

## Current Limitations and Potential Breakthroughs for the Early Diagnosis of Hepatocellular Carcinoma

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Recently, Gadoxetic acid (Gd-EOB-DTPA; Primovist®; Bayer Schering Pharma), a tissue-specific contrast material, has been used for clinical MR imaging. This agent is a biphasic hepatobiliary contrast agent because it behaves as both an extracellular and a hepatocyte-specific agent as it undergoes both renal and biliary excretion. Up to 50% of the injected dose is taken up into normal hepatocytes due to the presence of the lipophilic ethoxybenzyl group in its chemical structure. As such, dynamic imaging can be performed using this agent for the evaluation of hemodynamic perfusion or status and for hepatobiliary phase imaging (10 to 20 minutes after injection) for the evaluation of functional status. Compared to extracellular contrast materials, Gadoxetic acid-enhanced magnetic resonance imaging (MRI) provides comparable arterial enhancement and prominent venous washout of hepatocellular carcinoma (HCC) during dynamic imaging. Additional hepatobiliary phase images are useful for the detection of small lesions that are not readily visible during dynamic imaging. Current evidence and experience suggest that Gadoxetic acid-enhanced MRI will improve the accuracy of HCC imaging diagnosis by allowing better characterization of hypovascular lesions and better differentiation of small arterial enhancing lesions as well as by providing improved preoperative staging accuracy. Therefore, with the aid of Gadoxetic acid-enhanced MRI, very early HCC will be more commonly diagnosed, with patient treatment occurring in earlier stages of the disease. (*Gut Liver* 2011;5:15-21)

**Key Words:** Liver; Neoplasm; Primary; Pathology

### INTRODUCTION

Hepatocellular carcinoma (HCC) is currently considered a curable disease, as long as it is diagnosed early.<sup>1</sup> The definition of 'early diagnosis' of HCC can be controversial as curable HCC

may include lesions with a variety of histologic or clinical criteria. Early HCC, as defined by the International Consensus Group for Hepatocellular Neoplasia, is represented by small well-differentiated HCC of vaguely nodular type<sup>2</sup> and is regarded as a distinct clinical entity with a high rate of surgical cure.<sup>3</sup> According to the Barcelona Clinic Liver Cancer (BCLC) staging classification, patients with very early stage HCC (single HCC <2 cm, Child-Pugh class A, performance status 0) or early stage (single HCC or 3 nodules <3 cm, Child-Pugh class A or B, performance status 0) may anticipate curative treatments.<sup>4</sup> Often, an early HCC is defined by eligibility for liver transplantation or curative surgical resection (e.g., Milan criteria: a tumor 5 cm or less in diameter in patients with single HCCs and no more than three tumor nodules, each 3 cm or less in diameter).<sup>5,6</sup> No matter how 'early' or 'curable' HCC is defined, early diagnosis of HCC can be achieved by surveillance of at-risk populations.<sup>7</sup> Surveillance tests include serologic and radiologic examinations. Serum tumor markers, such as alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) are commonly used for surveillance, but their roles in surveillance are being intensely debated in the era of sensitive radiologic tests.<sup>8,9</sup>

### RADIOLOGIC SURVEILLANCE TESTS FOR HCC

#### 1. Ultrasonography

Among radiologic tests, ultrasonography (US) is most widely used for surveillance.<sup>10</sup> Detection and characterization issues for focal lesions should be considered when determining the success of US as a surveillance tool. If a lesion is found on US examination, the characterization process should follow current practice guidelines.<sup>10-12</sup> According to these guidelines, new lesions that are found in HCC patients with cirrhosis that show increased enhancement during the arterial phase and rapid washout of enhancement during the late phases of dynamic imaging are likely.<sup>13-15</sup> However, issues still remain if a lesion is ac-

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tually present, but is not identified. US examination is operator dependent, and US sensitivity can be markedly diminished in patients who are obese or have underlying cirrhosis, decreasing the ability for diagnosis even for expert radiologists. According to a meta-analysis of prospective surveillance studies, pooled sensitivity of HCC diagnosis by US was 94% for any HCC stage and 64% for early HCC defined by the Milan criteria.<sup>6</sup> A recent report using the data of a hepatitis C antiviral long-term treatment against cirrhosis trial,<sup>16</sup> US did not reveal any suspicious nodules when performed 6 to 12 months before diagnosis in 14 (36%) of 39 HCC patients, while the sensitivity of DCP and AFP were 74% and 61%, respectively. In a recent report from Santi *et al.*<sup>17</sup> that compared semiannual and annual surveillance, HCC cases were identified outside of Milan criteria in 30% of semiannual and in 42% of annual surveillance groups (Fig. 1).

