in different practical settings.

### Cost-Effectiveness Analyses of Gadoxetate MRI

Despite its limited sensitivity, US is widely used for HCC surveillance [99]. For new nodules > 1 cm detected on US in high-risk patients, further investigation using MDCT or MRI is mandatory. Gadoxetate MRI provides higher HCC detection rates and fewer false-negative findings than US [100] and


https://doi.org/10.3348/kjr.2021.0593

Korean Journal of Radiology
KJR

could be more cost-effective than US for surveillance of high-risk populations [101,102]. However, large prospective studies confirming the survival benefit of gadoxetate MRI over US are necessary for it to be considered a population screening tool.

Cost-effectiveness analyses are influenced by region-specific healthcare costs, reimbursement models, and many variables other than diagnostic accuracy alone. A study from Japan showed that gadoxetate MRI was associated with lower direct costs (US$18642; 2017 data) and generated a greater number of quality-adjusted life years (QALYs) (9.502) than ECCM MRI ($20274, 9.303 QALYs) or MDCT ($21279, 9.215 QALYs) [103]. An interesting health economic assessment of two different health systems (Korea and Thailand) drew similar conclusions [104]. In Korea, from the payer's perspective, the total cost to reach a confirmed treatment decision was US$3087/patient using gadoxetate MRI, versus $3205 for MDCT and $3403 for ECCM MRI. In Thailand, gadoxetate MRI was the least costly option for the payer ($702/patient vs. $931 for MDCT, $873 for ECCM MRI), though less so from the provider's (hospital's) perspective. Another study based only in Korea [105] on early-stage HCC reported that QALYs were higher for gadoxetate (5.52) than for MDCT (5.08). In China, He et al. [106] found that the total diagnostic and treatment costs per patient after initial gadoxetate MRI evaluation were similar to MDCT (US$4586 vs. $4653; 2018 data) and lower than that for ECCM MRI ($4753).

Overall, despite higher upfront costs, gadoxetate MRI appears to be as, if not more, cost-effective than other advanced imaging modalities in the management of HCCs, after considering the reduced need for confirmatory diagnostic procedures and unnecessary treatment. A consensus on treatment protocols and transitional probabilities would facilitate the direct comparison of health systems, which is particularly relevant in Asia as national guidelines move toward adopting HBP hypointensity as a major criterion for definite HCC diagnosis.

## PROMISING ROLES OF GADOXETATE MRI IN PATIENTS WITH HCC BESIDES THE HCC DIAGNOSIS

Here, we review emerging evidence for the future utility of gadoxetate in two promising domains: identifying HCC with pathologic features associated with poorer prognosis and one-stop pre-treatment assessment of regional liver function. A summary of the key references for each is provided in Table 2 [107-120] and Table 3 [121-132].

### Measure of Tumor Aggressiveness

OATP1B3 expression is regulated in part by β-catenin signaling [133]. Beta-catenin-activated HCCs are associated with reduced levels of markers of aggressive biological behavior (AFP and AFP-L3 fractions) [134] and HBP uptake of gadoxetate [135,136]. Incomplete capsules or non-capsules and intratumoral vessels have been reported to be associated with high *BRAF* and *RAF1* expression [113], with implications for the use of targeted therapies.

The established imaging features associated with prognosis in staging systems for HCC include tumor size, number, and location [46,48-50]. Less established are features that can signal microvascular invasion (MVI), a known pathologic marker for poor prognosis, including non-smooth tumor margins, irregular rim-like APHE, and HBP hypointensity (Fig. 4) [107,108,116,120,137]. Ahn et al. [112] showed that peritumoral hypointensity on HBP was a significant independent predictor of early recurrence, MVI, and tumor grade. This finding was corroborated by two meta-analyses [111,117]. Combined laboratory and imaging predictive models could predict MVI in single, small (≤ 3 cm) HCCs [118].

HCCs that express a progenitor phenotype, defined as positive for cytokeratin-19 (CK19) or epithelial cell adhesion molecule expression, are associated with poorer outcomes. Chen et al. [115] showed that in addition to serum AFP levels, skewness on T2W imaging, uniformity on pre-T1W imaging, irregular tumor margins, targetoid appearance, and absence of mosaic architecture were associated with the progenitor phenotype. In another study, Choi et al. [110] observed that irregular tumor margin, arterial rim enhancement, lower HBP tumor:liver signal intensity (SI) ratio, and lower tumor:liver apparent diffusion coefficient ratio were significant.

Quantitative parameters on DCE imaging of gadoxetate MRI can additionally provide information on the histologic grade and prognosis. The DCE-MRI-derived volume transfer constant correlated significantly with Ki-67 proliferation status (a measure of tumor growth rate) and histologic grade of HCC, and the reflux rate constant and volume fraction of the extracellular space correlated with tumor microvessel density [109]. Rhee et al. [119] found that gadoxetate MRI criteria based on the arterial phase hypovascular component were capable of stratifying the

 https://doi.org/10.3348/kjr.2021.0593 

**Table 2. Gadoxetate as a Measure of Tumor Aggressiveness**

| Authors | Patients | Assessments | Key Results | Conclusion(s) |
|---|---|---|---|---|
| Predicting MVI | | | | |
| An et al. 2015 [107] | 268 patients with single HCC | • Gadoxetate MRI prehepatectomy | • MRI features associated with early recurrence (< 2 years): rim enhancement (OR 3.83), peritumoral parenchymal enhancement in arterial phase (OR 2.64), satellite nodule (OR 4.07), and tumor size (OR 1.66)<br>• Model derived from these variables had AUC of 0.788 in prediction of risk of early recurrence | Prediction model derived from gadoxetate MRI variables preoperatively can estimate risk of early recurrence |
| Lee et al. 2017 [108] | 197 patients with HCC ≤ 5 cm | • Gadoxetate MRI prehepatectomy | • MRI features associated with MVI < 2 years: peritumoral APHE (OR 5.184), peritumoral hypointensity on HBP (OR 4.705), and non-smooth margins (OR 3.555)<br>• Early recurrence rates higher in patients with two or three significant MRI findings vs. none (27.9% vs. 12.6%; $p = 0.030$) | Combination of ≥ 2 gadoxetate MRI findings can be used as a preoperative imaging biomarker for predicting MVI, with specificity > 90% |
| Hu et al. 2018 [111] | 1163 patients (10 studies, meta-analysis) | • MRI presurgery<br>• Histopathology | • MVI associated with peritumoral enhancement (OR 4.04; $p < 0.05$) and peritumoral hypointensity on HBP (OR 10.62; $p < 0.05$)<br>• Diagnostic accuracy analysis revealed high specificity (0.90–0.94) but low sensitivity (0.29–0.40) for both features to assess MVI | Two peritumoral imaging features are significantly associated with MVI. These features highly suggest MVI only when present with a high false-negative rate |
| Ahn et al. 2019 [112] | 179 patients with single HCC | • Gadoxetate MRI prehepatectomy, including texture analysis of tissue heterogeneity | • MRI features associated with early recurrence (< 1 year), MVI, and tumor grade: satellite nodules and peritumoral HBP ($p < 0.05$)<br>• Texture analysis added to MRI findings increased diagnostic performance for predicting early recurrence from 0.70 to 0.83 | Gadoxetate MRI findings with texture parameters are useful to predict early recurrence, MVI, and higher grade |
| Kim et al. 2019 [114] | 167 patients with single HCC 2–5 cm | • Gadoxetate MRI radiomic model (3 or 5 mm peritumoral border extension)<br>• Postoperative clinicopathological model | • Prognostic performance of gadoxetate MRI radiomic model (3 mm peritumoral border extension) was comparable to clinicopathological model (c-index difference -0.021; $p = 0.758$) for DFS<br>• A combined gadoxetate MRI radiomic and clinicopathological model was not significantly different from the clinicopathological model | These findings suggest the importance of including peritumoral changes in the radiomic analysis of HCC |
| Min et al. 2020 [116] | 100 patients with single HCC ≤ 5 cm | • Gadoxetate MRI<br>• Histopathology | • Based on four imaging features (non-smooth tumor margin, irregular rim-like enhancement in arterial phase, peritumoral APHE, peritumoral HBP hypointensity), overall inter-observer agreement was fair to moderate for MVI probability ($\kappa = 0.41$)<br>• AUCs for diagnosis of MVI were lower for HCCs > 3 cm (range, 0.55–0.69) than for ≤ 3 cm (range, 0.59–0.75) | Considerable inter-observer variability exists in the assessment of MVI using MRI |

