REVIEW

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Insight into hepatocellular carcinoma biology with gadoxetate disodium-enhanced MRI

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Practice Points

- Gadoxetate disodium is a molecular imaging magnetic resonance contrast agent that targets OATP8 receptors on functioning hepatocytes.
- Gadoxetate disodium-enhanced MRI provides information not only on vascularity, but also on hepatocellular function.
- Emerging evidence suggests that gadoxetate disodium-enhanced MRI improves the detection of small progressed hepatocellular carcinomas (HCCs), early HCCs, and helps to differentiate HCCs from intrahepatic arterio-portal shunts.
- Preliminary observations suggest that gadoxetate disodium-enhanced MRI shows promise for predicting tumor grade, tumor origin, microvascular invasion, future hypervascularization and post-treatment recurrence.
- To date, most clinical research studies have been single center and retrospective, and they have been performed mainly in patients without advanced cirrhosis. Prospective studies in patients with advanced cirrhosis are needed.
- Many biological and technical factors may confound the quality and interpretation of gadoxetate disodium-enhanced MRI. Further research is needed to better understand and correct for these confounding factors.
- With further research and validation, gadoxetate disodium-enhanced MRI may alter the algorithmic pathway for diagnosis and management of patients with HCC.

SUMMARY The current algorithm for the imaging diagnosis of hepatocellular carcinoma accurately detects large, progressed tumors displaying the classical imaging features of arterial hyperenhancement with 'washout' and/or 'capsule' appearance. Liver MRI with the relatively newer hepatobiliary agent, gadoxetate disodium, provides information on hepatocellular function in addition to vascularity, facilitates detection of small progressed tumors, as well as early/vaguely nodular tumors, and shows promise for characterizing

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hepatocellular carcinoma biology. Prediction of tumor grade, presence of biliary and stem cell markers, microvascular invasion, future hypervascularization and post-treatment recurrence have all been studied with gadoxetate disodium-enhanced MRI with encouraging results. Incorporation of gadoxetate disodium-enhanced MRI into standard diagnostic and management algorithms will likely unfold in the future.

Hepatocellular carcinoma (HCC) arises most commonly in the setting of chronic liver disease with hepatocarcinogenesis attributed to either a multistep progression of successively more advanced lesions (low-grade dysplastic nodule [LGDN], high-grade dysplastic nodule [HGDN], early HCC and progressed HCC) or *de novo* development of overt carcinoma without evolving through histologically distinct precursor lesions [1–4]. The transition from a primary portal venous blood supply to an unpaired (or nontriadal) arterial supply during hepatocarcinogenesis is largely responsible for the well-documented features of arterial hyperenhancement and ‘washout appearance’ on dynamic contrast-enhanced imaging in progressed HCCs [5–7]. In addition, progressed HCCs frequently display a delayed enhancing rim, referred to as a ‘capsule’ or capsule appearance [8,9]. While these features may be present on both dynamic contrast-enhanced computed tomography (CT) and MRI, studies in academic centers have shown superior detection and characterization of hepatic nodules and HCC with MRI [10–22]. However, the comparative performance of CT and MRI in the community setting has not yet been studied.

The hallmark features of arterial enhancement and ‘washout’ appearance on dynamic contrast-enhanced MRI are sufficient for the imaging diagnosis of HCC nodules greater than 1 cm in patients at risk for HCC (from cirrhosis or other factors) according to the 2011 update of the American Association for the Study of Liver Disease (AASLD) HCC practice guidelines [23]. According to these guidelines, histologic diagnosis is only required if a suspicious imaging-detected nodule does not display these typical imaging features. Recent concern in the transplant community regarding appropriate allocation of the limited available livers has led to a more stringent diagnostic algorithm advocated by the Organ Procurement and Transplantation Network (OPTN) and United Network for Organ Sharing (UNOS) [24]. Similarly, the American College of Radiology (ACR) recognized the need for a standardized imaging lexicon and

diagnostic algorithm for HCC and released the Liver Imaging Reporting and Data System (LI-RADS) in 2011, recently updated in 2013 [101]. Both OPTN/UNOS and the updated version of LI-RADS are congruent for the diagnosis of HCC >2 cm (arterial hyperenhancement and at least one additional major feature: washout appearance, capsule appearance or threshold growth). Nodules between 1 and 2 cm must demonstrate arterial hyperenhancement and at least two additional major features to meet criteria for diagnosis. The more stringent criteria advocated by OPTN/UNOS and LI-RADS provide a higher level of specificity for the imaging diagnosis of HCC; however, this comes necessarily at the expense of lower sensitivity, especially for small HCC [25].