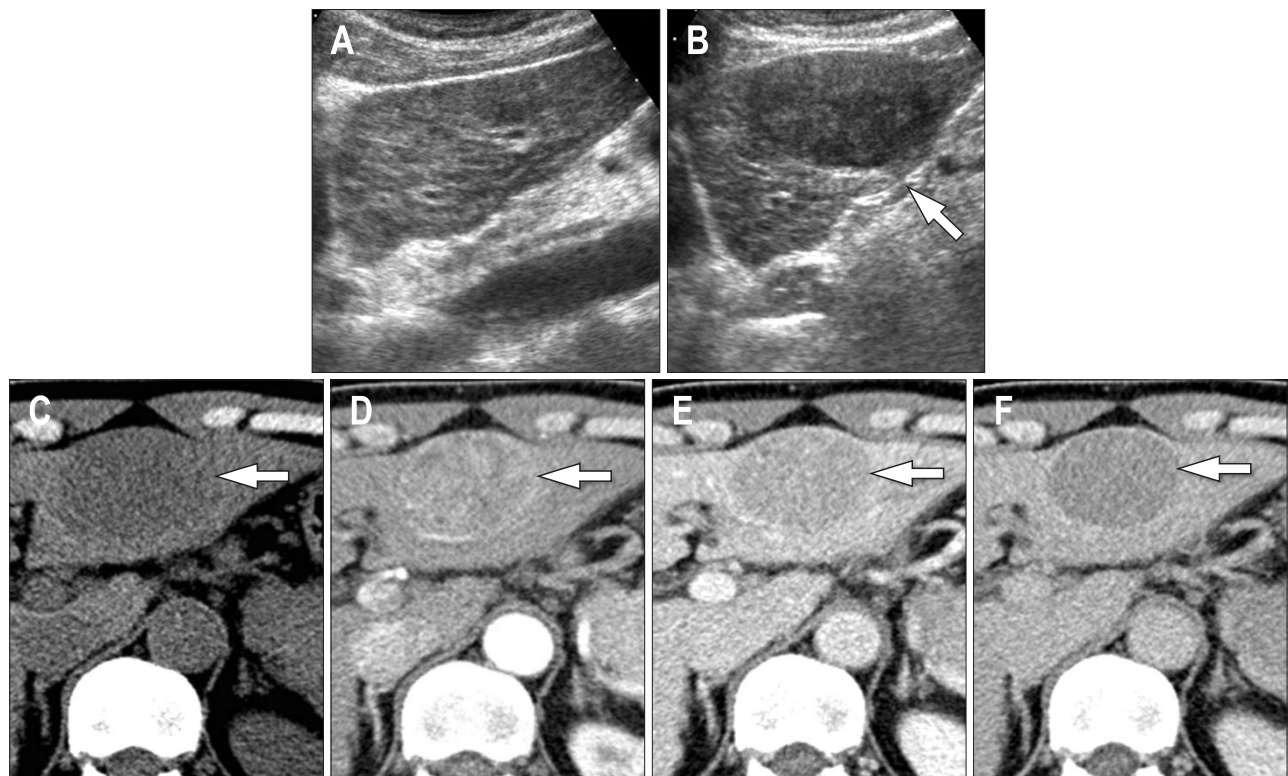
## 2. Computed tomography and magnetic resonance imaging

Therefore, there is a need for a more sensitive and accurate imaging modality for surveillance of early HCC diagnosis. The use of computed tomography (CT) or magnetic resonance imaging (MRI) for the purpose of HCC surveillance is limited,<sup>11,12,18</sup> as both CT and MRI examinations are expensive and not as readily available as US. In addition, CT and MRI also require the administration of contrast materials that cause side effects