**Table 2. Gadoxetate as a Measure of Tumor Aggressiveness (Continued)**

| Authors | Patients | Assessments | Key Results | Conclusion(s) |
|---|---|---|---|---|
| Hong et al. 2021 [117] | 4274 patients with HCC (36 studies, meta-analysis) | • MRI presurgery<br>• Histopathology | • MVI was associated with larger tumor size (> 5 cm; diagnostic OR 5.2), rim arterial enhancement (OR 4.2), arterial peritumoral enhancement (4.4), peritumoral hypointensity on HBP (8.2), non-smooth tumor margin (3.2), multifocality (7.1), and hypointensity T1WI (4.9)<br>• Peritumoral hypointensity on HBP and multifocality showed very high meta-analytic pooled specificities for diagnosing MVI (91.1% and 93.3%, respectively) | MRI features predictive of MVI can be useful in the management of HCC |
| Lee et al. 2021 [118] | 516 patients with single HCC ≤ 3 cm | • MRI before surgical resection and RFA | • MVI was associated with AFP (≥ 15 ng/mL), protein induced by vitamin K absence-II (≥ 48 mAU/mL), arterial peritumoral enhancement, and hepatobiliary peritumoral hypointensity<br>• AUC of the predictive model incorporating these factors was 0.87 and 0.82 in derivation and validation cohorts, respectively<br>• Resection was associated with lower rate of early recurrence (< 2 years) than RFA based on risk of MVI after propensity score matching ($p < 0.05$) | The model predicted risk of MVI with high accuracy in patients with a small HCC |
| Song et al. 2021 [120] | 1618 patients (11 studies, meta-analysis) | • MRI presurgery<br>• Histopathology | • MVI associated with non-smooth tumor margin (diagnostic OR 4.62) and incomplete tumor capsule (OR 2.25)<br>• Sensitivity and specificity of these 2 parameters were 0.757 and 0.597 vs. 0.646 and 0.552, respectively<br>• AUC of the non-smooth tumor margin variable for predicting MVI was 0.72 and AUC of the incomplete tumor capsule variable for predicting MVI was 0.62 | Non-smooth tumor margins and incomplete tumor capsules on MRI are important for preoperative prediction of MVI |
| Predicting other aggressive histological features | | | | |
| Chen et al. 2018 [109] | 34 patients with HCC | • Free-breathing DCE-MRI using gadoxetate<br>• Histology | • DCE-MRI-derived $K^{trans}$ was negatively correlated with Ki-67 indices (rho -0.408, $p = 0.017$) and histological grades (rho -0.444, $p = 0.009$) of HCC<br>• $K_{ep}$ and $V_e$ were related with tumor MVD (rho -0.405, $p = 0.017$; rho 0.385, $p = 0.024$, respectively)<br>• $K^{trans}$, $K_{ep}$, and iAUC demonstrated moderate diagnostic performance for discriminating high-grade from low-grade HCC without significant differences | Free-breathing DCE-MRI is technically feasible and offers a potential avenue to differentiate between low-grade and high-grade HCC |
| Choi et al. 2018 [110] | 242 patients with HCC (204 CK19-, 38 CK19+) | • Gadoxetate and diffusion-weighted MRI presurgical resection | • Predictors of CK19+ HCC: irregular tumor margin ($p = 0.024$), arterial rim enhancement ($p < 0.001$), lower tumor-to-liver SI ratio on HBP images (≤ 0.522; $p = 0.01$), and lower tumor-to-liver ADC ratio (≤ 0.820; $p < 0.001$)<br>• When all 4 criteria were satisfied, specificity of CK19+ HCC diagnosis was 99.5%<br>• RFS rates were lower in patients with CK19+ vs. CK19- HCCs after resection (63.9% vs. 79.9% at 2 years; $p = 0.001$) | Gadoxetate and diffusion-weighted MRI features may be helpful to predict CK19+ HCC with early recurrence after curative resection |


https://doi.org/10.3348/kjr.2021.0593

Korean Journal of Radiology KJR

**Table 2. Gadoxetate as a Measure of Tumor Aggressiveness (Continued)**

| Authors | Patients | Assessments | Key Results | Conclusion(s) |
|---|---|---|---|---|
| Dong et al. 2019 [113] | 91 patients with solitary HCC | • Gadoxetate MRI pre-resection<br>• Histopathology | • Tumor incomplete capsules or non-capsules ($p$ = 0.001) and intratumoral vessels ($p$ = 0.002) were associated with *BRAF* expression<br>• Tumor incomplete capsules or non-capsules ($p$ = 0.001) and intratumoral vessels ($p$ = 0.013) were associated with *RAF1* expression<br>• No MRI features were associated with expression of *VEGFR2* or *VEGFR3* | The presence of incomplete capsule or intratumoral vessels and the absence of capsule are potential indicators of high *BRAF* and *RAF1* expression. Gadoxetate MRI may facilitate choice of gene therapy in HCC |
| Chen et al. 2020 [115] | 115 patients with surgery-proven HCC | • Gadoxetate MRI presurgery<br>• Progenitor cell markers: CK19 or EpCAM expression | • Predictors of HCCs expressing progenitor cell markers were AFP ≥ 155.25 ng/mL ($p$ < 0.001), skewness on T2WI ≤ 1.10 ($p$ = 0.024), uniformity on pre-T1WI ≤ 0.91 ($p$ = 0.024), irregular tumor margin ($p$ = 0.006), targetoid appearance ($p$ = 0.001), and absence of mosaic architecture ($p$ = 0.014)<br>• Combining any three variables provided diagnostic accuracy of 0.86, sensitivity of 0.97, and specificity of 0.74 | Noninvasive prediction of HCCs with progenitor phenotype can be achieved with high accuracy by integrated interpretation of biochemical and radiological information |
| Rhee et al. 2021 [119] | 476 patients with single HCCs, including 84 with MTM-HCC | • Gadoxetate MRI pre-resection<br>• Histopathology | • MRIC for MTM-HCC:<br>• MRIC-1, ≥ 20% arterial phase hypovascular component. MRIC-1 showed high sensitivity and negative predictive value (88% and 95% in training cohort, and 88% and 97% in validation cohorts, respectively)<br>• MRIC-2, ≥ 50% hypovascular component and ≥ 2 ancillary findings (intratumoral artery, peritumoral APHE, and non-smooth tumor margin) MRIC-2 demonstrated moderate sensitivity and high specificity (47% and 94% in training cohort, and 46% and 96% in pooled validation cohorts, respectively). MRIC-2 was an independent poor prognostic factor for OS in both training and pooled validation cohorts | Gadoxetate MRI findings including arterial phase hypovascular component could stratify the probability of MTM-HCC and noninvasively obtain prognostic information |

ADC = apparent diffusion coefficient, AFP = alfa-fetoprotein, APHE = arterial phase hyperenhancement, AUC = area under the receiver operating characteristic curve, CK19 = cytokeratin 19, DCE = dynamic contrast-enhanced, DFS = disease-free survival, EpCAM = epithelial cell adhesion molecule, HBP = hepatobiliary phase, HCC = hepatocellular carcinoma, iAUC = area under the gadolinium concentration–time curve, $K_{ep}$ = reflux rate constant, $K^{trans}$ = volume transfer constant, MRI = magnetic resonance imaging, MRIC = MRI criteria, MTM = macrotrabecular massive, MVD = microvascular density, MVI = microvascular invasion, OR = odds ratio, OS = overall survival, RFA = radiofrequency ablation, RFS = recurrence-free survival, SI = signal intensity, T1WI = T1-weighted imaging, T2WI = T2-weighted imaging, $V_e$ = volume fraction