The above imaging algorithms for HCC have been developed for the use of extracellular contrast agents with CT and MRI. Unlike hepatobiliary agents, extracellular agents are distributed solely within the vascular and interstitial spaces and are primarily excreted through the urine. While extracellular agents allow reliable depiction of dynamic enhancement patterns for many liver lesions, including most large progressed HCCs, they may fail for most early (vaguely nodular) HCCs and many small progressed HCCs, which frequently lack one or more typical imaging features (Figure 1) [26].

Compared with extracellular contrast agents, the hepatobiliary contrast agent gadoxetate disodium allows for additional imaging during a prolonged hepatobiliary phase that peaks at approximately 20 min and can improve lesion detection and characterization [27–30]. Approximately 50% of the administered dose of gadoxetate disodium is excreted by the liver [31]. MRI with this contrast agent provides information on hepatocellular function in addition to vascularity, facilitates detection of small progressed tumors as well as early (vaguely nodular) tumors, and shows promise for characterizing HCC biology. This review discusses the emerging roles of gadoxetate disodium-enhanced MRI for the aforementioned lesions, as well as its potential role for characterizing tumor biology.

Gadoxetate disodium overview

Gadoxetate disodium is an ionic linear gadolinium-based contrast agent with a lipophilic ethoxybenzyl (EOB) moiety that allows for hepatocyte uptake. *In vitro* animal studies have shown that gadoxetate disodium is selectively transported into hepatocytes from the plasma by liver-specific multidrug organic anion-transporting polypeptides (OATP1B1/B3; also known as OATP8) on the sinusoidal membrane of hepatocytes, as well as the Na⁺/taurocholatesco transporting polypeptide (NTCP) [32–35]. Gadoxetate disodium is then excreted into the bile ducts via multidrug resistance protein 2 (MRP2) on the canalicular membrane [32–34,36] and back into the sinusoidal space by MRP3. The regulation of these cell surface transporters is complex and may be altered in the setting of cholestasis, inflammation and fibrosis. Likewise, endogenous compounds and drugs may compete for uptake potentially altering the degree of gadoxetate disodium uptake and subsequent parenchyma enhancement [37–40]. While these transporters are present in normal hepatocytes (including hepatocytes in cirrhotic nodules and in most dysplastic nodules), they are usually underexpressed or lacking in HCCs and in nonhepatocellular lesions, and therefore appear hypointense (dark) in the hepatobiliary phase, while nonneoplastic background hepatic parenchyma (composed of functioning hepatocytes) is hyperintense (bright) [30,41,42].

Analogous to extracellular contrast agents, gadoxetate disodium initially distributes within the vascular interstitial space, allowing for dynamic contrast enhancement in the first minutes after injection. Standard postcontrast liver MRI with gadoxetate disodium consists of late arterial phase (defined as contrast in the hepatic artery, portal veins and absent in the hepatic veins), portal venous phase (approximately 60–80 s after injection) and transitional phase (120–180 s after injection) [24]. Gadoxetate disodium acts as an extracellular agent until approximately 1–2 min following injection, permitting diagnosis of larger progressed HCCs based on the typical features discussed earlier. Subsequently, there is progressive uptake of the agent by hepatocytes, resulting in strong parenchymal enhancement that peaks at approximately 20 min after injection [43,44] in parallel with progressive clearance from the plasma and interstitial space. Owing to the overlap in the dynamic and hepatobiliary phases of gadoxetate