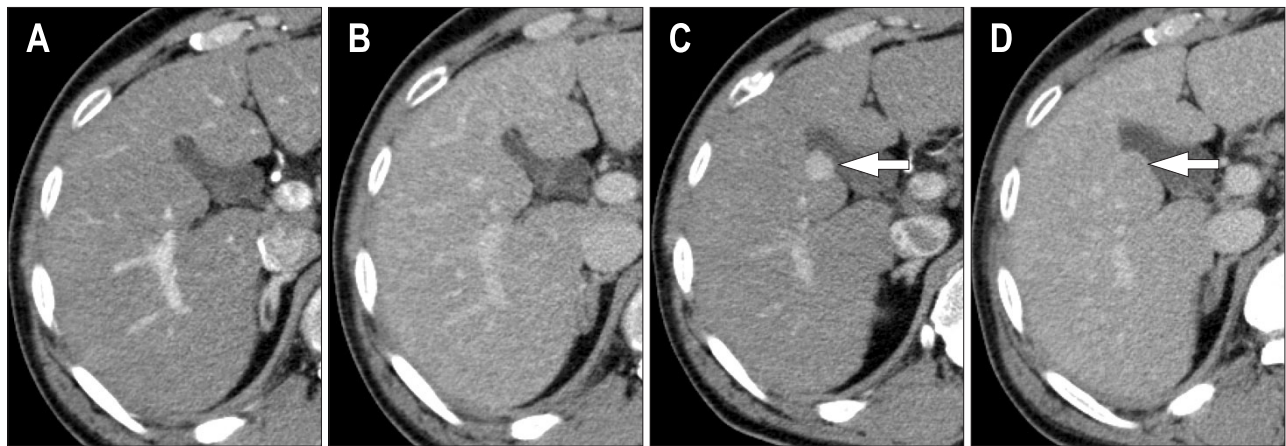
in most cases. There is no available data in moderate risk patients to determine the efficacy of surveillance using CT or MRI, although there are many results obtained when CT or MRI are used as a diagnostic test in patients with suspected or known HCC. According to the Japanese guidelines for the management of HCC,<sup>11,12</sup> periodic imaging by dynamic CT (by using multi-detector CT, MDCT) or dynamic MRI is recommended every 6 to 12 months for patients with hepatitis B or C-related cirrhosis, especially if a patient has confounding issues, including obesity or rough background liver parenchyma, which make it difficult to perform optimal US evaluation.

Unpublished data from my institute has shown that among 79 patients with HCC who showed negative findings on a previous CT scan obtained at various intervals, none of the patients who were followed within an interval of 1 year presented with HCC beyond the early stage, while 7 to 18% of patients who were followed at a longer interval were diagnosed with HCC(s) beyond the Milan Criteria (Fig. 2).

MRI provides various advantages for the evaluation of HCCs in that MRI offers higher tissue contrast compared to US or CT scan, images can be obtained utilizing various scan parameters or pulse sequences, and tissue-specific contrast media are available as well as extracellular contrast materials (ECCM). HCCs that are not identified on CT are frequently depicted on MRI and



**Fig. 1.** A 48-year-old man with liver cirrhosis who was under ultrasonography (US) surveillance for hepatocellular carcinoma (HCC). (A) A US image obtained six months earlier was interpreted as cirrhosis with multiple regenerative nodules. (B) A US image obtained at the time of diagnosis showed a large (5.3 cm) hypoechoic mass in the left lobe of the liver, where no focal lesion was identified on the previous US. Quadriphasic computed tomography demonstrated the typical appearance of a small HCC showing hypoattenuation on the precontrast (C), increased enhancement on the arterial phase (D), and washout on the venous (E) and equilibrium (F) phase images.



**Fig. 2.** A 56-year-old man with liver cirrhosis who was under computed tomography (CT) surveillance for hepatocellular carcinoma. CT images obtained at the arterial (A) and venous (B) phases showed no focal lesions in the liver. CT images obtained 8 months after the prior CT examination showed a small hypervascular nodule (arrow), hypervascularity on the arterial phase (C), and washout on the venous phase (D) images. The lesion was treated with transarterial chemoembolization. There has been no evidence of recurrence or progression during a follow-up of more than four years.

some nodules that look hypovascular may show typical arterial enhancement on dynamic MRI.<sup>19</sup> However, there are still some difficulties in the evaluation of patients with suspected HCC using ECCM-enhanced MRI. Small nodules that show hyperintensity on T1-weighted images and hypointensity on T2-weighted images can be evaluated as either low or high-grade dysplastic nodules or well-differentiated HCC. Identification of arterial hypervascularity is difficult for nodules that show hyperintensity on precontrast T1-weighted images. Washout of contrast enhancement, which is considered an important sign for the diagnosis of HCC, is frequently missing in HCCs that show obvious findings in other sequences. Small (<2 cm) arterial enhancing lesions that present hypervascularity at the arterial phase in the absence of hypointensity or washout at the venous phases are frequently benign, but some small HCCs also show a similar pattern. Detection of small or hypovascular HCC may also be difficult using conventional ECCM-enhanced MRI.