**Table 3. Gadoxetate for Determination of Regional Liver Function**

| Authors | Patients | Assessments | Key Results | Conclusion(s) |
|---|---|---|---|---|
| To estimate liver function | | | | |
| Ryeom et al. 2004 [125] | 10 rabbits with CC14-induced liver injury | • Gadoxetate MRI-derived HEF, calculated from deconvolution analysis of aortic and hepatic parenchymal time–intensity curves<br>• ICG retention at 15 minutes | • HEF correlated with change in ICG $R_{15}$ (Pearson $r$ = -0.965, $p$ = 0.000) | Gadoxetate MRI HEF correlates with ICG $R_{15}$ and represents a direct, noninvasive technique for quantitative evaluation of liver function |
| Yamada et al. 2011 [126] | 23 patients undergoing preoperative evaluation | • HUI derived from $V_L$ and mean SI on gadoxetate MRI<br>• $V_S$<br>• ICG-PDR | • HUI and $V_S$ correlated significantly with ICG-PDR ($R$ = 0.87) | Liver function can be estimated quantitatively from signal intensities and volumes of liver and spleen on gadoxetate MRI, which may improve estimation of segmental liver function |
| Geisel et al. 2017 [121] | 37 patients undergoing right PVE and extended right hemihepatectomy | • Lobar volume, KGR, RE, HUI, and FSF for each lobe, derived from gadoxetate MRI | • RE of LLL increased after PVE and decreased to 0.48 at 10 days after surgery<br>• KGR was 14.06% ± 9.82%/week from PVE to 14 days post PVE<br>• HUI of LLL increased after PVE ($p$ < 0.05 at 14 and 28 days) vs. pre-PVE<br>• HUI of residual liver decreased after surgery vs. presurgery | Gadoxetate MRI may be used to monitor increase in FLR function after PVE and to depict intraoperative liver injury leading to decreased FLR function |
| Haimerl et al. 2017 [122] | 131 patients with normal liver, Child-Pugh A and B | • Gadoxetate-enhanced T1 relaxometry-based indices and SI-based indices, including HUI<br>• ICG-PDR | • All gadoxetate MRI-based liver function indices correlated with ICG-PDR. Relaxometry-based indices provided better correlation than SI-based indices with ICG-PDR<br>• Taking account of liver volume provided stronger correlations for both SI-based and T1 relaxometry-based indices with ICG-PDR | Gadoxetate-enhanced T1 relaxometry, in combination with liver volume, is a potential tool for monitoring liver function |
| Jung et al. 2018 [123] | 29 patients undergoing image-guided SBRT | • SBRT targeting accuracy assessed by parenchymal changes on HBP gadoxetate MRI at 2–4 months<br>• ICD between treated HCC and parenchymal changes | • Median ICD in 3D direction was 6.81 mm (IQR 4.27–9.61 mm)<br>• No significant difference in ICD between intrahepatic marker and diaphragm guidance | Hepatic parenchymal changes on gadoxetate MRI can be used to assess targeting accuracy on SBRT |
| Rassam et al. 2019 [124] | 20 patients undergoing preoperative assessment of FRL function | • $^{99m}$Tc-metbromin HBS<br>• Dynamic gadoxetate MRI | • Gadoxetate MRI-derived mean Ki correlated with HBS-derived MUR for total and FRL function (Pearson $r$ = 0.70, $p$ = 0.001 and $r$ = 0.89, $p$ < 0.001, respectively) | Dynamic gadoxetate MRI is comparable to HBS for liver function assessment, with the potential to avoid PHLF |


https://doi.org/10.3348/kjr.2021.0593

Korean Journal of Radiology KJR

**Table 3. Gadoxetate for Determination of Regional Liver Function (Continued)**

| Authors | Patients | Assessments | Key Results | Conclusion(s) |
|---|---|---|---|---|
| To predict postoperative hepatic dysfunction | | | | |
| Asenbaum et al. 2018 [127] | 62 patients undergoing major liver resection (≥ 4 segments) | • RLE for each FLR (remnantRLE), derived from mean SI on preop gadoxetate MRI<br>• ICG-PDR<br>• functFLR, calculated as FLR x remnantRLE ÷ body weight | • Probability of PHLF in 16 patients related to FLR ($p$ = 0.015), proportion of FLR ($p$ = 0.004), weight-adapted FLR ($p$ = 0.003), remnant RLE ($p$ = 0.002), and functFLR ($p$ = 0.002) in univariate analyses and to functFLR in multivariate analyses (0.561; $p$ = 0.002) | functFLR was superior to established variables in predicting PHLF |
| Kim et al. 2018 [128] | 73 patients undergoing liver resection | • RLE, FRLV, rHUI, rHUI-BW<br>• ICG-PDR | • RLE, FRLV, rHUI, rHUI-BW, and ICG-PDR were independent predictors of PHLF in 18 patients ($p$ = 0.011, $p$ = 0.034, $p$ < 0.001, $p$ = 0.001, $p$ = 0.003, respectively) on multivariate analyses<br>• AUCs were larger for rHUI and rHUI-BW than other predictors, including significant differences vs. ICG-PDR ($p$ = 0.016 and $p$ = 0.0007, respectively) | Gadoxetate MRI predicted post-hepatectomy PHLF better than ICG-PDR |
| Bastati et al. 2020 [129] | 265 with CLD | • FLIS, derived from gadoxetate MRI HBP features: hepatic enhancement, biliary excretion, and SI in portal vein | • FLIS independently predictive of first hepatic decompensation in compensated advanced CLD (adjusted HR 3.7; $p$ = 0.04)<br>• FLIS independent risk factor for mortality in patients with compensated advanced CLD (adjusted HR 7.4; $p$ < 0.001) and decompensated advanced CLD (adjusted HR 3.8; $p$ = 0.004) | FLIS identified patients with advanced CLD at increased risk for first hepatic decompensation and mortality |
| Tsujita et al. 2020 [130] | 41 patients with HCC | • Gadoxetate MRI prehepatectomy for HCC with portal vein invasion | • 9 patients developed severe PHLF. LSR of the remnant liver was significantly higher than that of the resected liver ($p$ < 0.001)<br>• 9 patients with severe PHLF demonstrated significantly lower rHUI ($p$ < 0.001) and rHUI/HUI ($p$ < 0.001) vs. no/mild PHLF<br>• Decreased rHUI ($p$ = 0.012, AUC = 0.885) and rHUI/HUI ($p$ = 0.002, AUC = 0.852) were independent predictors of severe PHLF | Gadoxetate MRI may be a promising noninvasive examination for assessing global and regional liver function, allowing estimation of FLR and prediction of severe PHLF |
| Huang et al. 2021 [131] | 133 patients with HCC (45 patients received major hepatectomy) | • Gadoxetate MRI with computer-aided virtual hepatectomy<br>• ICG test | • T1 relaxation time reduction rate (T1ratio) and FV correlated with ICG test (rho -0.304 and -0.449; $p$ < 0.05)<br>• Low rT1ratio (< 66.5%) and high rT1pos (> 217.5 ms) may predict major complications (AUC 0.831 and 0.756, respectively; $p$ < 0.05)<br>• rT1ratio was an independent risk factor for postoperative major complications (OR 0.845; $p$ < 0.05) | Quantitative regional liver function assessed by gadoxetate MRI can predict short-term outcomes after major hepatectomy in patients with HCC |

https://doi.org/10.3348/kjr.2021.0593

Korean Journal of Radiology
KJR

**Table 3. Gadoxetate for Determination of Regional Liver Function (Continued)**

| Authors | Patients | Assessments | Key Results | Conclusion(s) |
|---|---|---|---|---|
| Notake et al. 2021 [132] | 67 patients undergoing major hepatectomy for biliary malignancy | • rHUI, derived from gadoxetate MRI<br>• Total bilirubin<br>• Prothrombin time<br>• Preoperative ICG<br>• ICGK-F<br>• FLRV<br>• FLR proportion (FLR:total $V_L$) | • rHUI predicted grade B or C PHLF in 8 patients (AUC 0.896)<br>• rHUI < 0.410 was predictive of increased risk of PHLF (OR 2.0 x $10^3$)<br>No other investigated indices were predictive of PHLF | rHUI is a potentially useful predictor of PHLF after major hepatectomy for biliary malignancy |

AUC = area under the curve, CLD = chronic liver disease, FLIS = functional liver imaging score, FLR = future liver remnant, FLRV = FLR volume, FRL = future remnant liver, FRLV = FRL volume, FSF = fat signal fraction, FV = functional liver volume, HBP = hepatobiliary phase, HBS = hepatobiliary scintigraphy, HEF = hepatic extraction fraction, HR = hazard ratio, HUI = hepatocellular uptake index, ICD = intercenter discrepancy, ICG = indocyanine green, ICGK = ICG plasma clearance rate, ICGK-F = ICGK x FLR proportion, IQR = interquartile range, KGR = kinetic growth rate, LLL = left liver lobe, LSR = liver-spleen ratio, MRI = magnetic resonance imaging, MUR = mebrofenin uptake ratio, OR = odds ratio, PDR = plasma disappearance rate, PHLF = post-hepatectomy liver failure, PVE = portal vein embolization, RE = relative enhancement, rHUI = remnant HUI, rHUI-BW = remnant HUI corrected for body weight, RLE = relative liver enhancement, SBRT = stereotactic body radiation therapy, SI = signal intensity, $V_L$ = liver volume, $V_S$ = spleen volume

probability of macrotrabecular-massive HCC, a subtype associated with aggressive behavior and poor prognosis.

Radiomic models can reduce inter-observer variability [112], but their performance remains limited. Kim et al. [114] compared radiomics with a postoperative clinicopathologic and combined clinicopathologic-radiomic (CCR) model for the prediction of early (≤ 2 years) and late (> 2 years) DFS. The radiomic model showed lower prognostic performance than the CCR and clinicopathological models. As with the other aforementioned predictive models, more extensive testing and validation, along with the use of standardized imaging and pathological criteria, are necessary.

## Assessment of Liver Function

$^{99m}$Tc-mebrofenin and indocyanine green (ICG) are recognized markers of liver function and are substrates of OATP1B1/B3 and OATP1B3, respectively [138]. Although the $^{99m}$Tc-mebrofenin test is not commonly performed, ICG remains a common test for preoperative decision-making. The extent of gadoxetate enhancement has been shown to correlate with $^{99m}$Tc-mebrofenin scintigraphy and ICG clearance and may therefore play a role in the assessment of liver functional reserve [124-126,139], with the distinct added advantage of segmental liver function evaluation [127].