Figure 1. 61-year-old male with chronic hepatitis C viral infection. Multiple axial magnetic resonance images through the liver with an extracellular contrast agent (top row) and with gadoxetate disodium (bottom row) demonstrating (A) a hypervascular tumor nodule (arrow) on arterial phase imaging that (B) retains contrast on the portal venous phase, and (C) blends in to background liver on the late dynamic phase (5 min). A similar dynamic enhancement pattern is seen with gadoxetate disodium-enhanced MRI on (D) arterial and (E) portal venous phase imaging, although (F) transitional phase (5 min) and hepatobiliary-phase ((G) 15 min; (H) 20 min) imaging demonstrate increased conspicuity with time. The nodule cannot be diagnosed as HCC based on the images enhanced with the extracellular agent, but it is highly suspicious for HCC based on its hypointensity in the hepatobiliary phase after gadoxetate disodium injection.

disodium enhancement, some authors suggest the term transitional phase to describe the time period between 120 and 300 s after injection [45].

The addition of the hepatobiliary phase to the standard dynamic imaging protocol provides supplementary information on hepatocellular function, which has been shown to improve lesion detection, conspicuity and characterization, as well as increase radiologists' diagnostic confidence [27,28,30]. The added value of gadoxetate disodium and hepatobiliary imaging will be discussed in the following sections with special interest paid to the more challenging cirrhosis-associated hepatocellular lesions.

Small progressed (distinctly nodular) HCC

Small HCC is defined as being less than 2 cm in diameter per the 1995 International Working Group Consensus [3]. Some small HCCs have a distinctly nodular morphology, show expansile growth, often consist of moderately differentiated malignant cells, are frequently encapsulated, have a rich intranodular network of tumoral neoarteries and are considered to be biologically progressed lesions with the ability to invade vessels and metastasize [46]. At dynamic imaging, these small progressed lesions may manifest the classical imaging features of HCC (arterial hyperenhancement, washout appearance and capsule

appearance). These features have been attributed to lesional neoarterialization, reduced portal venous blood supply, tumor capsule formation and other factors [4,46,47].

While some small progressed HCCs manifest these features and can be diagnosed at dynamic CT or MRI with extracellular agents, approximately half do not exhibit a washout or capsule appearance at imaging and therefore cannot be diagnosed definitively with extracellular agents [20]. The lack of sensitivity of extracellular agents for small progressed HCC is a major limitation of these agents and a critical obstacle to optimal management of patients with or at risk for HCC. The additional information provided by hepatobiliary-phase imaging may help address this problem. Specifically, hypointense lesional signal in the hepatobiliary phase indicates underexpression of OATP and in conjunction with arterial hyperenhancement strongly suggests the diagnosis of HCC, even in the absence of washout or capsule appearance (Figure 2) [20,27,48].

In addition, it should be emphasized that most small hypervascular observations depicted at dynamic CT and MRI in the chronically diseased liver are not HCCs but rather benign vascular pseudolesions attributed to arterioportal shunts and other focal perfusion alterations. Differentiation of HCC from vascular pseudolesions is of critical importance but can be challenging with extracellular agents. The addition of the hepatobiliary phase helps in this differentiation: most HCCs appear hypointense due to underexpression of OATP, while

pseudolesions generally appear isointense to background liver due to preserved expression (Figure 3) [21,49,50].

Early (vaguely nodular) HCC

In contrast to small progressed HCC, early HCCs have a vaguely nodular morphology, are unencapsulated, consist of well-differentiated neoplastic cells, and have incompletely developed neoarterialization [4,46]. Early HCC is essentially a low-grade incipient tumor that maintains its portal venous blood supply, does not invade vessels and rarely, if ever, metastasizes [46]. In recent radiology studies, most early HCCs demonstrate arterial phase iso-enhancement or hypoenhancement, and many show no evidence of washout appearance [12,20,51]. Therefore, early HCC nodules usually do not meet strict criteria for the diagnosis of HCC (LI-RADS and OPTN/UNOS) at CT or MRI with extracellular agents [24].