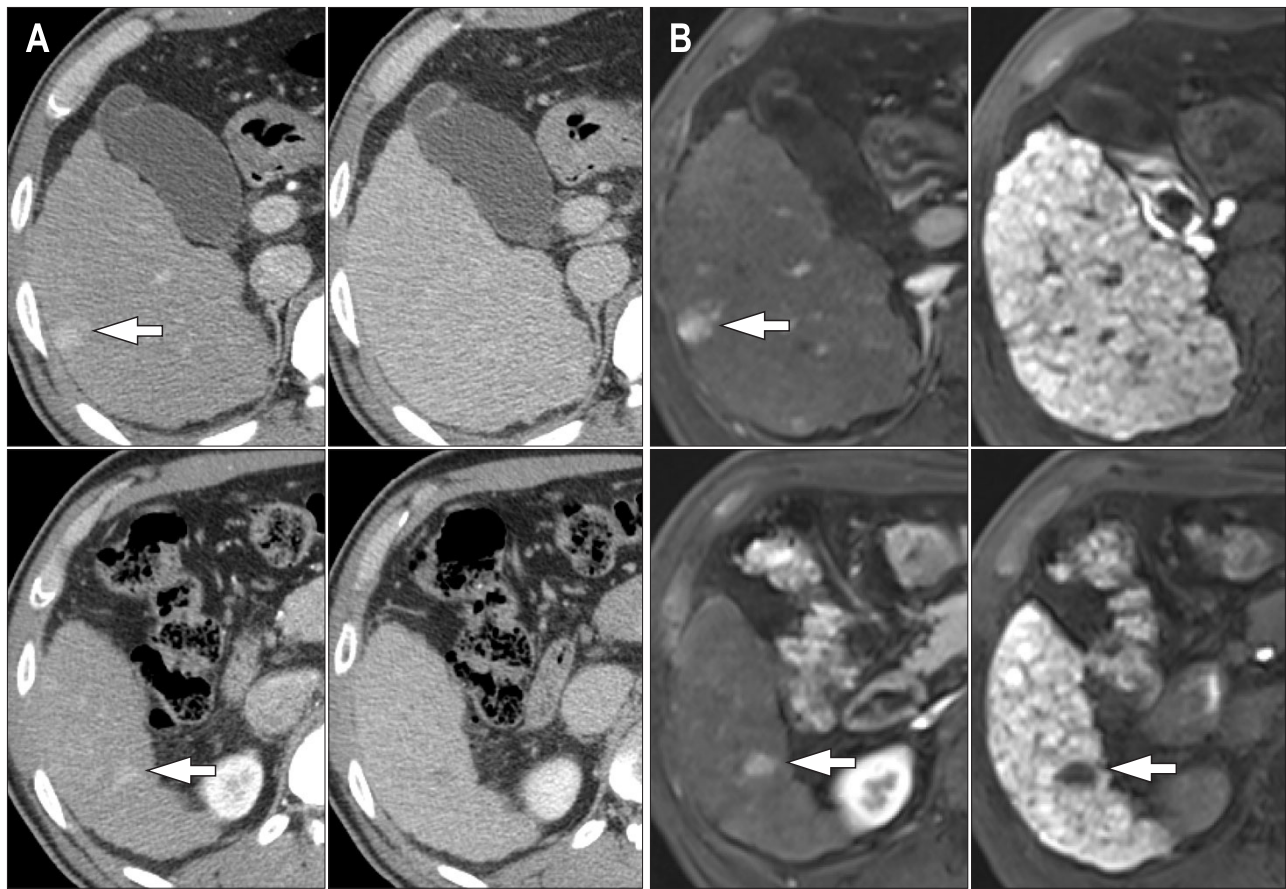
### GADOXETIC ACID-ENHANCED MRI

Gadoxetic acid disodium or Gadoxetate disodium (Gd-EOB-DTPA; Primovist®; Bayer Schering Pharma, Berlin, Germany), is a tissue-specific contrast material that has recently become available for use in clinical MRIs.<sup>20-23</sup> This agent is a biphasic hepatobiliary contrast agent because it behaves as both an extracellular and hepatocyte-specific agent<sup>24</sup> as it undergoes both renal and biliary excretion. Up to 50% of the Gadoxetic acid injected dose is taken up into normal hepatocytes due to the lipophilic ethoxybenzyl group in its chemical structure.<sup>25</sup> Therefore, dynamic MR images, as in ECCM-enhanced MRI, can be obtained for the evaluation of perfusion or hemodynamic status. In addition, hepatobiliary phase images can be obtained that maximize the hepatic parenchymal enhancement 10 to 20 min-