Bastati et al. [129] developed a functional liver imaging score (FLIS) from three HBP features of gadoxetate MRI: hepatic enhancement, biliary contrast excretion, and persistence of SI in the portal vein, predictive of first hepatic decompensation in patients with compensated advanced chronic liver disease (CLD), but not of decompensated advanced CLD. FLIS was an independent risk factor for mortality. Quantitative DCE assessment techniques have also been employed [124,125].

For the accurate evaluation of quantitative liver function using gadoxetate MRI, it is important to correct for liver volume and the contrast enhancement effect of gadoxetate in the extracellular fluid space [126]. The hepatocellular uptake index (HUI) has been retrospectively validated as the most reliable indicator of quantitative liver function corresponding to the ICG clearance test, with T1-relaxometry-based indices providing a better correlation than SI-based indices [122]. HUI has also been prospectively validated in patients with portal venous embolization for monitoring segmental liver function [121] and for identifying participants contraindicated for major hepatectomy (i.e., ICG $R_{15}$ > 20%) [139]. Gadoxetate MRI demonstrates post-stereotactic body


https://doi.org/10.3348/kjr.2021.0593

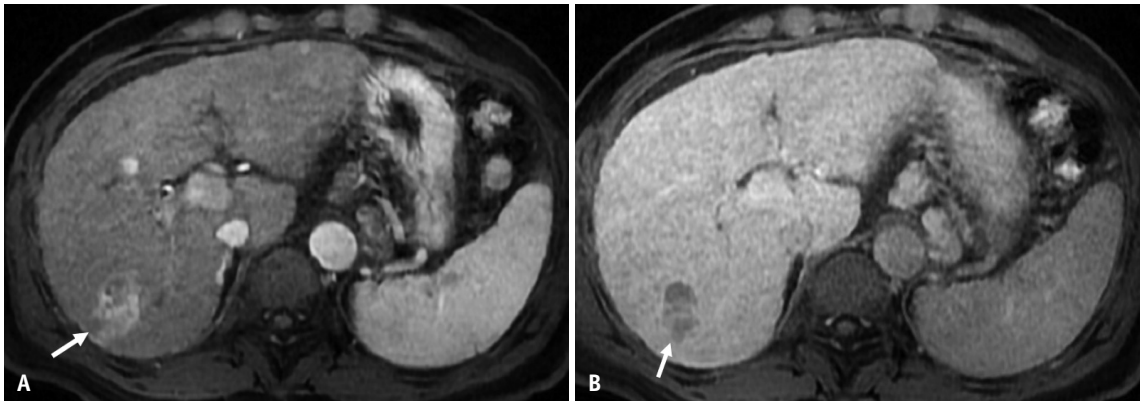


**Fig. 4. 55-year-old male with Child's B liver cirrhosis secondary to viral hepatitis B found to have HCC with MRI features that depict microvascular invasion.**
**A.** Axial fat-suppressed 3D gradient-recall echo image in the arterial phase showing a mass in segment 7, with peritumoral arterial phase hyperenhancement (arrow), rim-like enhancement, and non-smooth tumor margin. **B.** Axial image of the same lesion in the portal-venous phase shows corresponding peritumoral hypointensity (arrow). Histology confirmed HCC with microvascular invasion; the patient developed early recurrence of tumor 6.5 months following hepatic resection. HCC = hepatocellular carcinoma, 3D = three-dimensional

radiation therapy hepatic parenchymal changes as a relatively sharp SI gradient and could potentially determine the targeting accuracy [123].

Liver parenchymal SI on HBP gadoxetate MRI can also be used to predict post-hepatectomy liver failure (PHLF) [140]. Studies in this area are limited by small sample sizes due to the relatively low proportion of patients suffering from PHLF. Yamada et al. [126] were among the first to correlate HUI with the plasma disappearance rate of ICG (ICG-PDR). Remnant HUI (rHUI) and rHUI corrected for body weight have subsequently been shown to predict PHLF [128,130,132]. T1 relaxometry-based indices have also been shown to predict major complications after hepatectomy [131]. Prospective validation of the proposed models and development of automated techniques are desirable.

## CONCLUSIONS

Gadoxetate is a widely employed hepatocyte-specific MRI contrast agent with a favorable safety profile that combines the advantages of multiphasic MRI with functional uptake. The current literature alludes to the higher diagnostic accuracy that gadoxetate MRI confers over CT for the diagnosis of HCC; its advantage over ECCM is less certain.

Evolving evidence suggests that gadoxetate may improve treatment decision-making, thereby reducing disease recurrence and increasing patient survival. Limited data indicate some degree of cost-effectiveness, despite the higher cost of gadoxetate compared with ECCM in several Asian health systems. Newer applications of gadoxetate MRI are promising for determining HCC tumor biology and assessing non-tumorous liver function. Large prospective studies are necessary to address specific areas that would optimally define the use of gadoxetate MRI for the standard-of-care management of patients with HCC.

### Availability of Data and Material

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

### Conflicts of Interest

Ryosuke Tateishi has received lecture fees from Bayer AG. The remaining authors declare no potential conflicts of interest.

### Author Contributions

Conceptualization: Cher Heng Tan. Methodology: Cher Heng Tan. Supervision: Cher Heng Tan. Visualization: Cher Heng Tan. Writing—original draft: Cher Heng Tan. Writing—review & editing: Shu-cheng Chou, Nakarin Inmutto, Ke Ma, RuoFan Sheng, YingHong Shi, Zhongguo Zhou, Akira Yamada, Ryosuke Tateishi.

### ORCID iDs

Cher Heng Tan
https://orcid.org/0000-0003-3341-3111
Shu-cheng Chou
https://orcid.org/0000-0001-6468-9837
Nakarin Inmutto
https://orcid.org/0000-0002-5667-9986


https://doi.org/10.3348/kjr.2021.0593

Ke Ma
https://orcid.org/0000-0003-1436-3673
RuoFan Sheng
https://orcid.org/0000-0003-4215-9450
YingHong Shi
https://orcid.org/0000-0002-1833-8988
Zhongguo Zhou
https://orcid.org/0000-0002-1929-4278
Akira Yamada
https://orcid.org/0000-0002-4199-203X
Ryosuke Tateishi
https://orcid.org/0000-0003-3021-2517