Multiple recent studies have shown that gadoxetate disodium-enhanced MRI improves sensitivity for diagnosis of isovascular or hypovascular early HCCs that would be missed or seen only as nonspecific hypoenhancing nodules with conventional dynamic contrast techniques [12,20,48,51]. In a study by Sano *et al.*, nearly all (29 out of 30) surgically removed early HCCs demonstrated hypointense signal on hepatobiliary-phase imaging, with the majority of these nodules being isovascular or hypovascular in the arterial phase [20]. However, an isovascular or hypovascular nodule with hepatobiliary-phase hypointensity is not pathognomonic for early HCC, as HGDNs and even LGDNs may have a similar imaging appearance [48]. Thus, while gadoxetate disodium-enhanced MRI provides a powerful new capability to detect early HCCs, the imaging appearance of early HCC and non-malignant precursor nodules may overlap, and further research is needed to identify and validate discriminatory imaging features.

Tumor biology

Beyond diagnosis of HCC, an emerging role of gadoxetate disodium-enhanced MRI is characterizing key biological features with management and prognostic implications.

■ Tumor grade

An important primary predictor of postoperative recurrence of HCC is the histologic tumor grade [52,53]. Several retrospective analyses have correlated the degree of hepatobiliary-phase nodule

Figure 2. Small hepatocellular carcinoma in a 73-year-old male with chronic hepatitis C cirrhosis. Small hepatocellular carcinoma nodule (arrows) demonstrating (A) arterial phase hyperenhancement, (B) some peripheral contrast retention on portal venous phase imaging with central hypointensity, with (C) progressively more hypointense signal on transitional and (D) hepatobiliary-phase imaging. Hepatobiliary-phase hypointensity is essential in this case for a presumptive diagnosis of hepatocellular carcinoma. Note the background of cirrhosis with multiple regenerating nodules retaining contrast (appearing as hyperintense) separated by hypointense fibrotic reticulations, which are best depicted on hepatobiliary-phase imaging.

enhancement with tumor grade [54–56]. Kogita *et al.* analyzed 83 nodules (dysplastic nodules, well-differentiated, moderately differentiated and poorly differentiated HCCs) and calculated the enhancement ratios of tumor nodules relative to surrounding non-tumoral liver [54]. Their results demonstrate progressively lower tumor enhancement in the hepatobiliary phase with increasing tumor grade, although statistical significance was not achieved for moderately or poorly differentiated HCCs. Kim *et al.* discovered similar findings of decreasing signal intensity with higher tumor grade in 122 HCCs [57]. However, these findings were not applicable to patients with impaired liver function (i.e., Child–Pugh class B and C). Both authors used ratios to assess enhancement in the hepatobiliary phase. These include pre- and post-contrast intensity ratios (signal intensity of nodule/signal intensity of the adjacent nontumoral liver) and enhancement ratios of the nodule itself (post-/pre-contrast).

The ability to distinguish dysplastic nodules, well-differentiated HCC, and moderately or poorly differentiated HCC on hepatobiliary-phase imaging has been attributed to the progressive reduction in the expression of the uptake transporter OATP8 during hepatocarcinogenesis [58]. The downregulation of OATP8, in turn, is thought to be due to increased expression of various hepatic nuclear factors.

Further work is needed, if global applicability is to be obtained, to reproduce [59], prospectively study and standardize how hepatobiliary-phase enhancement is measured, especially in patients with more advanced fibrotic liver disease (i.e., Child–Pugh class B and C), in which impaired uptake by background fibrotic liver disease may confound analysis of nodule enhancement.

■ Tumors of stem cell origin

Most HCCs are believed to arise from progressive dedifferentiation of initially mature hepatocytes [46,60], but some cancers may arise from hepatic progenitor cells, which express tumor markers such as cytokeratin 19 (CK19) and epithelial cell adhesion molecule (EpCAM), among others [61,62]. In a recent study, Jeong and colleagues correlated preoperative gadoxetate disodium-enhanced MRI features with post-resection histological and immunochemical findings in 71 HCC nodules from 63 patients [62]. The investigators observed that, compared with HCCs without such markers, HCCs