utes after injection.<sup>24</sup> With Gadoxetic acid-enhanced dynamic MRI, HCCs may show comparable arterial enhancement as in ECCM-enhanced MRI, but venous washout of HCC can be seen more prominently. Additional hepatobiliary phase images are useful for the detection of small lesions that are not easily visible on dynamic imaging. Recently, Ahn *et al.*<sup>23</sup> reported a study comparing the diagnostic accuracy between image interpretation with and without hepatobiliary images for the diagnosis of HCC on Gadoxetic acid-enhanced MRI. Their results demonstrated that hepatobiliary phase images obtained after Gadoxetic acid-enhanced dynamic MRI may assist in better diagnosis of HCC, and thus may help guide treatment planning. In this study, two small hypointense nodules found only on hepatobiliary phase images were resected and confirmed as early HCC. This study also showed that very small (<1 cm) lesions that were only depicted on hepatobiliary phase images, but not considered as HCC on initial interpretation, were finally confirmed as HCC on follow-up examinations.

Current evidence and experience suggests that Gadoxetic acid-enhanced MRI will improve the accuracy of early diagnosis of HCC by allowing for better differentiation of small arterial enhancing lesions (SAEL), better characterization of hypovascular lesions, and better detection of well-differentiated HCC.<sup>25,26</sup> SAEL that shows arterial hypervascularity at the early phases of dynamic imaging without showing typical venous washout patterns at the late phases of dynamic imaging has long posed problems for the early diagnosis of HCC.<sup>27,28</sup> Although most SAELs turn out to be benign on subsequent follow-up examinations,<sup>29,30</sup> it is also true that small HCCs frequently present with the nonspecific appearance of SAELs in early stages.<sup>31,32</sup> To distinguish a small HCC from a benign SAEL, demonstration of hypointensity of the lesion at the late phase of dynamic imaging is important.<sup>33</sup> However, MR imaging of small HCCs using an





**Fig. 3.** Characterization of small arterial enhancing lesions using Gadoxetic acid-enhanced magnetic resonance imaging (MRI). (A) Computed tomography (CT) images (left column, arterial phase images at different locations; right column, equilibrium phase images at the same location as the left image for each image) showed two arterial enhancing lesions (arrows) that did not display clear washout on venous phase images. (B) Gadoxetic acid-enhanced arterial (left column) and hepatobiliary phase (right column) images at the same location as the CT images. Both lesions showed increased arterial enhancement on the arterial phase MR images similar to the corresponding CT images. However, the upper lesion showed isointensity on the hepatobiliary phase images, suggesting a benign, non-tumorous arterial enhancing lesion, whereas the lower lesion showed dark intensity on hepatobiliary phase images, suggesting a small hepatocellular carcinoma.