### Funding Statement
The advisory board meeting received funding from Bayer AG.

### Acknowledgments
Medical writing assistance was provided by Bill Wolvey at Parexel, and was funded by Bayer AG.

## REFERENCES

1. Tamada T, Ito K, Sone T, Yamamoto A, Yoshida K, Kakuba K, et al. Dynamic contrast-enhanced magnetic resonance imaging of abdominal solid organ and major vessel: comparison of enhancement effect between Gd-EOB-DTPA and Gd-DTPA. *J Magn Reson Imaging* 2009;29:636-640
2. Davenport MS, Viglianti BL, Al-Hawary MM, Caoili EM, Kaza RK, Liu PS, et al. Comparison of acute transient dyspnea after intravenous administration of gadoxetate disodium and gadobenate dimeglumine: effect on arterial phase image quality. *Radiology* 2013;266:452-461
3. Huh J, Kim SY, Yeh BM, Lee SS, Kim KW, Wu EH, et al. Troubleshooting arterial-phase MR images of gadoxetate disodium-enhanced liver. *Korean J Radiol* 2015;16:1207-1215
4. Kim YN, Song JS, Moon WS, Hwang HP, Kim YK. Intra-individual comparison of hepatocellular carcinoma imaging features on contrast-enhanced computed tomography, gadopentetate dimeglumine-enhanced MRI, and gadoxetic acid-enhanced MRI. *Acta Radiol* 2018;59:639-648
5. Stocker D, Hectors S, Bane O, Vietti-Violi N, Said D, Kennedy P, et al. Dynamic contrast-enhanced MRI perfusion quantification in hepatocellular carcinoma: comparison of gadoxetate disodium and gadobenate dimeglumine. *Eur Radiol* 2021;31:9306-9315
6. Min JH, Kim JM, Kim YK, Cha DI, Kang TW, Kim H, et al. Magnetic resonance imaging with extracellular contrast detects hepatocellular carcinoma with greater accuracy than with gadoxetic acid or computed tomography. *Clin Gastroenterol Hepatol* 2020;18:2091-2100.e7
7. Kim DH, Choi SH, Byun JH, Kang JH, Lim YS, Lee SJ, et al. Arterial subtraction images of gadoxetate-enhanced MRI improve diagnosis of early-stage hepatocellular carcinoma. *J Hepatol* 2019;71:534-542
8. Endrikat JS, Dohanish S, Balzer T, Breuer JA. Safety of gadoxetate disodium: results from the clinical phase II-III development program and postmarketing surveillance. *J Magn Reson Imaging* 2015;42:634-643
9. Behzadi AH, Zhao Y, Farooq Z, Prince MR. Immediate allergic reactions to gadolinium-based contrast agents: a systematic review and meta-analysis. *Radiology* 2018;286:471-482
10. Cowling T, Frey N. *CADTH rapid response reports*. In: Cowling T, Frey N, eds. *Macrocyclic and linear gadolinium based contrast agents for adults undergoing magnetic resonance imaging: a review of safety*. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2019
11. Davenport MS, Caoili EM, Kaza RK, Hussain HK. Matched within-patient cohort study of transient arterial phase respiratory motion-related artifact in MR imaging of the liver: gadoxetate disodium versus gadobenate dimeglumine. *Radiology* 2014;272:123-131
12. Kim DW, Choi SH, Park T, Kim SY, Lee SS, Byun JH. Transient severe motion artifact on arterial phase in gadoxetic acid-enhanced liver magnetic resonance imaging: a systematic review and meta-analysis. *Invest Radiol* 2022;57:62-70
13. Namimoto T, Shimizu K, Nakagawa M, Kikuchi Y, Kidoh M, Oda S, et al. Reducing artifacts of gadoxetate disodium-enhanced MRI with oxygen inhalation in patients with prior episode of arterial phase motion: intra-individual comparison. *Clin Imaging* 2018;52:11-15
14. Ringe KI, von Falck C, Raatschen HJ, Wacker F, Hinrichs J. Evaluation of transient respiratory motion artifact at gadoxetate disodium-enhanced MRI-influence of different contrast agent application protocols. *PLoS One* 2018;13:e0200887
15. Song JS, Choi EJ, Park EH, Lee JH. Comparison of transient severe motion in gadoxetate disodium and gadopentetate dimeglumine-enhanced MRI: effect of modified breath-holding method. *Eur Radiol* 2018;28:1132-1139
16. Pietryga JA, Burke LM, Marin D, Jaffe TA, Bashir MR. Respiratory motion artifact affecting hepatic arterial phase imaging with gadoxetate disodium: examination recovery with a multiple arterial phase acquisition. *Radiology* 2014;271:426-434
17. Zech CJ, Ba-Ssalamah A, Berg T, Chandarana H, Chau GY, Grazioli L, et al. Consensus report from the 8th International Forum for Liver Magnetic Resonance Imaging. *Eur Radiol* 2020;30:370-382
18. Kitao A, Zen Y, Matsui O, Gabata T, Kobayashi S, Koda W, et al. Hepatocellular carcinoma: signal intensity at gadoxetic acid-enhanced MR Imaging--correlation with molecular transporters and histopathologic features. *Radiology* 2010;256:817-826
19. Li TT, An JX, Xu JY, Tuo BG. Overview of organic anion

transporters and organic anion transporter polypeptides and their roles in the liver. *World J Clin Cases* 2019;7:3915-3933
20. Fujita N, Nishie A, Asayama Y, Ishigami K, Ushijima Y, Kakihara D, et al. Hyperintense liver masses at hepatobiliary phase gadoxetic acid-enhanced MRI: imaging appearances and clinical importance. *Radiographics* 2020;40:72-94
21. Goodwin MD, Dobson JE, Sirlin CB, Lim BG, Stella DL. Diagnostic challenges and pitfalls in MR imaging with hepatocyte-specific contrast agents. *Radiographics* 2011;31:1547-1568
22. Kim AY, Kim YK, Lee MW, Park MJ, Hwang J, Lee MH, et al. Detection of hepatocellular carcinoma in gadoxetic acid-enhanced MRI and diffusion-weighted MRI with respect to the severity of liver cirrhosis. *Acta Radiol* 2012;53:830-838
23. Nakamura Y, Date S, Toyota N, Tani C, Honda Y, Komoto D, et al. Effect of lapatinib on hepatic parenchymal enhancement on gadoxetate disodium (EOB)-enhanced MRI scans. *J Comput Assist Tomogr* 2011;35:351-352
24. Okubo H, Ando H, Kokubu S, Miyazaki A, Watanabe S, Fujimura A. Polymorphisms in the organic anion transporting polypeptide genes influence liver parenchymal enhancement in gadoxetic acid-enhanced MRI. *Pharmacogenomics* 2013;14:1573-1582
25. Tsurusaki M, Sofue K, Isoda H, Okada M, Kitajima K, Murakami T. Comparison of gadoxetic acid-enhanced magnetic resonance imaging and contrast-enhanced computed tomography with histopathological examinations for the identification of hepatocellular carcinoma: a multicenter phase III study. *J Gastroenterol* 2016;51:71-79
26. Imai Y, Katayama K, Hori M, Yakushijin T, Fujimoto K, Itoh T, et al. Prospective comparison of Gd-EOB-DTPA-enhanced MRI with dynamic CT for detecting recurrence of HCC after radiofrequency ablation. *Liver Cancer* 2017;6:349-359
27. Kim JH, Min YW, Gwak GY, Paik YH, Choi MS, Lee JH, et al. The utility of gadoxetic acid-enhanced magnetic resonance imaging in the surveillance for postoperative recurrence of hepatocellular carcinoma. *Medicine (Baltimore)* 2016;95:e5666
28. Hanna RF, Miloushev VZ, Tang A, Finklestone LA, Brejt SZ, Sandhu RS, et al. Comparative 13-year meta-analysis of the sensitivity and positive predictive value of ultrasound, CT, and MRI for detecting hepatocellular carcinoma. *Abdom Radiol (NY)* 2016;41:71-90
29. 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
30. Semaan S, Vietti Violi N, Lewis S, Chatterji M, Song C, Besa C, et al. Hepatocellular carcinoma detection in liver cirrhosis: diagnostic performance of contrast-enhanced CT vs. MRI with extracellular contrast vs. gadoxetic acid. *Eur Radiol* 2020;30:1020-1030
31. Li J, Wang J, Lei L, Yuan G, He S. The diagnostic performance of gadoxetic acid disodium-enhanced magnetic resonance imaging and contrast-enhanced multi-detector computed tomography in detecting hepatocellular carcinoma: a meta-analysis of eight prospective studies. *Eur Radiol* 2019;29:6519-6528
32. Feng Z, Zhao H, Guan S, Wang W, Rong P. Diagnostic performance of MRI using extracellular contrast agents versus gadoxetic acid for hepatocellular carcinoma: a systematic review and meta-analysis. *Liver Int* 2021;41:1117-1128
33. Min JH, Kim JM, Kim YK, Kang TW, Lee SJ, Choi GS, et al. Prospective intraindividual comparison of magnetic resonance imaging with gadoxetic acid and extracellular contrast for diagnosis of hepatocellular carcinomas using the liver imaging reporting and data system. *Hepatology* 2018;68:2254-2266
34. Kierans AS, Makkar J, Guniganti P, Cornman-Homonoff J, Lee MJ, Pittman M, et al. Validation of liver imaging reporting and data system 2017 (LI-RADS) criteria for imaging diagnosis of hepatocellular carcinoma. *J Magn Reson Imaging* 2019;49:e205-e215
35. Lee S, Kim MJ, Kim SS, Shin H, Kim DY, Choi JY, et al. Retrospective comparison of EASL 2018 and LI-RADS 2018 for the noninvasive diagnosis of hepatocellular carcinoma using magnetic resonance imaging. *Hepatol Int* 2020;14:70-79
36. Paisant A, Vilgrain V, Riou J, Oberti F, Sutter O, Laurent V, et al. Comparison of extracellular and hepatobiliary MR contrast agents for the diagnosis of small HCCs. *J Hepatol* 2020;72:937-945
37. Byun J, Choi SH, Byun JH, Lee SJ, Kim SY, Won HJ, et al. Comparison of the diagnostic performance of imaging criteria for HCCs ≤ 3.0 cm on gadoxetate disodium-enhanced MRI. *Hepatol Int* 2020;14:534-543
38. Hwang SH, Park MS, Park S, Lim JS, Kim SU, Park YN. Comparison of the current guidelines for diagnosing hepatocellular carcinoma using gadoxetic acid-enhanced magnetic resonance imaging. *Eur Radiol* 2021;31:4492-4503
39. Jeon SK, Lee JM, Joo I, Yoo J, Park JY. Comparison of guidelines for diagnosis of hepatocellular carcinoma using gadoxetic acid-enhanced MRI in transplantation candidates. *Eur Radiol* 2020;30:4762-4771
40. Lee S, Kim SS, Chang DR, Kim H, Kim MJ. Comparison of LI-RADS 2018 and KLCA-NCC 2018 for noninvasive diagnosis of hepatocellular carcinoma using magnetic resonance imaging. *Clin Mol Hepatol* 2020;26:340-351
41. Lee SM, Lee JM, Ahn SJ, Kang HJ, Yang HK, Yoon JH. Diagnostic performance of 2018 KLCA-NCC practice guideline for hepatocellular carcinoma on gadoxetic acid-enhanced MRI in patients with chronic hepatitis B or cirrhosis: comparison with LI-RADS version 2018. *Korean J Radiol* 2021;22:1066-1076
42. Park SH, Shim YS, Kim B, Kim SY, Kim YS, Huh J, et al. Retrospective analysis of current guidelines for hepatocellular