Figure 3. Benign pseudolesions and hepatocellular carcinoma. (A) Small peripheral wedge-shaped arterial enhancing foci (arrows) that blend into background liver parenchyma on (B) portal venous and (C) late dynamic phase imaging with an extracellular contrast agent. (D) Follow-up gadoxetate disodium-enhanced MRI demonstrates no abnormal uptake in segment VIII to correspond to the previously enhancing nodules (arrows). Hepatobiliary-phase imaging permits the identification of an isovascular, hypointense nodule (arrowhead) in segment VII, occult on prior dynamic vascular imaging with an extracellular agent and on (E) T2-weighted images. Gadoxetate disodium-enhanced MRI improves differentiation of hypervascular pseudolesions from hypervascular hepatocellular carcinoma – the former are isointense in the hepatobiliary phase due to preserved OATP expression in benign hepatocytes within the parenchyma affected by the perfusion alteration; the latter are hypointense in the hepatobiliary phase due to underexpression of OATP in malignant hepatocytes.

expressing stem cell markers had lower signal intensity in the hepatobiliary phase as well as atypical HCC dynamic enhancement patterns (i.e., progressive enhancement), a feature which is more commonly seen in the intrahepatic mass forming variant of cholangiocarcinoma. They ascribed biliary dedifferentiation as a potential cause for the atypical contrast enhancement dynamics, and suggested downregulation of OATP receptor expression in tumors expressing stem cell markers as a cause for the loss in signal intensity on hepatobiliary-phase imaging. Although in its infancy, the ability to identify tumors expressing progenitor cell markers is a potentially valuable tool as these tumors demonstrate a poorer prognosis [63].

■ Microvascular tumor invasion

Microvascular invasion of HCC is a known prognostic factor that can predict worse outcomes in patients after definitive surgical therapy (i.e., hepatectomy or transplantation) [64]. Although macroscopic tumor invasion can often be identified on contrast-enhanced cross-sectional imaging, microvascular tumor invasion is inherently more difficult if not impossible to detect since the involved vessels are too small to be directly visualized *in vivo*

with current imaging technology. Ariizumi *et al.* recently described a non-smooth tumor margin on hepatobiliary-phase imaging as a significant predictor of microscopic portal vein invasion and early post-resection recurrence [65]. Another study by Kim *et al.* demonstrated the ability of peritumoral hypointensity on hepatobiliary-phase imaging to predict microvascular invasion with a positive predictive value of 88.5% [66]. They surmised that perilesional perfusion changes due to microvascular tumor invasion affect hepatocyte function and, thus, result in abnormal expression of OATP8 or MRP2 receptors, affecting uptake of gadoxetate disodium. These promising early results, if validated in prospective studies, suggest that gadoxetate disodium-enhanced MRI may provide added value for treatment planning and prognostication.

■ Prediction of nodule hypervascularization

The arterialization of tumor nodules relies on the development of unpaired or nontriadal arteries supplying a progressed tumor, resulting in hypervascularity on cross-sectional late arterial phase imaging [46,60]. However, as described earlier, hepatocarcinogenesis begins prior to this phenomenon. Multiple recent studies with gadoxetate disodium-enhanced MRI have shown promise for identification of high-risk hypovascular or isovascular nodules prior to their progression into overt HCC. Higaki *et al.* demonstrated that 24 out of 76 initially non-hypervascular high-risk nodules (nodules that are hypointense on hepatobiliary-phase imaging) converted to hypervascularity within 6 months (median observation period of 186 days) [67]. Similarly, other authors have reported hypervascularization of high-risk nodules within 6–24 months, with all studies demonstrating increasing risk with increasing nodule size (i.e., greater than 10 or 15 mm) [68–71]. Preliminary observations suggest that some ancillary imaging features (such as T2-weighted signal hyperintensity, restricted diffusion and intralesional fat) may help identify the nodules most likely to progress to hypervascularization, but further work is needed to validate these ancillary features for this purpose [72,73]. Until these or other discriminatory features are validated, it may be prudent to advise close interval follow-up (i.e., ≤6 months) of all new >1 cm hypovascular or isovascular nodules showing hepatobiliary-phase hypointensity.