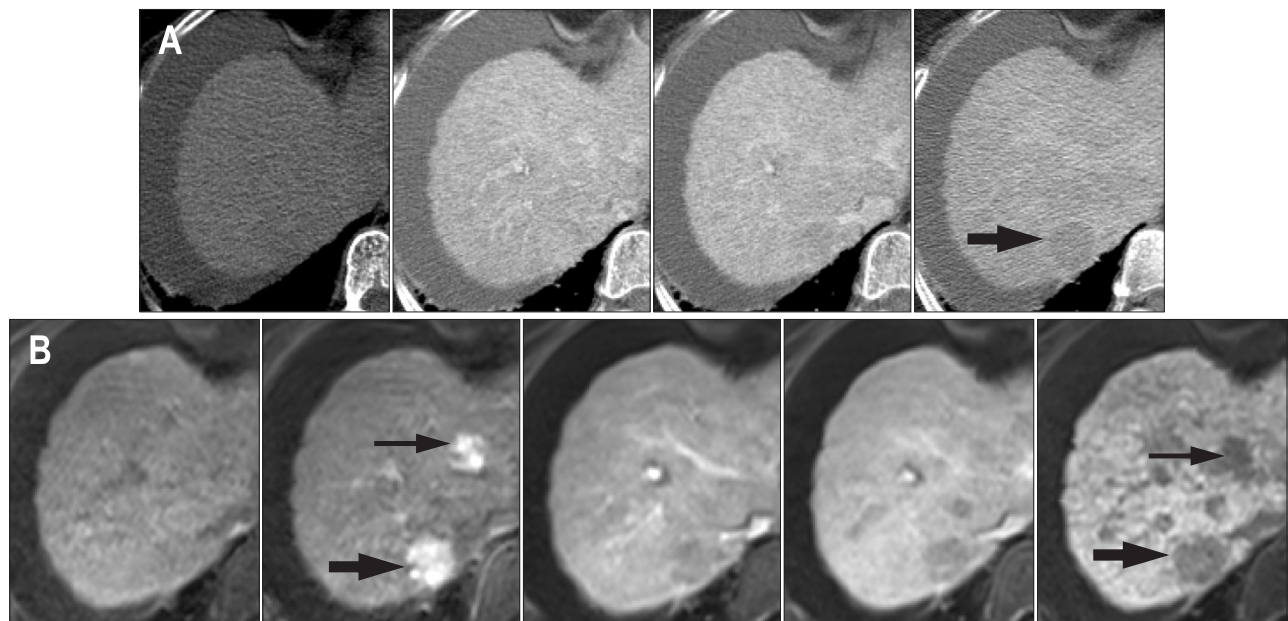
extracellular MR contrast agent frequently appear as isointense on equilibrium phase images.<sup>19,34,35</sup> According to a report by Sun *et al.*<sup>26</sup>, 95.4% of HCCs demonstrated hypointensity on Gadoxetic acid-enhanced hepatobiliary phase images, while only 3.7% of arterially enhancing pseudolesions showed such a finding (Fig. 3).

Gadoxetic acid-enhanced MRI may also play an important role in the evaluation of problematic hypovascular nodule lesions seen on CT or conventional MRI.<sup>25</sup> Some hypoattenuating lesions that do not clearly show arterial enhancement may actually show typical arterial enhancement and washout on dynamic and hepatobiliary imaging on Gadoxetate disodium-enhanced MRI. Many hypoattenuating HCCs depicted on CT may also show poor arterial enhancement on conventional ECCM-enhanced MRI, and some lesions show hyperintensity on precontrast T1-weighted images that preclude the appreciation of arterial hypervascularity. For these lesions, demonstration of marked hypointensity on Gadoxetic acid-enhanced hepatobiliary phase images may enhance confidence for HCC diagnosis

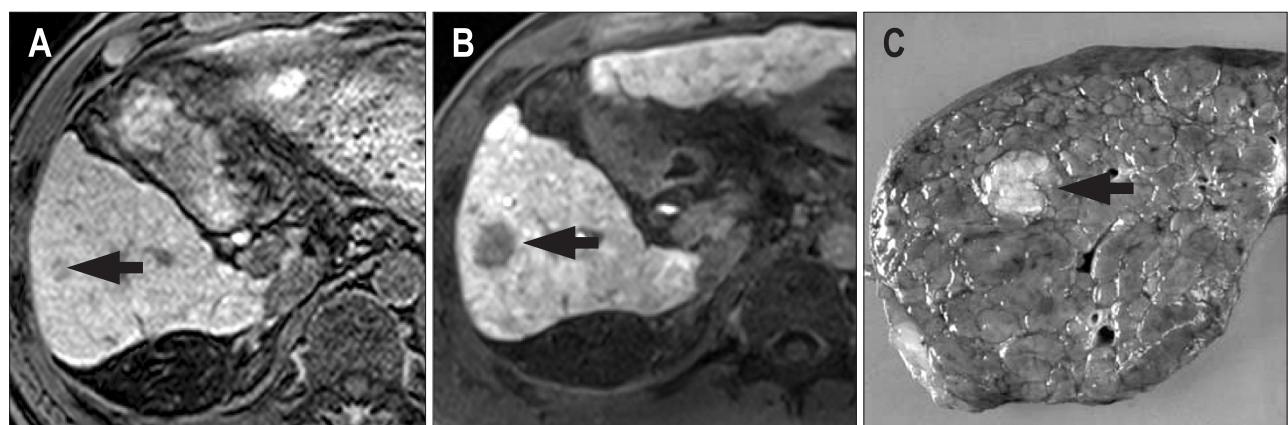
(Fig. 4).