https://doi.org/10.3348/kjr.2021.0593

carcinoma diagnosis on gadoxetic acid-enhanced MRI in at-risk patients. *Eur Radiol* 2021;31:4751-4763
43. Ding Y, Rao SX, Wang WT, Chen CZ, Li RC, Zeng M. Comparison of gadoxetic acid versus gadopentetate dimeglumine for the detection of hepatocellular carcinoma at 1.5 T using the liver imaging reporting and data system (LI-RADS v.2017). *Cancer Imaging* 2018;18:48
44. Zech CJ, Schwenke C, Endrikat J. Diagnostic efficacy and safety of gadoxetate disodium vs gadobenate dimeglumine in patients with known or suspected focal liver lesions: results of a clinical phase III study. *Magn Reson Insights* 2019;12:1178623x19827976
45. Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, et al. JSH consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 update by the Liver Cancer Study Group of Japan. *Liver Cancer* 2014;3:458-468
46. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int* 2017;11:317-370
47. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;69:182-236
48. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018;68:723-750
49. Zhou J, Sun HC, Wang Z, Cong WM, Wang JH, Zeng MS, et al. Guidelines for diagnosis and treatment of primary liver cancer in China (2017 edition). *Liver Cancer* 2018;7:235-260
50. Korean Liver Cancer Association, National Cancer Center. 2018 Korean Liver Cancer Association-National Cancer Center Korea practice guidelines for the management of hepatocellular carcinoma. *Gut Liver* 2019;13:227-299
51. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004;130:417-422
52. Yoon SK, Chun HG. Status of hepatocellular carcinoma in South Korea. *Chin Clin Oncol* 2013;2:39
53. Purcell Y, Copin P, Paulatto L, Pommier R, Vilgrain V, Ronot M. Hepatocellular carcinoma surveillance: Eastern and Western perspectives. *Ultrasonography* 2019;38:191-199
54. Choo SP, Tan WL, Goh BKP, Tai WM, Zhu AX. Comparison of hepatocellular carcinoma in Eastern versus Western populations. *Cancer* 2016;122:3430-3446
55. Kim TH, Kim SY, Tang A, Lee JM. Comparison of international guidelines for noninvasive diagnosis of hepatocellular carcinoma: 2018 update. *Clin Mol Hepatol* 2019;25:245-263
56. Korean Society of Abdominal Radiology. Diagnosis of hepatocellular carcinoma with gadoxetic acid-enhanced MRI: 2016 consensus recommendations of the Korean Society of Abdominal Radiology. *Korean J Radiol* 2017;18:427-443
57. Kokudo N, Takemura N, Hasegawa K, Takayama T, Kubo S, Shimada M, et al. Clinical practice guidelines for hepatocellular carcinoma: the Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. *Hepatol Res* 2019;49:1109-1113
58. Shao YY, Wang SY, Lin SM. Management consensus guideline for hepatocellular carcinoma: 2020 update on surveillance, diagnosis, and systemic treatment by the Taiwan Liver Cancer Association and the Gastroenterological Society of Taiwan. *J Formos Med Assoc* 2021;120:1051-1060
59. Torzilli G, Belghiti J, Kokudo N, Takayama T, Capussotti L, Nuzzo G, et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. *Ann Surg* 2013;257:929-937
60. Joo I, Lee JM, Lee DH, Jeon JH, Han JK. Retrospective validation of a new diagnostic criterion for hepatocellular carcinoma on gadoxetic acid-enhanced MRI: can hypointensity on the hepatobiliary phase be used as an alternative to washout with the aid of ancillary features? *Eur Radiol* 2019;29:1724-1732
61. Kim DH, Choi SH, Kim SY, Kim MJ, Lee SS, Byun JH. Gadoxetic acid–enhanced MRI of hepatocellular carcinoma: value of washout in transitional and hepatobiliary phases. *Radiology* 2019;291:651-657
62. Min JH, Kim YK, Sinn DH, Choi SY, Jeong WK, Lee WJ, et al. Adding ancillary features to enhancement patterns of hepatocellular carcinoma on gadoxetic acid-enhanced magnetic resonance imaging improves diagnostic performance. *Abdom Radiol (NY)* 2018;43:2309-2320
63. Zhou Y, Jing X, Zhang X, Ding J, Wang Y, Zhou H, et al. Combining the arterial phase of contrast-enhanced ultrasonography, gadoxetic acid-enhanced magnetic resonance imaging and diffusion-weighted imaging in the diagnosis of hepatic nodules ≤20 mm in patients with cirrhosis. *Ultrasound Med Biol* 2019;45:693-701
64. Kim YY, Park MS, Aljoqiman KS, Choi JY, Kim MJ. Gadoxetic acid-enhanced magnetic resonance imaging: hepatocellular carcinoma and mimickers. *Clin Mol Hepatol* 2019;25:223-233
65. Suh CH, Kim KW, Pyo J, Lee J, Kim SY, Park SH. Hypervascular transformation of hypovascular hypointense nodules in the hepatobiliary phase of gadoxetic acid–enhanced MRI: a systematic review and meta-analysis. *AJR Am J Roentgenol* 2017;209:781-789
66. Hwang JA, Kang TW, Kim YK, Kim SH, Paik YH, Ha SY, et al. Association between non-hypervascular hypointense nodules on gadoxetic acid-enhanced MRI and liver stiffness or hepatocellular carcinoma. *Eur J Radiol* 2017;95:362-369
67. Shimizu Y, Arai K, Yamashita T, Yamashita T, Shimakami T, Kawaguchi K, et al. Direct-acting antiviral agents reduce the risk of malignant transformation of hepatobiliary phase-hypointense nodule without arterial phase hyperenhancement to hepatocellular carcinoma on Gd-EOB-