■ Prediction of multicentric recurrence

In addition to predicting biological factors within a nodule, gadoxetate disodium-enhanced MRI has promise as an imaging biomarker to predict recurrence after hepatectomy. In a prospective study by Toyoda *et al.*, 77 patients undergoing hepatectomy were imaged during the hepatobiliary phase 2 weeks prior to surgery, and subsequently were followed for 1–5 years [74]. Recurrence categorization was divided into intrahepatic metastasis (same or lower degree of differentiation as primary resected tumor) or multicentric (well-differentiated HCC in a different segment or containing dysplastic nodules). Their results demonstrated a significantly higher rate of multicentric recurrence within livers that contained non-hypervascular hepatobiliary-phase hypointense nodules. Although most of the nodules resected with the hepatectomy specimen were non-cancerous (i.e., dysplastic nodules), the presence of such nodules is a marker of a ‘high-risk’ liver, capable of producing multiple HCCs in the future remnant.

■ Prediction of favorable biology

In addition to predicting poor prognostic factors such as microvascular invasion, conversion to hypervascularity and postsurgical recurrence, gadoxetate disodium-enhanced MRI also may have the ability to predict more favorable tumor biology. In a retrospective study by Kitao *et al.*, 180 resected HCCs were differentiated by signal intensity on preoperative hepatobiliary-phase imaging (Figure 4) [75]. A total of 22 hyperintense hepatobiliary-phase nodules demonstrated significantly higher differentiation grade, lower frequency of portal vein invasion, significantly lower expression of serum tumor markers (α -fetoprotein and protein induced by vitamin K absence or antagonist-II) and lower post-treatment recurrence rates [75]. Although not statistically significant, patients with hyperintense HCCs also trended toward prolonged survival after treatment. The authors speculate that hyperintense HCCs may arise from mature hepatocyte-like cells via clonal expansion rather than from progenitor cells, given the lack of α -fetoprotein (AFP) and EpCAM expression (both of which have previously been reported in HCCs with stem cell features). Further work is needed to confirm these observations and understand the underlying pathophysiologic mechanism.

A similar study by Kim *et al.* demonstrated that HCCs with iso- or hyper-intensity in the hepatobiliary phase after gadoxetate disodium injection had lower rates of microvascular invasion and were associated with older patient age and intranodular peliosis, all of which have been previously reported to convey more favorable prognosis [76]. However, these authors did not observe a significant difference with regards to nuclear histologic grade. It is important to note that the literature varies in terms of the definition of hyperintense HCC, employing a variety of qualitative and quantitative measures, which makes pooling of information across studies difficult. Standardization of these definitions will be necessary to facilitate progress in this field.

Potential pitfalls & challenges of gadoxetate

The signal intensity of a nodule in the hepatobiliary phase is determined by a complex interplay of transporter expression by both the nodule and the background hepatic parenchyma, as well as additional factors. This complex interplay yields added value and added challenges when characterizing liver lesions. Hepatobiliary-phase uptake of gadoxetate disodium by nodules is usually interpreted subjectively relative to background liver signal [59,77]. As mentioned, investigators have used various methods to attempt to quantify gadoxetate disodium uptake objectively; however, currently there is no consensus or standardized method for this purpose. Moreover, several biological and technical factors may confound the analysis of uptake.

As previously discussed, the uptake of gadoxetate disodium depends on the expression of transporters on the cell surface, which may be up- or down-regulated in the setting of liver disease, and also may be affected by drug–drug interactions, as well as by the degree of renal elimination of the agent. These confounders can affect the degree of background hepatic parenchymal enhancement and clearance of gadoxetate disodium [78], and they may reduce lesion-to-background contrast, thereby diminishing the conspicuity of HCC nodules in the hepatobiliary phase.