Improvement of the sensitivity of diagnosis of well-differentiated HCC is also expected in the era of Gadoxetate disodium-enhanced MRI. Many well-differentiated HCCs show isoattenuation or isovascularity on contrast-enhanced CT or ECCM-enhanced MRI. Even on Gadoxetic acid-enhanced MRI, these lesions may not be depicted on precontrast T1- or T2-weighted images or on dynamic imaging. However, some well-differentiated HCCs, especially early HCCs, may demonstrate as clear hypointensity on hepatobiliary phase images, allowing the early diagnosis of those well-differentiated HCCs presenting with atypical features in conventional imaging.

However, there are still problems for the characterization of hypointense lesions that are only seen on hepatobiliary phase images. Some of these lesions may progress to overt HCC within several months, while some lesions take much longer to enlarge and manifest other ancillary characteristics for a confident diagnosis. On the other hand, there are also some lesions that do not change for years. Therefore, diagnosis of all hypointense lesions



**Fig. 4.** Small hepatocellular carcinomas (HCCs) showing hypovascularity on computed tomography (CT) examination. (A) Quadriphasic (pre, arterial, portal, and equilibrium [from left to right]) phase dynamic CT images revealed a small hypoattenuating lesion (arrow) that did not display arterial hypervascularity. (B) Gadoxetic acid-enhanced dynamic (pre, arterial, portal, and equilibrium [from left to right]) and hepatobiliary phase (far right) images demonstrated marked hypervascularity of this lesion with clear hypointensity on late phase images. Another small HCC (thin arrow) that was not seen during the CT examination also showed marked hypervascularity on the arterial phase and hypointensity on hepatobiliary phase images.



**Fig. 5.** A small hepatocellular carcinoma (HCC) shown in a 45-year-old man. (A) A Gadoxetic acid-enhanced hepatobiliary phase image showed a small hypointense lesion (arrow) that was not seen on other sequences (not shown). (B) The lesion showed considerable enlargement on the follow-up image taken 1.5 years after the first examination. (C) Surgical specimens revealed a well-differentiated HCC.

based only on hepatobiliary phase images should be avoided. Identification of ancillary characteristics, such as slightly increased signal intensity on T2-weighted images, formation of peritumoral capsules, and presence of nodule-in-nodule patterns, are useful for the correct diagnosis of HCC in these cases.<sup>36</sup> Size criteria may be also important, as many experts believe that the 1.5 cm size threshold is useful for the diagnosis of early hypovascular HCC when a lesion that is identified in patients with chronic liver disease shows hypointensity on hepatobiliary phase images but do not present with other ancillary characteristics (Fig. 5).<sup>37</sup>

There are several options for lesions that are seen only on hepatobiliary phase images without clear arterial hypervascularity or venous washout. Biopsy is a good diagnostic tool when the results are malignant, but is frequently impossible to perform for small lesions, especially located in an area of the liver that is difficult to approach.<sup>38</sup> Resection is an option when these lesions are present in patients who have an overt HCC that is planned for surgical resection. Information from lesions that are resected could be important for the establishment of future guidelines for the management of these difficult lesions. Follow-up or close observation is another practical option. However,

lesions can grow faster than expected beyond the early stages during this follow-up period when a less sensitive exam, such as conventional CT or ECCM-MRI, is alternatively used, although it is common clinical practice pattern. Therefore, the use of the same modality that was used for the detection of such a lesion (Gadoxetic acid-enhanced MRI in this case) is important, although the ideal interval for the follow-up is yet to be determined. Finally, radiofrequency ablation is sometimes performed in clinical practice. However, ablation without definite diagnosis may impose psychological issues with the patients and increase total healthcare costs.

## SUMMARY AND FUTURE DIRECTIONS

In summary, in the era of Gadoxetic acid-enhanced MRI, early diagnosis of HCC will become more common leading to patient treatment at earlier stages of the disease. This can be attributed to better characterization of small arterial enhancing lesions and better detection and characterization of hypovascular or atypical lesions, especially well-differentiated HCC, that frequently manifest ambiguous features on conventional CT or MR imaging. For future directions, further studies are necessary to determine the clinical effectiveness and cost-effectiveness of Gadoxetic acid-enhanced MR imaging for the detection of HCC at early stage. Prospective clinical trials may also be warranted to compare the effectiveness of Gadoxetate disodium-enhanced MR imaging in comparison with current standard surveillance tools.

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