DPTA-enhanced imaging in the hepatitis C virus-infected liver. *Liver Cancer* 2020;9:261-274
68. Toyoda H, Yasuda S, Shiota S, Sone Y, Maeda A, Kaneoka Y, et al. Pretreatment non-hypervascular hypointense nodules on Gd-EOB-DTPA-enhanced MRI as a predictor of hepatocellular carcinoma development after sustained virologic response in HCV infection. *Aliment Pharmacol Ther* 2021;53:1309-1316
69. Kim YS, Song JS, Lee HK, Han YM. Hypovascular hypointense nodules on hepatobiliary phase without T2 hyperintensity on gadoxetic acid-enhanced MR images in patients with chronic liver disease: long-term outcomes and risk factors for hypervascular transformation. *Eur Radiol* 2016;26:3728-3736
70. Kim HI, Jang JK, Lim J, Chang S, An J, Kang HJ, et al. Hepatocyte-specific magnetic resonance imaging-based assessment of indeterminate hepatic nodules in the liver transplant evaluation of patients with cirrhosis. *Liver Transpl* 2020;26:359-369
71. Joo I, Kim SY, Kang TW, Kim YK, Park BJ, Lee YJ, et al. Radiologic-pathologic correlation of hepatobiliary phase hypointense nodules without arterial phase hyperenhancement at gadoxetic acid–enhanced MRI: a multicenter study. *Radiology* 2020;296:335-345
72. Motosugi U. Treat or wait? Hepatobiliary phase hypointense nodule without arterial phase hyperenhancement. *Radiology* 2020;296:346-347
73. Lee DH, Lee JM, Lee JY, Kim SH, Kim JH, Yoon JH, et al. Non-hypervascular hepatobiliary phase hypointense nodules on gadoxetic acid-enhanced MRI: risk of HCC recurrence after radiofrequency ablation. *J Hepatol* 2015;62:1122-1130
74. Song KD, Rhim H, Lee MW, Kim YS, Kang TW. Intrahepatic distant recurrence after radiofrequency ablation for hepatocellular carcinoma: precursor nodules on pre-procedural gadoxetic acid-enhanced liver magnetic resonance imaging. *Acta Radiol* 2017;58:778-785
75. Lee DH, Lee JM, Yu MH, Hur BY, Yi NJ, Lee KW, et al. Non-hypervascular hepatobiliary phase hypointense nodules on gadoxetic acid-enhanced MR can help determine the treatment method for HCC. *Eur Radiol* 2019;29:3122-3131
76. Takeishi K, Yoshizumi T, Itoh S, Yugawa K, Yoshiya S, Toshima T, et al. Surgical indications for hepatocellular carcinoma with non-hypervascular hypointense nodules detected by Gd-EOB-DTPA-enhanced MRI. *Ann Surg Oncol* 2020;27:3344-3353
77. Kim TH, Woo S, Han S, Suh CH, Lee DH, Lee JM. Hepatobiliary phase hypointense nodule without arterial phase hyperenhancement: are they at risk of HCC recurrence after ablation or surgery? A systematic review and meta-analysis. *Eur Radiol* 2020;30:1624-1633
78. Park CJ, An C, Park S, Choi JY, Kim MJ. Management of subcentimetre arterially enhancing and hepatobiliary hypointense lesions on gadoxetic acid-enhanced MRI in patients at risk for HCC. *Eur Radiol* 2018;28:1476-1484
79. Jang KM, Kim SH, Kim YK, Choi D. Imaging features of subcentimeter hypointense nodules on gadoxetic acid-enhanced hepatobiliary phase MR imaging that progress to hypervascular hepatocellular carcinoma in patients with chronic liver disease. *Acta Radiol* 2015;56:526-535
80. Woo JH, Song KD, Kim SH. Subcentimeter hypervascular nodules with typical imaging findings of hepatocellular carcinoma on gadoxetic acid-enhanced MRI: outcomes of early treatment and watchful waiting. *Eur Radiol* 2017;27:4406-4414
81. Song KD, Lee MW, Rhim H, Kang TW, Cha DI, Sinn DH, et al. Percutaneous US/MRI fusion–guided radiofrequency ablation for recurrent subcentimeter hepatocellular carcinoma: technical feasibility and therapeutic outcomes. *Radiology* 2018;288:878-886
82. Naugler WE, Alsina AE, Frenette CT, Rossaro L, Sellers MT. Building the multidisciplinary team for management of patients with hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2015;13:827-835
83. Siddique O, Yoo ER, Perumpail RB, Perumpail BJ, Liu A, Cholankeril G, et al. The importance of a multidisciplinary approach to hepatocellular carcinoma. *J Multidiscip Healthc* 2017;10:95-100
84. Agarwal PD, Phillips P, Hillman L, Lucey MR, Lee F, Mezrich JD, et al. Multidisciplinary management of hepatocellular carcinoma improves access to therapy and patient survival. *J Clin Gastroenterol* 2017;51:845-849
85. Gaba RC, Kallwitz ER, Parvinian A, Bui JT, Von Roenn NM, Berkes JL, et al. Imaging surveillance and multidisciplinary review improves curative therapy access and survival in HCC patients. *Ann Hepatol* 2013;12:766-773
86. Serper M, Taddei TH, Mehta R, D'Addeo K, Dai F, Aytaman A, et al. Association of provider specialty and multidisciplinary care with hepatocellular carcinoma treatment and mortality. *Gastroenterology* 2017;152:1954-1964
87. Sinn DH, Choi GS, Park HC, Kim JM, Kim H, Song KD, et al. Multidisciplinary approach is associated with improved survival of hepatocellular carcinoma patients. *PLoS One* 2019;14:e0210730
88. Ricke J, Steffen IG, Bargellini I, Berg T, Bilbao Jaureguizar JI, Gebauer B, et al. Gadoxetic acid-based hepatobiliary MRI in hepatocellular carcinoma. *JHEP Rep* 2020;2:100173
89. 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
90. Yoo SH, Choi JY, Jang JW, Bae SH, Yoon SK, Kim DG, et al. Gd-EOB-DTPA-enhanced MRI is better than MDCT in decision making of curative treatment for hepatocellular carcinoma. *Ann Surg Oncol* 2013;20:2893-2900
91. Kim HD, Lim YS, Han S, An J, Kim GA, Kim SY, et al. Evaluation of early-stage hepatocellular carcinoma by magnetic resonance imaging with gadoxetic acid


https://doi.org/10.3348/kjr.2021.0593

detects additional lesions and increases overall survival. *Gastroenterology* 2015;148:1371-1382
92. Kakihara D, Nishie A, Harada N, Shirabe K, Tajima T, Asayama Y, et al. Performance of gadoxetic acid-enhanced MRI for detecting hepatocellular carcinoma in recipients of living-related-liver-transplantation: comparison with dynamic multidetector row computed tomography and angiography-assisted computed tomography. *J Magn Reson Imaging* 2014;40:1112-1120
93. Kang TW, Kong SY, Kang D, Kang MW, Kim YK, Kim SH, et al. Use of gadoxetic acid–enhanced liver MRI and mortality in more than 30 000 patients with hepatocellular carcinoma: a nationwide analysis. *Radiology* 2020;295:114-124
94. Kim DK, An C, Chung YE, Choi JY, Lim JS, Park MS, et al. Hepatobiliary versus extracellular MRI contrast agents in hepatocellular carcinoma detection: hepatobiliary phase features in relation to disease-free survival. *Radiology* 2019;293:594-604
95. Kim AY, Sinn DH, Jeong WK, Kim YK, Kang TW, Ha SY, et al. Hepatobiliary MRI as novel selection criteria in liver transplantation for hepatocellular carcinoma. *J Hepatol* 2018;68:1144-1152
96. Lee S, Kim KW, Jeong WK, Kim MJ, Choi GH, Choi JS, et al. Gadoxetic acid-enhanced MRI as a predictor of recurrence of HCC after liver transplantation. *Eur Radiol* 2020;30:987-995
97. Cha DI, Jang KM, Kim SH, Kim YK, Kim H, Ahn SH. Preoperative prediction for early recurrence can be as accurate as postoperative assessment in single hepatocellular carcinoma patients. *Korean J Radiol* 2020;21:402-412
98. Kang TW, Rhim H, Lee J, Song KD, Lee MW, Kim YS, et al. Magnetic resonance imaging with gadoxetic acid for local tumour progression after radiofrequency ablation in patients with hepatocellular carcinoma. *Eur Radiol* 2016;26:3437-3446
99. Simmons O, Fetzer DT, Yokoo T, Marrero JA, Yopp A, Kono Y, et al. Predictors of adequate ultrasound quality for hepatocellular carcinoma surveillance in patients with cirrhosis. *Aliment Pharmacol Ther* 2017;45:169-177
100. Kim SY, An J, Lim YS, Han S, Lee JY, Byun JH, et al. MRI with liver-specific contrast for surveillance of patients with cirrhosis at high risk of hepatocellular carcinoma. *JAMA Oncol* 2017;3:456-463
101. Besa C, Lewis S, Pandharipande PV, Chhatwal J, Kamath A, Cooper N, et al. Hepatocellular carcinoma detection: diagnostic performance of a simulated abbreviated MRI protocol combining diffusion-weighted and T1-weighted imaging at the delayed phase post gadoxetic acid. *Abdom Radiol (NY)* 2017;42:179-190
102. Kim HL, An J, Park JA, Park SH, Lim YS, Lee EK. Magnetic resonance imaging is cost-effective for hepatocellular carcinoma surveillance in high-risk patients with cirrhosis. *Hepatology* 2019;69:1599-1613
103. Nishie A, Goshima S, Haradome H, Hatano E, Imai Y, Kudo M, et al. Cost-effectiveness of EOB-MRI for hepatocellular carcinoma in Japan. *Clin Ther* 2017;39:738-750.e4
104. Lee JM, Kim MJ, Phongkitkarun S, Sobhonslidsuk A, Holtorf AP, Rinde H, et al. Health economic evaluation of Gd-EOB-DTPA MRI vs ECCM-MRI and multi-detector computed tomography in patients with suspected hepatocellular carcinoma in Thailand and South Korea. *J Med Econ* 2016;19:759-768
105. Suh CH, Kim KW, Park SH, Kim SY, Woo DC, Shin S, et al. Performing gadoxetic acid-enhanced MRI after CT for guiding curative treatment of early-stage hepatocellular carcinoma: a cost-effectiveness analysis. *AJR Am J Roentgenol* 2018;210:W63-W69
106. He X, Wu J, Holtorf AP, Rinde H, Xie S, Shen W, et al. Health economic assessment of Gd-EOB-DTPA MRI versus ECCM-MRI and multi-detector CT for diagnosis of hepatocellular carcinoma in China. *PLoS One* 2018;13:e0191095
107. An C, Kim DW, Park YN, Chung YE, Rhee H, Kim MJ. Single hepatocellular carcinoma: preoperative MR imaging to predict early recurrence after curative resection. *Radiology* 2015;276:433-443
108. Lee S, Kim SH, Lee JE, Sinn DH, Park CK. Preoperative gadoxetic acid-enhanced MRI for predicting microvascular invasion in patients with single hepatocellular carcinoma. *J Hepatol* 2017;67:526-534
109. Chen J, Chen C, Xia C, Huang Z, Zuo P, Stemmer A, et al. Quantitative free-breathing dynamic contrast-enhanced MRI in hepatocellular carcinoma using gadoxetic acid: correlations with Ki67 proliferation status, histological grades, and microvascular density. *Abdom Radiol (NY)* 2018;43:1393-1403
110. Choi SY, Kim SH, Park CK, Min JH, Lee JE, Choi YH, et al. Imaging features of gadoxetic acid-enhanced and diffusion-weighted MR imaging for identifying cytokeratin 19-positive hepatocellular carcinoma: a retrospective observational study. *Radiology* 2018;286:897-908
111. Hu HT, Shen SL, Wang Z, Shan QY, Huang XW, Zheng Q, et al. Peritumoral tissue on preoperative imaging reveals microvascular invasion in hepatocellular carcinoma: a systematic review and meta-analysis. *Abdom Radiol (NY)* 2018;43:3324-3330
112. Ahn SJ, Kim JH, Park SJ, Kim ST, Han JK. Hepatocellular carcinoma: preoperative gadoxetic acid-enhanced MR imaging can predict early recurrence after curative resection using image features and texture analysis. *Abdom Radiol (NY)* 2019;44:539-548
113. Dong Z, Huang K, Liao B, Cai H, Dong Y, Huang M, et al. Prediction of sorafenib treatment-related gene expression for hepatocellular carcinoma: preoperative MRI and histopathological correlation. *Eur Radiol* 2019;29:2272-2282
114. Kim S, Shin J, Kim DY, Choi GH, Kim MJ, Choi JY. Radiomics on gadoxetic acid–enhanced magnetic resonance imaging for prediction of postoperative early and late recurrence of single hepatocellular carcinoma. *Clin Cancer Res*