In addition, the focal or diffuse presence of iron or fat within a lesion or within the surrounding liver can alter the signal intensity of nodules relative to liver. Finally, the observed signal intensity of nodules and liver may be affected by numerous technical factors such as

scanner field strength, manufacturer and model; imaging parameters; contrast agent dose; and hepatobiliary-phase timing. These biological and technical factors make it difficult to create standardized models for lesion characterization at hepatobiliary imaging. Widespread implementation of quantitative methods will require standardization of hepatobiliary-phase timing and acquisition parameters, as well as correction for confounding biological and technical factors. Given the complexity of hepatocyte uptake and excretion, it is likely that subjective evaluation of lesion-to-parenchymal uptake will remain standard practice in the near future.

In addition to the challenges associated with the hepatobiliary phase, there are technical challenges related to the acquisition of dynamic post-contrast imaging with gadoxetate disodium. A recently recognized phenomenon of acute transient dyspnea has been described with use of gadoxetate disodium [79]. This is usually experienced shortly after injection and may result in degradation of the late arterial phase images in up to 20% of patients, which could have a significant impact on the evaluation of HCC. Several authors have suggested dilution of the contrast media, differing injections rates and acquisition of multiple arterial phases to offset the impact on diagnosis [80–82]. However, the presence of arterial phase imaging artifacts after gadoxetate disodium injection remains a challenge in clinical practice.

An additional concern regarding the enhancement properties of gadoxetate disodium in regards to HCC assessment revolves around the overlap in dynamic and hepatobiliary phases (i.e., the transitional phase). ‘Washout’ appearance of

Figure 4. Hepatobiliary-phase hyperintense probable hepatocellular carcinoma in a 57-year-old man with hepatitis C cirrhosis. Multiple axial images demonstrate a segment VII/VIII nodule (arrows) that is (A) isointense on precontrast imaging, (B) shows strong diffuse enhancement in the hepatic arterial phase, (C) fades to isointensity in the portal venous and (D) transitional phases, and (E) becomes hyperintense in the hepatobiliary phase. Hepatocellular carcinomas with this appearance are likely to have more indolent biological behavior than hepatocellular carcinomas with hypointensity in the hepatobiliary phase.

contrast is one of the major criteria for HCC diagnosis and is often assessed on the portal venous and conventional delayed postcontrast phases when using extracellular agents. Due to the strong and early enhancement of the background liver after gadoxetate disodium injection, however, many non-HCC lesions such as hemangiomas may appear to ‘washout’ (‘pseudowashout’), which potentially may cause diagnostic confusion [83]. Care should be taken to recognize that the hepatobiliary-phase uptake can occur as early as the portal venous phase and any lesion that does not contain hepatocytes may appear hypointense. Similarly, it is important to recognize that hypointensity in the hepatobiliary phase is not specific to HCC, but can be seen in any lesion not composed of functioning hepatocytes, such as metastases, cholangiocarcinoma, biphenotypic tumors and many benign lesions (e.g., cysts, hemangiomas, focal or confluent fibrosis).

Conclusion & future perspective

Gadoxetate disodium-enhanced MRI has been shown in numerous recent studies to improve the diagnosis of challenging tumors such as small progressed HCCs, as well as early HCCs. Furthermore, emerging evidence suggests that gadoxetate disodium-enhanced MRI may provide insight into tumor biology by helping to predict tumor grade, presence of biliary and stem cell markers, microvascular invasion, future hypervascularization and

post-treatment recurrence. The underlying basis is that hepatobiliary-phase nodule enhancement reflects OATP8 expression, which progressively declines during hepatocarcinogenesis prior to complete neoarterialization.

Until now, much of the evidence supporting the use of gadoxetate disodium-enhanced MRI for diagnosis of small or early HCCs and for characterizing HCC tumor biology has consisted of single-center retrospective studies in patients without advanced cirrhosis. Prospective studies with larger cohorts of patients and more diverse geographical and racial backgrounds are needed to validate these findings and better estimate the true diagnostic sensitivity and specificity. With further research and validation, there is high probability that hepatobiliary-phase imaging with gadoxetate disodium will alter the algorithmic pathway for diagnosis and management of patients with HCC.

Financial & competing interests disclosure

A Kagen is on the Speakers' Bureau for Bayer Healthcare. C Sirlin is a consultant for Bayer, is on the Speakers' Bureau for Bayer and is an advisory board member for Bayer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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