 https://doi.org/10.3348/kjr.2021.0593 

2019;25:3847-3855
115. Chen J, Wu Z, Xia C, Jiang H, Liu X, Duan T, et al. Noninvasive prediction of HCC with progenitor phenotype based on gadoxetic acid-enhanced MRI. *Eur Radiol* 2020;30:1232-1242
116. Min JH, Lee MW, Park HS, Lee DH, Park HJ, Lim S, et al. Interobserver variability and diagnostic performance of gadoxetic acid-enhanced MRI for predicting microvascular invasion in hepatocellular carcinoma. *Radiology* 2020;297:573-581
117. Hong SB, Choi SH, Kim SY, Shim JH, Lee SS, Byun JH, et al. MRI features for predicting microvascular invasion of hepatocellular carcinoma: a systematic review and meta-analysis. *Liver Cancer* 2021;10:94-106
118. Lee S, Kang TW, Song KD, Lee MW, Rhim H, Lim HK, et al. Effect of microvascular invasion risk on early recurrence of hepatocellular carcinoma after surgery and radiofrequency ablation. *Ann Surg* 2021;273:564-571
119. Rhee H, Cho ES, Nahm JH, Jang M, Chung YE, Baek SE, et al. Gadoxetic acid-enhanced MRI of macrotrabecular-massive hepatocellular carcinoma and its prognostic implications. *J Hepatol* 2021;74:109-121
120. Song L, Li J, Luo Y. The importance of a nonsmooth tumor margin and incomplete tumor capsule in predicting HCC microvascular invasion on preoperative imaging examination: a systematic review and meta-analysis. *Clin Imaging* 2021;76:77-82
121. Geisel D, Raabe P, Lüdemann L, Malinowski M, Stockmann M, Seehofer D, et al. Gd-EOB-DTPA-enhanced MRI for monitoring future liver remnant function after portal vein embolization and extended hemihepatectomy: a prospective trial. *Eur Radiol* 2017;27:3080-3087
122. Haimerl M, Verloh N, Zeman F, Fellner C, Nickel D, Lang SA, et al. Gd-EOB-DTPA-enhanced MRI for evaluation of liver function: comparison between signal-intensity-based indices and T1 relaxometry. *Sci Rep* 2017;7:43347
123. Jung J, Kim H, Yoon SM, Cho B, Kim YJ, Kwak J, et al. Targeting accuracy of image-guided stereotactic body radiation therapy for hepatocellular carcinoma in real-life clinical practice: in vivo assessment using hepatic parenchymal changes on Gd-EOB-DTPA-enhanced magnetic resonance images. *Int J Radiat Oncol Biol Phys* 2018;102:867-874
124. Rassam F, Zhang T, Cieslak KP, Lavini C, Stoker J, Bennink RJ, et al. Comparison between dynamic gadoxetate-enhanced MRI and 99mTc-mebrofenin hepatobiliary scintigraphy with SPECT for quantitative assessment of liver function. *Eur Radiol* 2019;29:5063-5072
125. Ryeom HK, Kim SH, Kim JY, Kim HJ, Lee JM, Chang YM, et al. Quantitative evaluation of liver function with MRI using Gd-EOB-DTPA. *Korean J Radiol* 2004;5:231-239
126. Yamada A, Hara T, Li F, Fujinaga Y, Ueda K, Kadoya M, et al. Quantitative evaluation of liver function with use of gadoxetate disodium-enhanced MR imaging. *Radiology* 2011;260:727-733
127. Asenbaum U, Kaczirek K, Ba-Ssalamah A, Ringl H, Schwarz C, Waneck F, et al. Post-hepatectomy liver failure after major hepatic surgery: not only size matters. *Eur Radiol* 2018;28:4748-4756
128. Kim DK, Choi JI, Choi MH, Park MY, Lee YJ, Rha SE, et al. Prediction of posthepatectomy liver failure: MRI with hepatocyte-specific contrast agent versus indocyanine green clearance test. *AJR Am J Roentgenol* 2018;211:580-587
129. Bastati N, Beer L, Mandorfer M, Poetter-Lang S, Tamandl D, Bican Y, et al. Does the functional liver imaging score derived from gadoxetic acid-enhanced MRI predict outcomes in chronic liver disease? *Radiology* 2020;294:98-107
130. Tsujita Y, Sofue K, Komatsu S, Yamaguchi T, Ueshima E, Ueno Y, et al. Prediction of post-hepatectomy liver failure using gadoxetic acid-enhanced magnetic resonance imaging for hepatocellular carcinoma with portal vein invasion. *Eur J Radiol* 2020;130:109189
131. Huang M, Shen S, Cai H, Peng Z, Chiu WHK, Li ZP, et al. Regional liver function analysis with gadoxetic acid-enhanced MRI and virtual hepatectomy: prediction of postoperative short-term outcomes for HCC. *Eur Radiol* 2021;31:4720-4730
132. Notake T, Shimizu A, Kubota K, Ikehara T, Hayashi H, Yasukawa K, et al. Hepatocellular uptake index obtained with gadoxetate disodium-enhanced magnetic resonance imaging in the assessment future liver remnant function after major hepatectomy for biliary malignancy. *BJS Open* 2021;5:zraa048
133. Yoneda N, Matsui O, Kitao A, Kozaka K, Gabata T, Sasaki M, et al. Beta-catenin-activated hepatocellular adenoma showing hyperintensity on hepatobiliary-phase gadoxetic-enhanced magnetic resonance imaging and overexpression of OATP8. *Jpn J Radiol* 2012;30:777-782
134. Mailey B, Artinyan A, Khalili J, Denitz J, Sanchez-Luege N, Sun CL, et al. Evaluation of absolute serum α-fetoprotein levels in liver transplant for hepatocellular cancer. *Arch Surg* 2011;146:26-33
135. Choi JW, Lee JM, Kim SJ, Yoon JH, Baek JH, Han JK, et al. Hepatocellular carcinoma: imaging patterns on gadoxetic acid-enhanced MR Images and their value as an imaging biomarker. *Radiology* 2013;267:776-786
136. Kitao A, Matsui O, Yoneda N, Kozaka K, Kobayashi S, Sanada J, et al. Hepatocellular carcinoma with β-catenin mutation: imaging and pathologic characteristics. *Radiology* 2015;275:708-717
137. An C, Kim MJ. Imaging features related with prognosis of hepatocellular carcinoma. *Abdom Radiol (NY)* 2019;44:509-516
138. de Graaf W, Häusler S, Heger M, van Ginhoven TM, van Cappellen G, Bennink RJ, et al. Transporters involved in the hepatic uptake of (99m)Tc-mebrofenin and indocyanine green. *J Hepatol* 2011;54:738-745
139. Yoon JH, Lee JM, Kang HJ, Ahn SJ, Yang H, Kim E, et al.


https://doi.org/10.3348/kjr.2021.0593

Quantitative assessment of liver function by using gadoxetic acid–enhanced MRI: hepatocyte uptake ratio. *Radiology* 2019;290:125-133

140. Cho SH, Kang UR, Kim JD, Han YS, Choi DL. The value of gadoxetate disodium-enhanced MR imaging for predicting posthepatectomy liver failure after major hepatic resection: a preliminary study. *Eur J Radiol* 2011;80:e195-e200


https://doi.org/10.3348/kjr.2021.0593